



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Botulinum toxin type A

Proprietary Product Name: Botox

Sponsor: Allergan Australia Pty Ltd

July 2012

TGA Health Safety
Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	20 March 2012
<i>Active ingredient(s):</i>	Botulinum toxin, Type A
<i>Product Name(s):</i>	Botox
<i>Sponsor's Name and Address:</i>	Allergan Australia Pty Ltd 810 Pacific Highway Gordon NSW 2073
<i>Dose form(s):</i>	Sterile, vacuum dried, powder for reconstitution
<i>Strength(s):</i>	100 U, 200 U
<i>Container(s):</i>	Clear glass vial with a rubber stopper and tamper proof aluminium seal, containing a white powder for reconstitution
<i>Approved Therapeutic use:</i>	Botox is approved for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder.
<i>Route(s) of administration:</i>	Intramuscular (IM)
<i>Dosage:</i>	200 U
<i>ARTG Number (s)</i>	AUST R 67311, AUST R 172264

Product background

This AusPAR describes an application by the sponsor, Allergan Australia Pty Ltd, to register Botox (botulinum toxin type A) for a new indication, as second line treatment of urinary incontinence related to neurogenic detrusor overactivity (NDO) when anticholinergic agents have been ineffective or are not tolerated.

Botox purified neurotoxin complex is currently registered in Australia for multiple indications including the treatment of chronic migraine, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), focal spasticity in children two years and older, focal spasticity in adults, severe primary hyperhidrosis of the axillae, spasmodic dysphonia and is also indicated for the cosmetic indications, temporary improvement in the appearance of upper facial rhytides in adults.

Regulatory status

Similar submissions have been made to a number of regulatory agencies, as shown in Table 1. At the time of the Australian submission, no country had rejected Botox for the NDO indication.

Table 1: Summary of international regulatory status of Botox for the NDO indication.

Country	Submission Date	Approval Date
USA	27 th October 2010	Pending
New Zealand	30 th November 2010	Pending
EU (Ireland is the RMS for the mutual recognition procedure)	27 th October 2010	Pending
Canada	22 nd November 2010	Pending
Switzerland	21 st December 2010	Pending
UK	3 rd November 2010	Pending
The Netherlands	17 January 2011	Pending

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

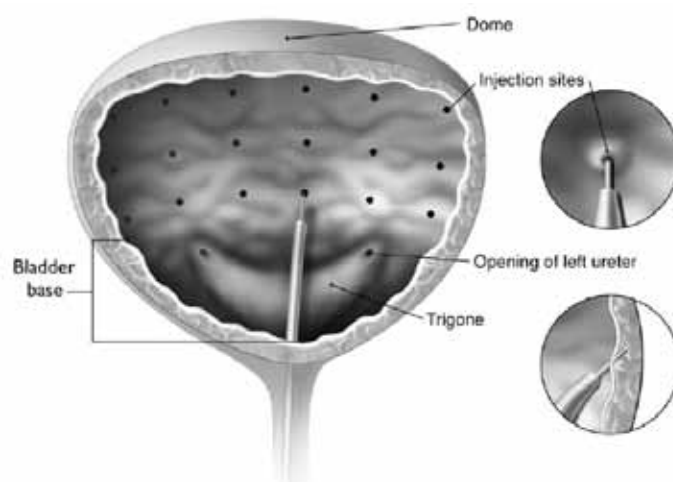
II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

Botox is registered for multiple indications and has been in widespread clinical use for many years. This submission was intended to provide nonclinical support for the extension of indications, to include the treatment of urinary incontinence in patients with NDO resulting from neurogenic bladder. The new indication represents the first use of Botox in smooth muscle. The proposed clinical dose is 200 U divided across 30 sites in the detrusor urinae muscle via cystoscopy. The 200 U should be reconstituted to 30 mL with normal saline prior to injection. The injections are to be spaced 1 cm apart, with 6.7 U injected per site, as shown in Figure 1. The detrusor urinae muscle contracts when urinating to squeeze out urine, otherwise it remains relaxed to allow the bladder to fill. The proposed retreatment schedule is no sooner than three months from the prior bladder injection. The proposed total dose and dosage regimen is similar to that for currently approved indications for Botox.

Figure 1: Injection pattern of Botox in the detrusor urinae muscle.

In support of the new route of administration, the sponsor provided toxicity studies in rats and monkeys to assess the local toxicity to the bladder and peribladder regions. The general quality of the submitted package was high, with all pivotal studies complying with Good Laboratory Practice (GLP). The only deficiency of note was a lack of pharmacology studies to support the new indication. Therefore, demonstration of efficacy will need to rely on clinical data.

Toxicology

The sponsor provided one single dose toxicity study in rats, and three single dose and one repeat dose toxicity study in monkeys, using the intended clinical route of administration, which is into the detrusor muscle of the urinary bladder. The duration (up to nine months), frequency (every three months), and route of dosing (intradetrusor [ID]) in the repeat dose toxicity study were appropriate for the proposed extension of indication. Clinically, Botox injection into the detrusor muscle is intended to be accomplished by cystoscopy. Injections into the detrusor muscle via cystoscopy in rats and Cynomolgus monkeys were stated to be impractical due to the small size of the urethra and the lack of suitably sized injection port cannulae for either species. Therefore, ID injection was via laparotomy in rats, and ultrasound guided transabdominal ID injection in monkeys. Given that these procedures achieved significant exposure of all areas of the bladder wall to Botox, this is considered acceptable. Mature Cynomolgus monkeys were chosen as the most appropriate species to evaluate the safety of Botox ID injections due to functional and anatomical similarities to the human bladder. Due to the nature of ID injection in rats, repeat dosing in this species was impractical.

Observation periods in the single dose toxicity studies ranged from 2-8 weeks. Given that the toxic effects of Botox were delayed (4-6 days post dose) and clinical signs of systemic toxicity were still seen after two weeks in both rats and Cynomolgus monkeys, longer observation periods may have been more appropriate. However, as the systemic effects of Botox are well known and there were no unexpected systemic findings, this is not considered a major deficiency. The small group size in the pivotal repeat dose toxicity study (three per group at the end of treatment and one per group for recovery) combined with a high mortality rate made it difficult to clearly discern significant dose dependent changes.

The safety of Botox when injected into peribladder tissues was studied in three single dose toxicity studies (injection into the prostatic urethra, rectum and seminal vesicle in males, and the uterus in females) and one repeat dose toxicity study in monkeys (intraprostatic

injection). These studies were conducted in the event of inadvertent exposure to tissues close to the bladder. Appropriate organs were examined.

As the activity of Botox in the currently proposed indication is intended to be exerted locally, and the potential systemic (neuro)toxic effects are of great concern, both local and systemic toxicities were examined in the submitted studies. No toxicokinetic studies accompanied the submitted toxicity studies, and given the nature of Botox, this is considered acceptable. Dose comparisons were made on a U/kg basis for systemic effects and a U/site and U/mL basis for local effects (Table 2). Doses in the toxicity studies were appropriate, representing several multiples of the proposed clinical dose, with dosing limited by systemic toxicity in the rat study and the pivotal repeat dose toxicity study in monkeys.

Table 2: Exposure multiples.

Study details	Injection site	U/site	Dose (U/kg)	Conc. (U/mL)	Comparison (animal/human) based on		
					U/site	U/kg	U/mL
TX01064 Rat <u>Intradetrusor</u> Single dose (14-day obs.), 4F/group	0.05mL×1 site (bladder; intradetrusor via laparotomy)	2.5	10	50	0.4	2.5	7.5
		12.5	50	250	1.9	12.5	37
		25	100	500	3.7	25	75
TX02086 Monkey <u>Intradetrusor</u> Single dose (4-week obs.), 2F/group	0.2mL×3sites (transabdominal into bladder dome, right & left dorsolateral wall of bladder)	12	12	60	1.8	3	9
		24	24	120	3.6	6	18
TX02042 Monkey <u>Peribladder</u> Single dose (8 week obs.), 2M/group	0.4 mL×2 sites (transabdominal into prostatic, urethra & proximal rectum or urinary bladder base & left seminal vesicle)	20	6.8	50	3	1.7	7.5
		20	6.8	50	3	1.7	7.5
TX03052 Monkey <u>Intradetrusor or Uterine</u> Single dose (8 week obs.), 5F/group	0.2 mL×3sites (transabdominal into bladder dome, right lateral & left lateral wall of bladder)	12	12	60	1.8	3	9
		24	24	120	3.6	6	18
		36	36	180	5	9	27
	0.2mL×1site (uterus)	6	2	30	0.9	0.5	4.5
TX07077-TX Monkey <u>Intraprostatic</u> Single dose (0.2mL×2 sites of prostate)	Transabdominal into inferior ventral lobe of the prostate (L&R areas)	60	20	300	9	5	45
TX05046 Monkey <u>Intradetrusor</u> Repeat-dose every 13 weeks, 4 cycles 4/sex/group	0.2mL×3 sites (bladder dome, right lateral & left lateral wall of bladder)	12	12	60	1.8	3	9
		24	24	120	3.6	6	18
		36	36	180	5	9	27
TX05055 Monkey <u>Intraprostate</u> Repeat-dose every 13 weeks, 4 cycles 6/sex/group	0.2mL×2 sites (R&L ventral areas of prostate)	24	8	120	3.6	2	18
		36	12	180	5	3	27
		60	20	300	9	5	45
Recommended human dose	1mL×30 sites	6.7	4U/kg (200U/50-kg)	6.7 (100U/15mL)	NA	NA	NA

NA=not applicable

Local toxicity – bladder

After ID injection to rats and monkeys, there were no clinical signs or histopathological evidence of local toxicity to the smooth muscle of the bladder at single doses up to 25

U/site in rats or repeat doses of 36 U/site in monkeys (3.7 and 5 times the clinical dose at an individual injection site). Increased bladder weights and an elongated bladder were seen in rats at ≥ 12.5 U/site, but without histopathological correlates. The absence of local toxicity contrasts with the atrophy of the skeletal musculature seen after a single IM dose of as little as 14 U/site to monkeys (Study 99-3406) and histopathological findings in the prostate following repeated intraprostatic injections of 24 U/site (see below). Therefore, the local adverse effects after a single injection of Botox seem to be dependent on the kind of tissue present at the injection site. This may be due to differences in innervation and function of skeletal muscle (used for IM injections), smooth muscle (such as that in the detrusor muscle and the urethra), and fibromuscular/glandular tissues (such as those in the prostate). Adverse reactions observed in clinical trials (Botox PI document) such as urinary tract infections and urinary retention were not observed in the submitted animal studies.

Local toxicity – peribladder tissues

Single and repeat dose toxicity studies were conducted in Cynomolgus monkeys to assess the toxicity to peribladder tissues. No adverse local effects were seen after a single intrauterine injection of 6 U/site (approximately equivalent to the clinical dose). Given the low dose tested, effects on female reproductive organs are not considered to have been adequately assessed. However, the likelihood of inadvertent exposure to the uterus or other female reproductive organs is considered low with the proposed cystoscopic administration method.

A single dose of 20 U/site (3 times the clinical dose) caused no local effects after injection in the proximal rectum and seminal vesicle. A single injection of the same dose into the prostatic urethra caused calculi formation in the lumen of the urinary bladder in 1/4 monkeys. Bladder stones and urethral obstruction were also observed after repeated injection of Botox into the prostate (≥ 36 U/site; NOEL [No Observable Effects Limit] 24 U/site, 3.6 times the clinical dose). Bladder obstruction appeared to be the result of an accumulation of amorphous material (consistent with the secretory matrix of the seminal vesicles) and the formation of ejaculatory coagulum within the urethra.

Microscopic findings in the seminal vesicles and prostate following intraprostatic administration included oliguria and decreased seminal vesicle weights following a single dose of 60 U/site (9 times the clinical dose). Repeated injections of ≥ 24 U/site (3.6 times the clinical dose) led to seminal vesicle distension with secretion. Multifocal pigmented macrophages were seen in the seminal vesicle lumen at higher doses (≥ 36 U/site). Findings in the prostate following a single intraprostatic dose (60 U/site) included cellular debris deposition in the acini of the caudal lobe and angiectasia in the periurethral interstitium. Following multiple doses of ≥ 24 U/site (NOEL not established), multifocal haemorrhage was seen in the lumen of the prostate. After a six month treatment free period, all previously treated males had a dilated or cystic prostate gland. Findings in the bladder, prostate and seminal vesicles were still seen after a six month treatment free period, suggesting the effects were not readily reversible.

The sponsor argued that the occurrence of bladder stones in monkeys following intraprostatic administration of Botox is an effect specific to monkeys and not necessarily applicable to humans due to anatomical differences in the seminal vesicles and ejaculatory ducts in relation to the prostate and with respect to the injection site. Unfortunately, no specific studies were provided to confirm this. In an independent literature search, a number of published papers reporting effects of intraprostatic injection of botulinum toxin

A to male subjects were identified.¹ None of these papers reported bladder stones as a side effect, suggesting the argument put forward by the sponsor may have some merit. However, until further studies have been provided, bladder stone formation should remain a potential risk in the event of inadvertent prostate injection.

Systemic toxicity

Systemic toxicity was observed following a single ID injection in rats and multiple ID injections in Cynomolgus monkeys, suggesting diffusion from the injection site into the systemic circulation. Botox related deaths were seen after a single dose of 100 U/kg in rats and repeated doses of ≥ 24 U/kg in Cynomolgus monkeys. Clinical signs of systemic toxicity included respiratory distress, toes curled over, hunched posture, and abnormal gait in rats at ≥ 10 U/kg (2.5 times the maximum recommended human dose [MRHD]; NOEL not established) and eyelid ptosis, lethargy and respiratory distress in Cynomolgus monkeys treated with repeated doses of ≥ 24 U/kg (6 times the MRHD). Eyelid ptosis was observed after the first dose at ≥ 24 U/kg in monkeys receiving ID Botox. Ptosis was still seen after a six month treatment free period in one male previously treated with 12 U/kg. Deaths and clinical signs occurred typically several days after dosing, consistent with the delayed toxicity of Botox reported previously. These clinical signs lasted for up to two weeks.

Skeletal muscle atrophy and necrosis was observed in the diaphragm of rats treated with 100 U/kg (NOEL 50 U/kg; 12.5 times the MRHD). Myocyte degeneration was seen in the skeletal muscle of the diaphragm and thigh of Cynomolgus monkeys treated with ≥ 24 U/kg every three months. These skeletal muscle effects are attributed to an exaggerated pharmacological effect. Aside from slight body weight loss, no systemic effects were seen in Cynomolgus monkeys given a single ID dose of 36 U/kg. Previous studies have shown mortality after repeated administration of 16 U/kg IM to monkeys, but only when the dose was administered in one site at two-month intervals (Study 91-3708 in SN 2007-1065-1), compared to six sites at three-month intervals (Study 98-3382 in SN 2007-1065-1), in which case no mortality was observed. This suggests that an increase of time between doses and division of the doses among several sites could potentially decrease the systemic toxicity of Botox injections.

The ID doses causing systemic toxicity in both rats and monkeys were similar to IM doses reported previously to cause systemic toxicity. Clinical signs of systemic toxicity were seen at ≥ 5 U/kg IM in rats (Study 1658P-3526-5 in CTX 97-1-4010) and Botox related deaths were seen at ≥ 24 U/kg IM (gastrocnemius muscle) in Cynomolgus monkeys (Study 96-3334 in CTX 97-1-4010). In Cynomolgus monkeys, no treatment related effects were seen at 4 or 8 U/kg IM except for transient eyelid ptosis in a female treated with 8 U/kg.

¹ Chartier-Kastler E, et al. (2011) Botulinum neurotoxin A for male lower urinary tract symptoms. *Curr. Opin. Urol.* 21: 13-21; Chuang YC, Chancellor MB. (2006) The application of botulinum toxin in the prostate. *J. Urol.* 176: 2375-2382; Chuang YC, et al. (2006) Sustained beneficial effects of intraprostatic botulinum toxin type A on lower urinary tract symptoms and quality of life in men with benign prostatic hyperplasia. *BJU Int.* 98: 1033-1037; Chuang YC, et al. (2006) Intraprostatic injection of botulinum toxin type-A relieves bladder outlet obstruction in human and induces prostate apoptosis in dogs. *BMC Urol.* 6: 12; Lim SK, Quek PL. (2008) Intraprostatic and bladder-neck injection of botulinum A toxin in treatment of males with bladder-neck dyssynergia: a pilot study. *Eur Urol.* 53: 620-625; Maria G, et al. (2003) Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. *Urology* 62: 259-264; Maria G, et al. (1998) Relief by botulinum toxin of voiding dysfunction due to prostatitis. *Lancet* 352: 625; Nikoobakht M, et al. (2010) Intraprostatic botulinum toxin type A injection for the treatment of benign prostatic hyperplasia: Initial experience with Dysport. *Scand. J. Urol. Nephrol.* 44: 151-157; Silva J, et al. (2009) Intraprostatic Botulinum Toxin Type A injection in patients with benign prostatic enlargement: duration of the effect of a single treatment. *BMC Urol.* 9: 9.

Given the above findings, and the fact that the proposed total dose (200 U) for this site of administration is less than the maximum currently approved for IM administration (360 U), ID administration should not pose any greater systemic toxicity risk than that expected with currently approved IM doses for other indications.

Comments on the Safety Specification in the Risk Management Plan

Results and conclusions drawn from the nonclinical program for Botox detailed in the sponsor's Risk Management Plan (RMP) are generally consistent with the current and previous nonclinical evaluations conducted at the TGA. However, it should be noted that statements referring to the animal studies conducted specifically for other indications have not been evaluated by the TGA. Therefore the accuracy of these statements cannot be verified.

Nonclinical summary and conclusions

- Allergan Australia Pty Ltd has applied to extend the indications of Botox to include the treatment of urinary incontinence in patients with neurogenic detrusor overactivity resulting from neurogenic bladder. The new indication represents the first use of Botox in smooth muscle. The proposed clinical dose is 200 U divided across 30 sites in the detrusor muscle at 6.7 U per site. The proposed total dose and dosage regimen is similar to that for currently approved indications for Botox.
- No pharmacology studies were submitted to support the new indication. Demonstration of efficacy will need to rely on clinical data.
- Single dose and repeat dose toxicity studies were conducted in rats and/or monkeys to assess the toxicity to the bladder and peribladder tissues. Systemic toxicity was also examined in these studies.
- There were no clinical signs or microscopic evidence of local toxicity to the smooth muscle of the bladder at single doses up to 25 U/site in rats or repeat doses of 36 U/site in monkeys (3.7 and 5 times, respectively, the clinical dose at an individual injection site).
- No adverse local effects were seen after a single intrauterine injection (6 U/site) or single doses of 20 U/site (3 times the clinical dose) in the proximal rectum and seminal vesicle of Cynomolgus monkeys.
- Intraprostatic injections of ≥ 24 U/site (3.6 times the clinical dose) was associated with an accumulation of amorphous material and formation of ejaculatory coagulum within the urethra causing bladder obstruction. A NOEL was not established for the prostate and seminal vesicle changes, and there was no evidence of reversibility.
- Signs of systemic toxicity were seen following ID injections to both rats and Cynomolgus monkeys and included known toxic effects of Botox: respiratory distress, toes curled over, abnormal gait and/or ptosis, with Botox related deaths at higher doses. Atrophy and necrosis of the skeletal musculature of the diaphragm was observed at necropsy. The ID doses causing systemic toxicity in both rats and monkeys were similar to previously reported IM doses causing systemic toxicity.

IV. Clinical findings

Introduction

The submission consists of seven studies of Botox in the treatment of detrusor overactivity, including:

- six studies of NDO; and
- one study in idiopathic overactive bladder (IOAB) with urinary urge incontinence.

The sponsor's claim for efficacy largely rests on two Phase 3 pivotal studies in NDO (Studies 515 and 516), which had almost identical designs and were therefore subjected to a pooled analysis. These studies assessed up to two doses of ID Botox for the treatment of NDO in patients with multiple sclerosis (MS) or spinal cord injury (SCI), who had failed to respond adequately to anticholinergic agents.

The submission also includes a short, single dose Phase 2 feasibility study (511), a Phase 2 dose ranging study (518), a long term extension study (094) and interim results of an ongoing Phase 3 safety study in a special population of subjects with respiratory compromise (082).

The seventh study (077) was not included in the Summary of Clinical Efficacy and it was merely given a brief mention in the sponsor's submission letter. It is of less immediate relevance to the submission because it did not treat patients with NDO but instead involved patients with IOAB. It is nonetheless important because the efficacy results in this study were much less impressive than in any of the six NDO studies, suggesting that the efficacy of Botox might vary according to the aetiology of IOAB. It was another dose ranging study completed in June 2008, but it is described as 'ongoing' in the sponsor's submission letter. Of the 313 patients enrolled in the study, 56, 53, 49, 54 and 57 were randomised to Botox 300, 200, 150, 100 and 50 U and 44 to placebo, respectively. This is at least twice as many, per dose group, as were assigned to the different dose groups in the other dose ranging study, Study 518 (that had 16 to 21 patients per dose group). This makes it a much more substantial study than either of the two Phase 2 studies that *were* included in the clinical report – and indeed it is larger than both of them combined, so it probably should have been mentioned in the Summary of Clinical Efficacy.

As shown in Table 3, most of the NDO studies recruited a mixture of patients with SCI or MS; the exception was the smaller of the two dose ranging studies (Study 518), which assessed a more homogenous population of SCI patients

Table 3: Summary of clinical studies.

Study (region)	No. patients in submission	Etiology	No. treatments	Dose	Duration of follow-up (analysis provided in submission)
Phase 2 191622-511 (EU)	N = 59	SCI + MS	Single	Placebo, BOTOX® 200 or 300 U	6 months (final analysis)
Phase 2 191622-518 (EAME/AP)	N = 74	SCI	Up to 2	Treatment 1: Placebo, BOTOX® 50, 100 or 200 U Treatment 2: BOTOX® 200 U	Up to 1.5 years (primary analysis) ^c
Pivotal Phase 3 191622-515 (US/CAN/EAME/AP)	N = 416	SCI + MS	Up to 2	Treatment 1: Placebo, BOTOX® 200 or 300 U Treatment 2: BOTOX® 200 or 300 U	At least 1 year (final analysis)
Pivotal Phase 3 191622-516 (US/CAN/EAME/AP/BRA)	N = 275	SCI + MS	Up to 2	Treatment 1: Placebo, BOTOX® 200 or 300 U Treatment 2: BOTOX® 200 or 300 U	At least 1 year (final analysis)
Phase 3 (extension study to 515/516) 191622-094 (US/CAN/EAME/AP/BRA)	N = 285 (155 treated in study as of cut-off)	SCI + MS	Multiple	BOTOX® 200 or 300 U	3 years (interim analysis) ^b
Phase 3 191622-082 (US/CAN/AP)	N = 34	SCI + MS	Up to 2	Treatment 1: Placebo, BOTOX® 200 or 300U Treatment 2: BOTOX® 200 or 300 U	At least 1 year (interim analysis) ^d

SCI = spinal cord injury; MS = multiple sclerosis; EU = Europe; EAME = Europe, Africa, and Middle East; US = United States; CAN = Canada; AP = Asia-Pacific/Australia/India; BRA=Brazil.

No new pharmacokinetic or pharmacodynamic studies were presented, as the drug is already well established in clinical and cosmetic practice. Pharmacokinetic data for the drug have always been scarce because it used locally rather than systemically (and could indeed be dangerous if administered systemically). The pharmacodynamic effects of the drug on bladder function were assessed via urodynamic studies, however, as part of the pivotal studies, and this assessment contributed to some efficacy and safety endpoints.

Overall, for each of the six studies in Table 3, the data were clearly and fairly presented, and with the exception of some minor concerns discussed below, the studies used broadly appropriate methodologies and statistical analysis. (The seventh study was not misrepresented but was simply ignored.)

The initial treatment in the two dose, Phase 3, pivotal studies (Studies 515 and 516) was randomised, placebo controlled and double blind; the second treatment was merely dose controlled, as all patients received active treatment. The Phase 2 studies (Studies 511 and 518) also used a placebo comparator and so the only study lacking a placebo group was the Phase 3 extension study (Study 094). A placebo controlled design was appropriate given the lack of a suitable active comparator in patients who have failed anticholinergic therapy. An anticholinergic comparator study would be appropriate if the sponsor sought registration for first line therapy of NDO.

The treatment groups in the pivotal studies were well matched and corresponded to the target population. Follow up (about 80%) was as complete as could be expected for studies of this nature, and no major methodological biases were identified. Multiple endpoints were assessed in the pivotal studies, but the primary endpoint (weekly frequency of urinary incontinence at six weeks) was indicated prospectively and achieved clear statistical significance. All secondary efficacy endpoints also achieved clear statistical significance, so the sponsor's conclusions did not appear to rest on the selection of any particular favourable endpoint. (The Hochberg method was used to compensate for the

use of multiple endpoints.) The efficacy endpoints were appropriate to the indication being assessed and included incontinence frequency, urodynamic measures and quality of life assessments. The magnitude of the observed treatment effect was clinically meaningful. Subgroup analyses and sensitivity analyses with and without data imputation by a last-observation-carried forward (LOCF) method produced consistent findings.

The pivotal study designs were modified during development of the study program, in response to recruitment difficulties and on the basis of discussions with the US Food and Drug Administration (FDA). (In particular, a second placebo controlled treatment cycle in pivotal Study 191622-515 was removed, to be replaced by a randomised, active, dose controlled cycle, and the duration of the two pivotal studies was aligned). Such modifications can raise concerns about methodological bias but it does not appear that this change had any significant effect on the conclusions. Also, it does not appear that the changes were made in response to interim study results.

As will be discussed in the Safety section of this report, the submitted studies showed that ID Botox increases the risk of urinary retention and urinary tract infections (UTIs) by impairing bladder emptying. Unfortunately, this is an anticipated side effect of Botox that is intrinsically related to its mode of action. Some patients receiving Botox for detrusor overactivity will need to commence catheterisation as a direct consequence of the treatment. (This is much less of an issue for patients already performing intermittent catheterisation prior to treatment.) Also, if the bladder's holding capacity is increased by Botox but this increase is matched by a corresponding increase in the post void residual urine volume (PVR), the actual gain in *available* storage capacity for non catheter using patients is zero. The sponsor took appropriate steps to monitor this downside of the proposed treatment, but the efficacy analysis essentially ignored the issue, and instead the increase in post void residual urine volume was presented entirely as a safety concern. It would have been appropriate to compare increases in maximum bladder volume (maximum cystometric capacity) with increases in post void residual volume, to put the volume gains into context and allow assessment of the bladder's reserve capacity after voiding.

The primary endpoint for the pivotal studies was incontinence frequency, but a careful reading of the study protocols revealed that not all incontinence was recorded; this was not mentioned in the clinical summaries. In particular, incontinence data during UTIs was not collected. This could have biased the studies in favour of Botox, given that active treatment increased the risk of UTIs. The sponsor did not address this point elsewhere.

In conclusion, the main issues of concern raised by the submission were the sponsor's failure to acknowledge the relatively unfavourable dose ranging Study 077, the fact that ID Botox was associated with poor bladder emptying, and the censorship of UTI associated incontinence.

Pharmacokinetics

No pharmacokinetic data were submitted.

Pharmacodynamics

The sponsor performed urodynamic monitoring within the pivotal efficacy studies, and the relevant data are presented there.

Efficacy

Pivotal Efficacy Studies (515 and 516)

Pivotal Study Designs

Design Overview

The two pivotal efficacy studies (Study 515, n=275; Study 516, n=416) shared a similar design and differed only in the level of urinary incontinence required before patients were eligible for a second Botox treatment. They are therefore described here together, though the individual results will also be presented. Across both studies, a total of 691 patients with NDO were enrolled and were subsequently randomised to receive either Botox 200 U (n=227), Botox 300 U (n=223) or placebo (n=241).

Patients received up to two randomised, double blind treatments: the first treatment was placebo controlled, and the second was dose controlled. Both studies followed patients for one year, plus additional time where needed to ensure 12 weeks of follow up were available after the second treatment.

Both pivotal studies recruited patients with urinary urge incontinence associated with NDO due to either a SCI or MS. The NDO had to have been present for at least three months, had to be confirmed on urodynamic assessment and had to be associated with at least 14 episodes of incontinence per week, with no more than two incontinence free days per week. A previous trial of anticholinergic agents for at least one month had to have failed because of side effects or poor efficacy.

Patients were eligible regardless of whether they were still receiving anticholinergics at baseline or whether they performed intermittent self catheterisation (clean intermittent catheterisation [CIC]), but these concurrent bladder treatments had to be kept stable throughout the study, that is, patients were kept on the same anticholinergic dose and the same frequency of CIC to avoid confounding the Botox assessment. Where necessary on clinical grounds, CIC could be commenced during the study, and the proportion of patients needing this constituted an important safety endpoint (and was elevated in the Botox groups). Patients with an in dwelling urinary catheter were not eligible.

Further details of the inclusion and exclusion criteria are contained below; in general, these were commonsense criteria aimed at including patients with sufficiently severe incontinence and excluding conditions that could confound the assessment or threaten patient safety. It should be noted that, amongst SCI patients, cord lesions had to be T1 or below ; patients with cervical cord lesions were excluded. Safety in this group has therefore not been adequately assessed, but further information is expected from the ongoing safety study (Study 082) in patients with respiratory compromise due to cervical cord lesions or severe MS.

For their first treatment, patients in both studies were randomised to saline placebo, Botox 200 U or Botox 300 U in a 1:1:1 ratio. They received this as 30 x 1 ml injections administered into the detrusor muscle at an approximate depth of 2 mm under cystoscopic guidance. The pattern of administration is illustrated in Figure 1.

After a minimum of 12 weeks, regardless of their initial response to the first treatment, patients were eligible for retreatment upon request, provided their incontinence was sufficiently severe at that stage (either because the effect of the first treatment had worn off, or it had not been effective). The severity threshold for retreatment differed in the two studies. In Study 515, incontinence had to be $\geq 50\%$ of baseline, that is, a reduction of $<50\%$ in incontinence had to be present relative to baseline. In Study 516, incontinence had to be $\geq 70\%$ of baseline, that is, a reduction of $<30\%$ in incontinence. All three criteria had to be met to receive retreatment: at least 12 weeks since the first treatment, a patient

request, and sufficient incontinence. Time to retreatment, time to patient request and time to the different incontinence thresholds gives some indication of the duration of efficacy.

The second treatment consisted of active therapy with Botox 200 U or 300 U. Patients who had already received active treatment in the first cycle received the same dose in the second cycle, and patients who had received placebo were randomised to either of the two active doses in a 1:1 ratio. To preserve blinding, this treatment was assigned at baseline.

Although this study design means that placebo controlled data is only available for a single cycle, it is understandable in the context of a relatively long study (at least a year), ongoing distressing symptoms (sufficient for the patient to ask for more treatment), and an invasive procedure. In fact, the sponsor initially intended to have two placebo controlled cycles in Study 515, but then changed the design after discussions with the FDA. Asking patients to attend for a second invasive procedure when they will possibly only receive saline (facing the risk of the procedure with no potential benefit) might have been asking too much and could have led to recruitment difficulties. Also, the time to retreatment might also have been affected in a complex and unpredictable way by the use of placebo in a second cycle: patients who had failed to respond to blinded treatment in the first cycle might not be keen to risk having a second sham procedure, and might defer a second treatment cycle. On the other hand, placebo recipients might be expected to be more incontinent than the Botox recipients and thus might be more enthusiastic to have another attempt. These potentially opposing effects on the time to retreatment would have confounded any attempts to interpret the time to retreatment data in the placebo versus the active group. Thus, overall, the study design actually adopted seems reasonable, even though it departs from the ideal of a fully placebo controlled study.

In addition to their blinded, randomised treatment, patients also received empirical periprocedural antibiotics for three days prior to the procedure and for three days post procedure. (The pretreatment antibiotic was given for five days if a UTI was detected on a pre procedure urine sample, and the antibiotic was chosen to match urine culture sensitivities.) Patients variously received local anaesthetic (infused into the bladder), a general anaesthetic, sedation, or no anaesthetic treatment according to their personal wishes and the usual cystoscopic practices at the treating institution.

The primary endpoint was the change in weekly incontinence frequency, as this represents the core symptom for which patients were receiving treatment. Secondary endpoints included objective urodynamic measures of detrusor overactivity and subjective quality of life assessments, as discussed further below.

Statistical Analysis Plan

Both pivotal studies were analysed as superiority studies in comparison to placebo.

The primary statistical method was an analysis of covariance (ANCOVA), using the baseline incontinence frequency as covariate and the treatment group, neurological diagnosis (SCI or MS), concurrent anticholinergic therapy at screening (use or non use), and investigator as factors. The primary analysis was based on the intent to treat (ITT) population.

Power calculations were justified by the sponsor as follows (Study 515 report body, corresponding calculations for Study 516):

“A total of 101 patients per treatment group were required to give the study a power of 90% to detect a between group difference of 7.5 episodes in change from baseline in weekly frequency of urinary incontinence. Assuming the mean weekly frequency at baseline (randomisation/day 1) was 25 incontinence episodes, a 7.5 episode difference in change from baseline between the Botox and placebo groups in weekly frequency of

episodes of urinary incontinence would represent a 30 percentage point difference in percent improvement between the Botox and placebo groups. The calculation assumed a common standard deviation of 15 episodes and a two sided type I error rate of 0.025, taking into account the multiple comparisons using the Hochberg procedure. In order to address patient attrition (estimated to be 25%), the sample size in this study was increased from 101 to 135 patients per treatment group."

These assumptions appear reasonable. More importantly, given that both pivotal studies were superiority studies that achieved strong statistical significance, the studies obviously had adequate power.

Inclusion and Exclusion Criteria

Patients were eligible to enter the pivotal studies if they:

- had urinary incontinence due to NDO, as a result of SCI or MS, for \geq three months
- were not adequately managed with anticholinergic therapy
- had ≥ 14 episodes of urinary incontinence per week
- had no more than two incontinence free days per week
- were aged 18 to 80 years old
- weighed ≥ 50 kg
- (for SCI patients) had a stable neurological injury level at T1 or below, for \geq six months prior
- (for MS patients) were clinically stable for \geq three months prior and had an Expanded Disability Status Scale (EDSS) score ≤ 6.5 (that is, they could not be bed bound)
- had a phasic rise in bladder pressure during the filling phase of a urodynamic study (prior to randomisation)
- had not been controlled with a prior trial of anticholinergics (inadequate efficacy response or intolerable side effects after at least one month on an optimised dose)
- had a negative pregnancy result if female and of childbearing potential
- were willing to use CIC
- were willing to take an antibiotic in the periprocedural period

Patients were *excluded* if they had:

- elevated serum creatinine (>2 times the upper limit of normal)
- a history of recent or uninvestigated haematuria, interstitial cystitis, or recent bladder stones
- a history of bladder surgery or bladder disease other than NDO (with the exception of surgery for bladder stones)
- stress incontinence, uterine prolapse, rectocele, or cystocele
- ever received previous botulinum toxin therapy for any urological condition
- received botulinum toxin within the previous three months for any other condition

- discontinued anticholinergic medication <21 days prior
- prostate cancer or a prostate specific antigen (PSA) level >10.0 ng/mL.
- a 24 hour total volume voided >3L
- (for micturating patients) a PVR urine volume above 200 mL; this restriction did not apply to patients solely managed with CIC
- active genital infection, other than genital warts, within four weeks
- use of any antiplatelet or anticoagulant therapy within three days prior to treatment (these could be withheld for the procedure if appropriate)
- haemophilia or other clotting factor deficiencies or bleeding disorders
- treatment within six months with capsaicin or resiniferatoxin
- current or planned use of an electrostimulation/neuromodulation device
- known allergy or sensitivity to any components of the treatment
- any medical condition putting them at increased risk with Botox exposure, including myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis.

Endpoints

The major endpoints assessed in the pivotal studies are shown in Table 4.

Table 4: Summary of key parameters for assessment of efficacy in pivotal Phase 3 studies.

	Measure	Assessment Tool
Primary	Weekly frequency of urinary incontinence episodes (and a responder analysis of proportion of patients with at least 50% and 100% reduction in urinary incontinence)	Bladder diary
Secondary	Maximum cystometric capacity (MCC)	Urodynamics
	Maximum detrusor pressure (MDP) during first involuntary detrusor contraction (IDC)	Urodynamics
	Incontinence Quality of Life (I-QOL) total summary score	Patient questionnaire
Selected Others	Volume per void	Bladder diary
	Volume at first IDC (including proportion of patients with no IDC)	Urodynamics

Primary Endpoint – Incontinence Frequency

For both pivotal studies, the primary endpoint was the change in mean number of incontinence episodes per week, identified from patient diaries. The same parameter was also subjected to a responder analysis (proportion of patients with 50% or 100% reduction from baseline incontinence).

Of note, there was one built in bias potentially in favour of Botox for this endpoint: patients were explicitly instructed not to collect bladder data if they were experiencing symptoms of a UTI, or at the time of a urodynamic procedure. While it is true that bladder symptomatology is affected by UTIs, the UTIs are part of the study patients' total experience; censoring their bladder symptoms during UTIs potentially gives a skewed view of what patients actually experienced. Given that significantly more UTIs occurred in the Botox group, and that UTIs increase urgency and urge incontinence, this design feature meant that the true incontinence of all patients was not assessed, and that periods of

increased incontinence due to Botox induced UTIs were censored, whereas periods of decreased incontinence were included. Whether this compromised the results of the study is somewhat unclear. Missing data were imputed via a LOCF approach, and sensitivity analyses with and without imputation were similarly positive, so the level of incontinence *outside the setting of a UTI* was adequately assessed. What was not clear was how much the continence gains due to Botox were offset by continence losses during Botox induced UTIs. *The sponsor should be asked to comment on this and to perform an explicit sensitivity analysis on the data to determine to what extent this is a problem.*²

Secondary Endpoints – MCC, MDP and I-QOL

Two urodynamic parameters were assessed as secondary endpoints, based on urodynamic studies performed six weeks after treatment: the maximum cystometric capacity (MCC) and the maximum detrusor pressure (MDP) during the first involuntary detrusor contraction (IDC) during filling.³

The MCC represents the maximum volume infused into the bladder during urodynamic studies, up to the point that micturition could no longer be delayed, leakage occurred or filling stopped (minus the volume that was lost due to incontinence during filling). As such, it broadly represents the holding capacity of the bladder, which has a direct effect on a patient's ability to defer visits to the toilet and retain continence between visits. At smaller MCCs, a patient is forced to void more frequently, drink less to limit urine production, or run the risk that reflex emptying will occur when maximum holding volume is reached. Note that, in a patient not using CIC to achieve full emptying between voids, it is also important to consider the PVR, as it is the difference between the MCC and the PVR that determines how much urine can be added to the bladder between voids. Thus, if a treatment increased the MCC and PVR by the same volume, this would not actually lead to an increased capacity to store urine between voids, and so consideration of the MCC in isolation could give a spurious measure of efficacy. The sponsor generally failed to acknowledge this point, and PVR was not considered in the efficacy analysis.

The MDP represents the pressure generated in the bladder during involuntary reflex contractions during cystometry. It therefore reflects the pressure that must be opposed by the urinary sphincter to preserve continence. High detrusor pressures (especially >40 cmH₂O) also play a role in vesicoureteric reflux, a condition in which urine from the bladder travels retrogradely back into the ureter and potentially as far as the renal pelvis, with subsequent risks of renal infection and impaired renal function. One of the aims of treating NDO, apart from improving continence, is to protect the bladder and kidney from such reflux, so this is an important secondary endpoint.⁴

The other major secondary endpoint assessed in the pivotal studies was the patients' quality of life as measured with a specific incontinence related quality of life questionnaire

² The sponsor subsequently addressed this issue and the sensitivity analysis suggested that this potential bias did not make any important difference to the conclusions.

³ Note that IDC is commonly used as an abbreviation for 'in dwelling catheter' but is used throughout the sponsor's submission and hence in this report as an abbreviation for 'involuntary detrusor contraction'.

⁴ One potential problem with interpreting this endpoint is that as NDO improves in response to therapy, an increasing proportion of patients will not display involuntary detrusor contractions during filling and so no pressure will be recorded on follow up. Since it is the milder cases that might be expected to improve in this manner, a bias could result that disguised some of the treatment effect. Indeed, a reduction in the number of patients with IDC was observed in the active groups. Despite this, improvements in MDP were observed anyway, as noted below.

(I-QOL). This assessment tool has been validated in previous studies, as indicated in references supplied by the sponsor.⁵ The questionnaire includes subdomains related to the full behavioural and psychological fallout of urinary incontinence, including the avoidance of socialising because of fears of embarrassment.

Other Endpoints

Tertiary endpoints included the volume per void as assessed from the patients' diaries, the volume at which IDC occurred, detrusor compliance, and a range of quality of life assessments, as shown in Table 5.

⁵ Wagner TH, et al. (1996) Quality of life of persons with urinary incontinence: development of a new measure. *Urology* 47: 67-71; Patrick DL, et al. (1999) Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). *Urology* 53: 71-76.

Table 5: Key efficacy evaluations in clinical studies.

Efficacy parameter	191622-515	191622-516	191622-094	191622-511	191622-518	191622-082
Patient Bladder Diary						
Number of episodes of urinary incontinence	X	X	X	X	X	X
Proportion of responders	X	X	X		X	
Duration of effect / time between treatments	X	X	X			X
Number of episodes of voluntary voiding	X	X	X		X	X
Number of CIC episodes	X	X	X	X	X	X
Total 24-hour voided volume	X	X	X	X ¹	X	
Volume per void	X	X	X	X ²	X	
Urodynamics						
MCC	X	X		X	X	X
MDP during first IDC	X	X		X	X	X
Volume at first IDC	X	X		X	X	X
End-fill pressure (EFP)	X	X			X	X
Detrusor compliance (DC)	X	X		X	X	X
Health Outcomes						
I-QOL total summary score	X	X	X	X		
I-QOL neurogenic module	X	X				
SF-36 health survey	X	X		X		
EQ-5D	X	X				
OAB-PSTQ	X	X				
Patient Global Assessment	X	X				

CIC = clean intermittent catheterization; DC = detrusor compliance; EFP = end fill pressure; EQ-5D = EuroQol Group 5 Dimension Questionnaire; IDC = involuntary detrusor contraction; I-QOL = Incontinence Quality of Life Instrument; MCC = maximum cystometric capacity; MDP = peak (amplitude) detrusor pressure during first IDC; OAB-PSTQ = OAB Patient Satisfaction with Treatment Questionnaire; PGA = Patient Global Assessment; SF-36 = Short Form (36) Health Survey

The PVR is an important urodynamic parameter that was monitored in the pivotal studies but *not* incorporated into the efficacy analysis. (Instead, it was discussed in the safety analysis, because it was adversely affected by treatment.) PVR reflects the downside of weakening the detrusor: Botox induced bladder weakness would be expected to increase the volume of urine left in the bladder after maximal voluntary emptying. This not only increases the risk of urinary infections (a safety issue), it also lessens the degree to which the bladder's increased holding capacity (the MCC) is actually available for storing urine between voids (an efficacy issue). The failure to discuss this parameter in the context of efficacy was one of the weaknesses of the submission.

Pivotal Study Results

Baseline Characteristics

In terms of demographics, the patients were well matched at baseline, with the exception of gender in Study 515. The placebo group had a relatively higher proportion of males (49.0%), and the Botox 300 U group had a relatively lower proportion of males (32.6%), with the Botox 200U group in between (40.7%). This inequality was statistically significant ($p=0.020$). In subsequent subgroup analyses, the reduction of incontinence tended to be higher in females than in males within each treatment group (including placebo), so an excess of females in the active groups might be expected to produce a weak bias towards a finding of efficacy. On the other hand, efficacy was demonstrated in both gender subgroups independently so the overall conclusions are not altered.

Disease characteristics were also generally balanced across treatment groups within each of the disease categories, but there was a significant across-group difference in SCI patients for weekly frequency of catheterisation, with the highest frequency in the placebo group ($p=0.026$). For the proportion of patients with different neurological diagnoses (MS

or SCI), the severity of their initial incontinence and the use of anticholinergics, there was no significant difference at baseline. MS patients constituted 52-57% of the patient population in Study 515, and 54-58% of Study 516.

Most patients had about 30 episodes of incontinence per week at baseline, and about half of them were still using anticholinergics (49-52% in Study 515 and 56-62% in Study 516). Of note, only 43%% of patients in Study 515 and 48% of patients in Study 516 were attempting to empty the bladder solely by voluntary voids at baseline; the majority were already using CIC either solely or as part of a mixed approach in combination with voluntary voiding. These CIC patients had less at stake when weakening the detrusor with Botox, as they already had a means of coping with the increased residual volume that may result from such treatment.

Patient Disposition

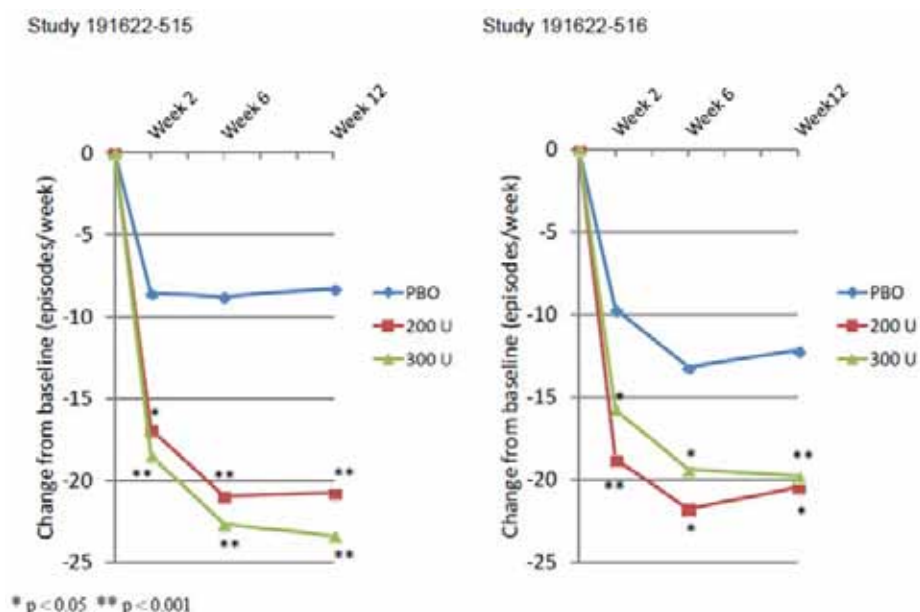
In the larger of the two pivotal studies, Study 515, a total of 416 patients were randomised. Of these, 407 received study medication: 127, 135, and 145 patients received Botox 300 U, 200 U, and placebo, respectively. Most patients (329/416, 79.1%) completed the study but 87 (20.9%) discontinued the study early, including 13 patients (13/416, 3.1%) who discontinued due to adverse events (AEs) (5, 3, and 5 patients in the 300 U, 200 U and placebo groups, respectively). As shown in the table below, the discontinuation rate due to AEs or loss of efficacy was slightly higher in the 300 U group than the placebo group, raising the possibility of withdrawal bias in favour of active treatment, but this seems relatively unlikely in view of the low numbers of discontinuations and the strong statistical results obtained for all endpoints.

In Study 516, a total of 275 patients were randomised and 230 completed the study (83.6%). Discontinuations occurred for a number of reasons, but only low numbers of patients reported each type of reason and no overall pattern was observed.

Results for Primary Endpoint

Results for the primary endpoint, mean change in urinary incontinence frequency (episodes/week), are shown in Figure 5 and Table 6. From a baseline of about 30 incontinence episodes each week, Botox recipients showed a reduction of about 21-23 episodes, compared to a reduction in the placebo group of about 8-13 episodes across the different studies and time points. Both pivotal studies produced similar results, with a significant treatment effect for each study individually as well as in the pooled analysis.

Figure 5: Mean change from baseline in weekly frequency of urinary incontinence episodes during treatment cycle 1 for the two pivotal Phase 3 studies (ITT population with LOCF imputation).



The difference between active treatment and placebo was apparent by Week 2 on both studies, but it was more pronounced by the primary time point, Week 6, and was still much the same at Week 12. The comparison between active treatment and placebo was statistically significant for both dose groups at all three time points, but the difference between the two active dose groups was minor and did not show a consistent pattern across the two studies. In Study 515, the 300 U group had a greater mean reduction than the 200 U group, but in Study 516 the 200 U group showed the greater reduction.

Table 6: Weekly frequency of urinary incontinence episodes during treatment cycle 1: Baseline and change from baseline (ITT population with LOCF imputation).**Study 515**

Timepoint	Parameter	BOTOX®		Placebo (N = 149)
		300 U (N = 132)	200 U (N = 135)	
Study Baseline	N	132	135	149
	Mean (SD)	31.1 (17.02)	32.3 (22.76)	28.3 (15.82)
Week 2	N	132	135	149
	Mean change (SD)	-18.5 (19.14)	-16.9 (22.69)	-8.6 (14.00)
	Difference from placebo ^a	-8.18	-5.32	N/A
	p-value	< 0.001	0.008	N/A
Week 6	N	132	135	149
	Mean change (SD)	-22.7 (17.10)	-21.0 (23.77)	-8.8 (16.18)
	Difference from placebo ^a	-12.34	-9.29	N/A
	p-value	< 0.001	< 0.001	N/A
Week 12	N	122	132	139
	Mean change (SD)	-23.4 (18.64)	-20.8 (22.38)	-8.3 (15.11)
	Difference from placebo ^a	-14.17	-11.04	N/A
	p-value	< 0.001	< 0.001	N/A

Study 516

Timepoint	Parameter	BOTOX®		Placebo (N = 92)
		300 U (N = 91)	200 U (N = 92)	
Study Baseline	N	91	92	92
	Mean (SD)	31.2 (18.14)	32.5 (18.44)	36.7 (30.67)
Week 2	N	91	92	92
	Mean change (SD)	-15.8 (25.81)	-18.8 (16.67)	-9.7 (17.87)
	Difference from placebo ^a	-8.37	-10.27	N/A
	p-value	0.006	<0.001	N/A
Week 6	N	91	92	92
	Mean change (SD)	-19.4 (25.67)	-21.8 (18.06)	-13.2 (20.02)
	Difference from placebo ^a	-9.02	-9.04	N/A
	p-value	0.002	0.002	N/A
Week 12	N	85	91	89
	Mean change (SD)	-19.8 (18.55)	-20.5 (18.92)	-12.2 (22.24)
	Difference from placebo ^a	-10.07	-8.86	N/A
	p-value	< 0.001	0.002	N/A

N/A = not applicable; SD = standard deviation

Note: p-values from pair-wise contrasts between BOTOX® and placebo groups for post-treatment visits are from an ANCOVA model with factors for treatment group, etiology at study entry, concurrent anticholinergic therapy at screening, and investigator, using baseline as a covariate.

^a Difference is between BOTOX® and placebo (BOTOX® minus placebo) using least square means.

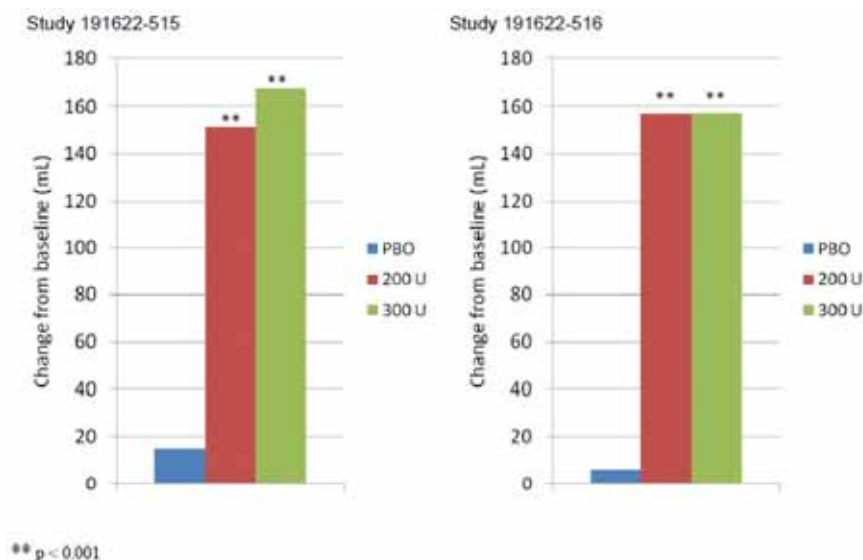
Similar findings were obtained with a responder analysis, which showed that a 50% reduction in incontinence was observed at Week 6 in 74.4% and 75.8% of the pooled 300 U and 200 U groups, respectively, but only 38.6% of the placebo group ($p < 0.001$). The results in individual studies were similar to the pooled analysis, as shown in the table below, and achieved significance ($p < 0.001$) at Week 6 for a range of incontinence thresholds. For the clinically ideal result of 100% reduction in incontinence (that is, the patient was 'dry'), this was about four times more likely with active treatment.

Results for Secondary Endpoints

Secondary endpoints also favoured both active groups over placebo, with MCC increasing by 163.1 and 153.6 mL at Week 6 in the pooled 300 U and 200 U groups, respectively, from a baseline of about 250 mL, compared to a mean increase of only 11.9 mL in the pooled placebo group (Figure 6). Results were similar in both dose groups, and in both pivotal studies considered separately, as shown in the table and figure below ($p < 0.001$ for all comparisons versus placebo). This gain in holding capacity was at least partially offset,

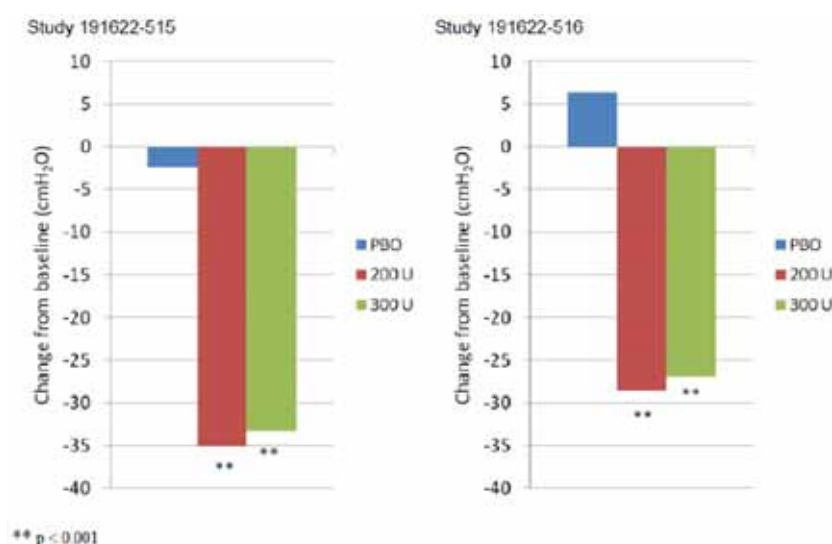
however, by increases in the post void residual volume in both active groups, as discussed in the Safety section.

Figure 6: Mean change from baseline in Maximum Cystometric Capacity (mL) at Week 6 of treatment cycle 1 for the two pivotal Phase 3 studies (ITT population).



The MDP was substantially reduced in the active treatment groups. From a baseline of 45-52 cmH₂O in the pooled pivotal studies, the pressure was reduced by a mean of 30-32 cmH₂O in the 300 U and 200 U groups, respectively, compared to a minor increase of 1 cmH₂O in the placebo group (p<0.001 for either dose group versus placebo, in the pooled analysis and in either study) (Figure 7).

Figure 7: Mean change from baseline in Maximum Detrusor Pressure (MDP) during first involuntary detrusor contraction (cmH₂O) at Week 6 of treatment cycle 1 for the two pivotal Phase 3 studies (ITT population).



Given that the primary reason for treating NDO is to relieve subjective patient discomfort, inconvenience and psychological distress, rather than because incontinence poses a major threat to physical health, it is important to demonstrate that the improvements in objective clinical measures are accompanied by an overall improvement in patient well being. The magnitude of the observed changes in urinary incontinence frequency (about 9-

10 less episodes per week) would be expected to be clinically meaningful for patients, but the benefits are offset to some degree by increases in PVR, increases in the number of UTIs and an increased need for catheterisation, as will be discussed in the Safety section. In the pivotal studies, quality of life endpoints provided one way to assess the balance between improvements in some aspects of bladder function versus Botox induced deteriorations in other aspects, and these endpoints were generally in favour of active treatment. In particular, the I-QOL showed improvements in quality of life, which were highly significant ($p < 0.001$) at Week 6 and Week 12, for both dose groups and in both studies (Figure 8 and Table 7). (Higher values indicate better quality of life.) Similar findings were produced in a responder analysis.

Figure 8: Mean change from baseline in I-QOL total summary score during treatment cycle 1 for the two pivotal Phase 3 studies (ITT population with LOCF imputation).

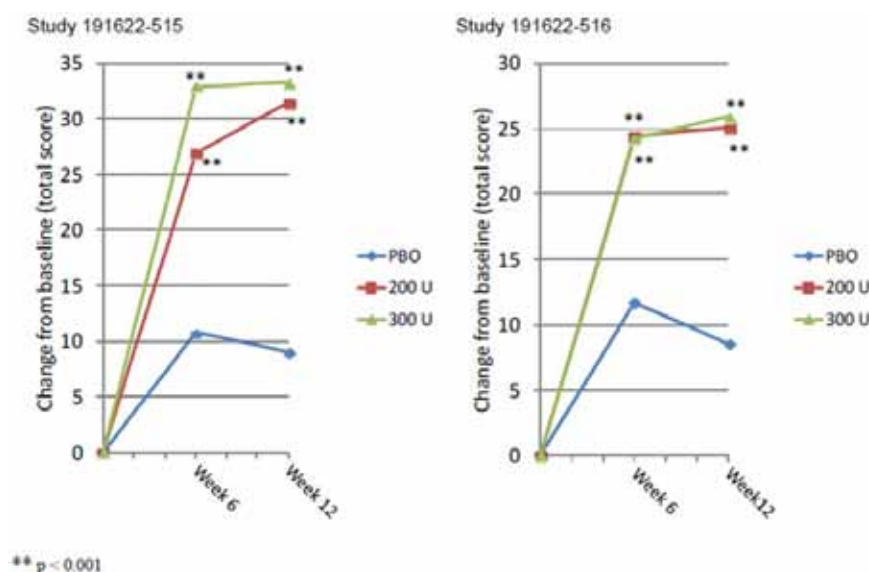


Table 7: Number (%) of I-QOL responders by visit during treatment cycle 1 (ITT population).

Timepoint	Threshold	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Week 6	≥ 8-point increase	98/117 (83.8%)	93/130 (71.5%)	67/140 (47.9%)	54/86 (62.8%)	56/90 (62.2%)	43/86 (50.0%)	152/203 (74.9%)	149/220 (67.7%)	110/226 (48.7%)
	p-value ^a	< 0.001	< 0.001		0.091	0.102		< 0.001	< 0.001	
	≥ 11-point increase	95/117 (81.2%)	87/130 (66.9%)	53/140 (37.9%)	54/86 (62.8%)	53/90 (58.9%)	37/86 (43.0%)	149/203 (73.4%)	140/220 (63.6%)	90/226 (39.8%)
	p-value ^a	< 0.001	< 0.001		0.009	0.035		< 0.001	< 0.001	
Week 12	≥ 8-point increase	96/117 (82.1%)	100/128 (78.1%)	58/135 (43.0%)	54/81 (66.7%)	62/85 (72.9%)	40/84 (47.6%)	150/198 (75.8%)	162/213 (76.1%)	98/219 (44.7%)
	p-value ^a	< 0.001	< 0.001		0.013	< 0.001		< 0.001	< 0.001	
	≥ 11-point increase	90/117 (76.9%)	100/128 (78.1%)	48/135 (35.6%)	53/81 (65.4%)	59/85 (69.4%)	31/84 (36.9%)	143/198 (72.2%)	159/213 (74.6%)	79/219 (36.1%)
	p-value ^a	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	

^a BOTOX[®] group versus placebo group, p-values are from pairwise comparison using a Fisher's exact test or Pearson's Chi-squared test, as appropriate

Other minor endpoints are shown (Table 8-12): volume at first IDC, mean volume per void, detrusor compliance and frequency of voiding either spontaneously or via CIC. These were generally consistent with the major endpoints, showing a significant benefit for active treatment at either dose, in both studies, for volume at first IDC, mean volume per

void, detrusor compliance and the number of voluntary voids per week. The increase in mean volume per void is somewhat difficult to interpret because it includes catheter voids as well as unassisted voids. The mean number of voids via CIC was *not* improved with active treatment, but instead showed an adverse trend with active treatment, because a greater proportion of patients had poor urinary emptying and needed to void with the help of a catheter. This is an expected and integral part of Botox treatment of NDO, as discussed further in the Safety section.

Table 8: Volume at First IDC (mL) in treatment cycle 1: Baseline and Change from Baseline at Week 6 (ITT population).

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	132	135	148	90	92	90	222	227	238
	Mean	194.0	207.7	211.0	191.3	199.5	206.7	192.9	204.4	209.3
	SD	129.56	143.14	129.73	121.05	126.88	132.41	125.90	136.56	130.49
Week 6	N	108	123	130	83	88	83	191	211	213
	Mean change	205.0	184.0	23.6	199.0	182.7	7.9	202.4	183.4	17.5
	SD	166.02	175.34	127.96	212.83	167.84	141.20	187.29	171.85	133.17
	p-value *	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	

Note: volume at first IDC analysis was performed with imputation of MCC in patients with IDC confirmed as absent; SD = standard deviation

* P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with baseline volume at first involuntary detrusor contraction as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Table 9: Mean Volume per Void (mL): Baseline and change from baseline in treatment cycle 1 (ITT population).

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	126	125	147	89	89	88	215	214	235
	Mean	154.0	154.5	156.6	167.9	158.8	147.4	159.7	156.3	153.2
	SD	87.94	95.15	90.28	118.42	112.99	94.15	101.64	102.72	91.65
Week 2	N	110	113	132	80	85	79	190	198	211
	Mean change	84.4	63.8	11.4	62.6	55.3	12.7	75.2	60.2	11.9
	SD	111.56	104.34	58.10	140.63	117.57	71.41	124.74	110.00	63.24
	p-value *	< 0.001	< 0.001		0.003	0.003		< 0.001	< 0.001	
Week 6	N	111	116	129	82	83	81	193	199	210
	Mean change	135.5	107.9	14.9	101.8	109.1	16.7	121.2	108.4	15.6
	SD	119.18	146.62	64.98	155.38	120.10	80.32	136.39	135.87	71.11
	p-value *	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	
Week 12	N	109	113	132	76	79	79	185	192	211
	Mean change	126.7	90.8	14.7	100.3	105.2	21.5	115.8	96.7	17.2
	SD	113.45	111.91	70.72	140.76	122.49	73.21	125.70	116.28	71.56
	p-value *	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	

SD = standard deviation

* P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with baseline volume per void as covariate, and group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Table 10: Detrusor Compliance (mL/cmH₂O): Baseline and change from baseline at Week 6 in treatment cycle 1 (ITT population).

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	130	132	145	89	90	88	219	222	233
	Mean	47.3	56.4	67.9	64.7	54.6	58.1	54.4	55.7	64.2
	SD	74.71	91.84	101.33	87.64	63.53	76.21	80.48	81.40	92.60
Week 6	N	102	120	126	80	84	79	182	204	205
	Mean change	-42.1	51.7	-10.2	60.9	71.5	2.7	50.4	59.8	-5.2
	SD	147.76	162.48	126.66	147.25	157.10	97.82	147.43	160.19	116.31
	p-value ^a	0.027	0.008		0.005	0.002		< 0.001	< 0.001	

SD = standard deviation

^a P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with baseline detrusor compliance as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors**Table 11: Weekly frequency of episodes of spontaneous voiding in treatment cycle 1: Baseline and change from baseline (ITT population).**

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	127	130	148	90	92	91	217	222	239
	Mean	36.3	40.2	37.9	37.4	38.4	34.5	36.8	39.5	36.6
	SD	36.27	40.50	38.69	36.46	37.09	38.73	36.27	39.04	38.66
Week 2	N	113	124	135	82	89	85	195	213	220
	Mean change	-9.9	-11.4	-1.8	-7.1	-8.2	0.1	-8.7	-10.0	-1.1
	SD	29.37	28.18	11.74	25.85	25.23	10.88	27.91	26.97	11.40
	p-value ^a	0.003	0.008		0.037	0.067		< 0.001	0.001	
Week 6	N	114	125	134	83	87	86	197	212	220
	Mean change	-17.3	-15.3	-2.0	-15.5	-13.7	-0.4	-16.5	-14.6	-1.4
	SD	27.49	29.02	14.61	29.13	25.12	12.28	28.13	27.44	13.74
	p-value ^a	< 0.001	< 0.001		< 0.001	0.004		< 0.001	< 0.001	
Week 12	N	113	119	131	79	86	84	192	205	215
	Mean change	-15.8	-16.5	-3.3	-12.1	-15.5	-0.6	-14.3	-16.1	-2.3
	SD	27.67	31.00	17.72	28.43	24.21	12.19	27.97	28.29	15.81
	p-value ^a	< 0.001	< 0.001		0.002	0.001		< 0.001	< 0.001	

SD = standard deviation

^a P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with baseline frequency of episodes of spontaneous voiding as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Table 12: Volume frequency of episodes of voiding by CIC in treatment cycle 1: Baseline and change from baseline (ITT population).

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX [®]			BOTOX [®]			BOTOX [®]		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	127	130	148	90	92	91	217	222	239
	Mean	18.6	16.8	20.1	13.6	18.2	20.4	16.5	17.4	20.2
	SD	20.53	19.66	20.22	17.76	22.39	27.19	19.54	20.79	23.07
Week 2	N	113	124	135	82	89	85	195	213	220
	Mean change	0.8	2.3	-0.8	1.8	2.1	0.4	1.2	2.2	-0.4
	SD	13.59	10.42	7.10	9.26	10.41	8.01	11.95	10.39	7.47
	p-value *	0.377	0.074		0.974	0.603		0.458	0.064	
Week 6	N	114	125	134	83	87	86	197	212	220
	Mean change	3.3	1.8	-0.3	3.4	2.6	0.9	3.3	2.2	0.1
	SD	16.71	11.22	9.00	12.32	12.15	7.41	14.98	11.59	8.42
	p-value *	0.078	0.477		0.730	0.955		0.108	0.464	
Week 12	N	113	119	131	79	86	84	192	205	215
	Mean change	2.9	3.3	0.2	3.1	1.7	0.7	3.0	2.6	0.4
	SD	14.60	13.52	10.57	12.75	11.44	7.35	13.84	12.68	9.43
	p-value *	0.337	0.335		0.949	0.940		0.370	0.311	

SD = standard deviation

* P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with baseline weekly frequency of episodes of voiding by CIC as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Duration of Effect

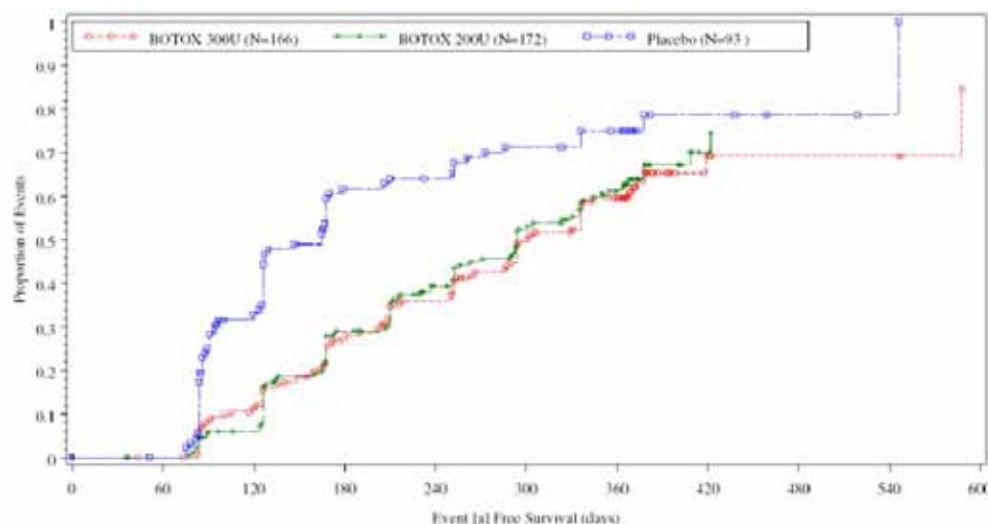
Given that Botox treatment of NDO requires an invasive procedure with the attendant risks of trauma, infection and anaesthetic complications, it is important to consider how long the benefit of the procedure can be expected to last. For the primary parameter of incontinence frequency, one measure of duration of effect is the median time for responding patients to have incontinence that is only <50% reduced from baseline. By this measure, the duration of effect for the 300 U and 200 U groups was 301 and 294 days, respectively, compared to 165 days in the placebo group. This analysis excluded patients who did not achieve an improvement of $\geq 50\%$ from baseline; inclusion of all patients gave median durations of 210 days in both dose groups, and only 1 day in the placebo group (because less than half achieved the threshold reduction). The differences from placebo were significant (Table 13) and the Kaplan-Meier curves (Figures 9-11) show both active groups had a similar benefit over placebo.

For the more subjective measure of time to request for retreatment, similar results were obtained. More placebo recipients requested retreatment, and they requested it sooner, after a median of 92 days, whereas recipients of active treatment at either dose asked for retreatment after a median of 254 and 256 days in the 300 U and 200 U dose groups, respectively ($p < 0.001$ for either dose group versus placebo). This parameter is of clinical interest because it reflects the patient's perception of the risk-benefit balance as clinical efficacy wanes over time. The time to qualification for retreatment was also significantly longer with active treatment ($p < 0.001$), but this parameter varied across the two studies because of different qualification criteria.

Table 13: Median duration of effect in treatment cycle 1: Kaplan-Meier Analysis (ITT population).

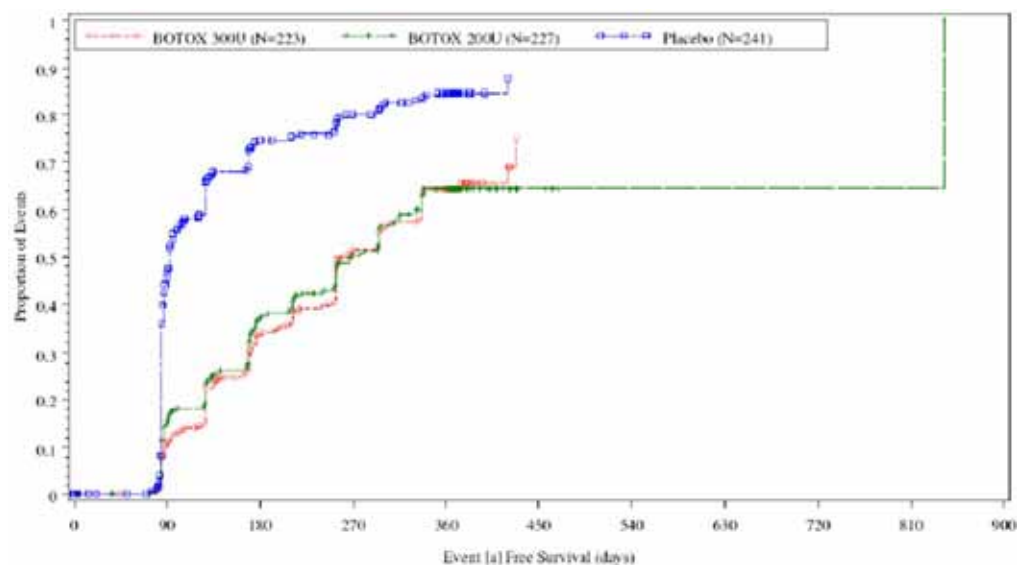
Measure	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX ^a			BOTOX ^a			BOTOX ^a		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Time to $\leq 50\%$ Reduction in UI (Responders)	N (responders) ^a	102	101	57	64	71	36	166	172	93
	N (events in responders) ^a	67	61	43	30	41	25	97	102	68
	Median duration of effect (days)	286.0	293.0	165.0	345.0	324.0	147.0	301.0	294.0	165.0
	p-value ^b	0.024	0.009		< 0.001	0.006		< 0.001	< 0.001	
Time to Request for Re-treatment (All patients)	N (events in all patients) ^c	79	86	121	52	52	73	131	138	194
	Median duration of effect (days)	254.0	256.0	92.0	295.0	295.0	92.0	265.0	269.0	92.0
	p-value ^b	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	
Time to Qualification for Re-treatment (All patients) ^d	N (events in all patients) ^e	70	77	118	39	47	66	NA	NA	NA
	Median duration of effect (days)	337.0	295.0	96.0	421.0	337.0	127.0			
	p-value ^b	< 0.001	< 0.001		< 0.001	< 0.001				
Time to $\leq 50\%$ Reduction in UI (All patients)	N (events in all patients) ^a	97	95	135	57	62	81	154	157	216
	Median duration of effect (days)	209	210	1.0	254	210	1.0	210.0	210.0	1.0
	p-value ^b	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	

NA = not applicable; UI = urinary incontinence

^a Responder is defined as a patient with at least 50% reduction from baseline at week 6 following the first treatment. Event is based on time to first visit after week 6 with less than 50% reduction from baseline in weekly UI^b P-values based on pairwise comparison using log-rank test^c Time to request of re-treatment for all patients was assessed by the time between treatment 1 randomization/day 1 and request for treatment 2 (regardless of fulfillment of the re-treatment criteria).^d Based on first occasion patient reported as qualifying for the diary re-treatment criterion ($\leq 50\%$ reduction from baseline in weekly urinary incontinence for study 191622-515 and $\leq 30\%$ reduction for study 191622-516). Since re-treatment criteria were different between the studies, pooled data not relevant to present.^e Event is based on time to first visit after week 6 with less than 50% reduction from baseline in weekly UI for all patients. For patients who never had 50% reduction from study baseline, time to event is set to day 1**Figure 9: Kaplan-Meier curve for weekly frequency of urinary incontinence episodes duration of effect (Treatment Responders: Time to <50% reduction from study baseline (Studies 191622-515/516 pooled, ITT population)).**

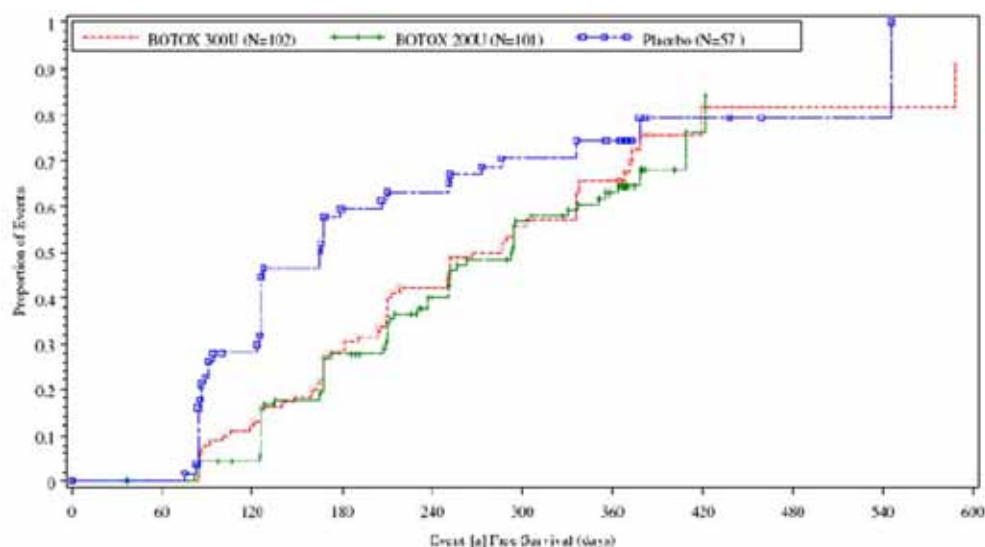
Note: A responder is a patient who had $\geq 50\%$ decrease from baseline in urinary incontinence episodes at week 6 after the first treatment
 Event is defined as the first visit after week 6 following the first treatment with less than a 50% reduction from baseline in weekly frequency of urinary incontinence episodes

Figure 10: Kaplan-Meier curve for duration of effect: Time to request of retreatment (Studies 191622-515/516 pooled, ITT population).



Note: Event is defined as request for the second treatment.

Figure 11: Kaplan-Meier curve for duration of effect in treatment responders in treatment cycle 1: Time to <50% reduction in weekly frequency of urinary incontinence episodes from study baseline (ITT population).



Note: A responder is a patient who has $\geq 50\%$ decrease from baseline in urinary incontinence episodes at week 6 after the first treatment.

Event is defined as the first visit after week 6 following the first treatment with $< 50\%$ reduction from baseline in weekly frequency of urinary incontinence episodes.

Repeat Efficacy

Placebo controlled data was only available for the first treatment cycle, so it is not possible to draw firm conclusions about the efficacy of repeat doses of Botox. For the primary efficacy variable, urinary incontinence frequency, the dose controlled data are shown in the tables below for Studies 515 and 516 individually. All groups showed a significant improvement after treatment cycle 2, compared to study baseline ($p < 0.001$), regardless of

whether they were receiving their second active dose (first two groups in the table below) or their first active dose after initial placebo (last two groups). Note that these improvements *include* whatever improvements might be expected from regression to the mean and the placebo effect. Between group comparisons were not assessed statistically, because all patients received Botox.

The magnitude of the treatment effect after treatment cycle 2 was broadly similar to that observed after cycle 1, with reductions of 19-24 incontinence episodes per week, but the patient populations in the different cycles were not strictly comparable. When compared to the *pre cycle* baseline, rather than study baseline, similar results were obtained.

Urodynamic studies also showed a broadly similar response to the second treatment (Table 14).

Table 14: Baseline and change from baseline at Week 6 in urodynamic measures by treatment cycle (placebo controlled pivotal study ITT population).

		Cycle 1		Cycle 2	
		BOTOX ^a		BOTOX ^a	
		300 U (N = 223)	200 U (N = 227)	300 U (N = 101)	200 U (N = 116)
MCC					
Study baseline	N	223	227	101	116
	Mean	252.2	250.2	244.3	228.3
Week 6	N	190	211	91	98
	Mean change	163.1	153.6	162.4	141.2
	SD	176.15	167.81	170.74	167.02
	p-value ^a	< 0.001	< 0.001	< 0.001	< 0.001
MDP during first IDC					
Study baseline	N	223	227	101	116
	Mean	45.0	51.5	50.6	53.0
Week 6	N	62	70	23	32
	Mean change	-30.1	-32.4	-38.8	-35.6
	SD	35.39	40.94	40.49	44.06
	p-value ^a	< 0.001	< 0.001	< 0.001	< 0.001
Volume at first IDC ^b					
Study baseline	N	222	227	101	116
	Mean	192.9	204.4	179.6	192.5
Week 6	N	191	211	91	98
	Mean change	202.4	183.4	217.8	157.5
	SD	187.29	171.85	162.55	161.54
	p-value ^a	< 0.001	< 0.001	< 0.001	< 0.001

IDC = involuntary detrusor contraction; MCC = maximum cystometric capacity (mL); MDP = maximum detrusor pressure (cm H₂O); SD = standard deviation

Note: Study baseline is the baseline prior to any treatment in studies 191622-515 and 191622-516

^a P-values for within-group changes from study baseline are from paired t-tests

^b With imputation of MCC if no IDC

Subgroup Analyses

Subgroup analyses were performed based on gender, aetiology of NDO (MS or SCI), concurrent use of anticholinergic agents, age and Botox naïve status. All major endpoints including the primary endpoint of incontinence frequency were achieved for both MS patients and SCI patients, apart from volume at first IDC, which did not show a significant increase in the SCI subgroup but merely showed a favourable trend (Table 15). The primary endpoint was achieved for all major subgroups, but the reduction in incontinence was more pronounced in females than males (Table 16). Concurrent use of anticholinergics made very little difference to the magnitude of the treatment effect.

Table 15: Baseline and change from baseline in select efficacy measures by etiology at Week 6 in treatment cycle 1 (placebo controlled pivotal study ITT population).

Endpoint/ Timepoint		Attribute	Patients with MS			Patients with SCI		
			BOTOX®			BOTOX®		
			300 U (N = 120)	200 U (N = 130)	Placebo (N = 131)	300 U (N = 103)	200 U (N = 97)	Placebo (N = 110)
MCC (mL)								
Study Baseline	N	120	130	131	103	97	110	
	Mean	250.8	251.3	240.5	253.8	248.9	269.0	
	SD	156.24	160.60	141.92	134.76	138.81	140.87	
Week 6	N	108	122	121	82	89	93	
	Mean change	165.1	149.3	6.8	160.6	159.5	18.6	
	SD	173.95	169.20	120.18	180.05	166.66	151.03	
	p-value ^a	< 0.001	< 0.001		< 0.001	< 0.001		
MDP During First IDC								
Study Baseline	N	120	130	131	103	97	110	
	Mean	36.6	41.6	40.6	54.8	64.7	55.2	
	SD	29.80	29.92	29.60	38.25	41.90	40.79	
Week 6	N	29	35	95	33	35	76	
	Mean change	-24.1	-22.1	10.7	-35.3	-42.7	-10.9	
	SD	27.81	34.08	41.98	40.62	44.98	40.51	
	p-value ^a	< 0.001	< 0.001		0.020	0.034		
Volume at First IDC								
Study Baseline	N	108	119	117	97	84	100	
	Mean	173.8	170.1	183.1	183.7	198.2	215.2	
	SD	120.46	119.76	119.96	101.79	123.39	129.97	
Week 6	N	26	34	93	33	33	70	
	Mean change	75.8	129.7	10.7	60.5	117.1	13.0	
	SD	159.74	177.16	107.24	137.23	142.78	126.16	
	p-value ^a	0.040	0.001		0.558	0.251		

Table 16: Weekly frequency of urinary incontinence episodes with LOCF imputation for treatment cycle 1 by sex: Study baseline and change from study baseline (Studies 191622-515/516 pooled, ITT population).

Timepoint	Male			Female		
	BOTOX®			BOTOX®		
	300 U (N = 82)	200 U (N = 93)	Placebo (N = 116)	300 U (N = 141)	200 U (N = 134)	Placebo (N = 125)
Study Baseline						
N	82	93	116	141	134	125
Mean	28.1	29.5	30.3	32.9	34.3	32.7
SD	13.74	18.79	23.24	19.10	22.39	22.76
Week 2						
N	82	93	116	141	134	125
Mean change	-12.5	-12.0	-7.5	-20.2	-21.6	-10.4
SD	24.85	19.81	16.26	19.87	20.02	14.82
p-value ^a	0.114	0.299		< 0.001	< 0.001	
Week 6						
N	82	93	116	141	134	125
Mean change	-17.6	-16.7	-9.6	-23.5	-24.6	-11.3
SD	21.92	21.44	16.32	20.26	21.19	19.16
p-value ^a	0.002	0.047		< 0.001	< 0.001	
Week 12						
N	74	92	112	133	131	116
Mean change	-18.5	-15.8	-9.0	-23.8	-24.0	-10.7
SD	17.06	22.14	15.39	19.27	19.52	20.72
p-value ^a	< 0.001	0.060		< 0.001	< 0.001	

SD = standard deviation

^a P-values for between-group comparison (BOTOX® versus placebo) at each visit are based on an ANCOVA model with baseline weekly frequency of urinary incontinence episodes as covariate and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Only selected endpoints were considered for subgroups defined by baseline CIC status. The frequency of 'spontaneous' (that is, unassisted) voiding was decreased regardless of whether or not patients were using CIC at baseline, and the frequency of voiding via CIC was increased in those who were not using CIC at baseline (because many patients commenced CIC). For patients not using CIC at baseline, Botox treatment carries the risk that bladder emptying will deteriorate to the point that catheterisation needs to be commenced, and this could have impacts on quality of life. Reassuringly, quality of life assessments showed a significant improvement even in those forced to take up CIC (Table 17).

Table 17: Baseline and change from baseline in select efficacy measures by etiology at Week 6 in treatment cycle 1 (placebo controlled pivotal study ITT population).

Endpoint/ Timepoint		Patients with MS			Patients with SCI		
		BOTOX®			BOTOX®		
		300 U (N = 120)	200 U (N = 130)	Placebo (N = 131)	300 U (N = 103)	200 U (N = 97)	Placebo (N = 110)
Attribute							
MCC (mL)							
Study Baseline	N	120	130	131	103	97	110
	Mean	250.8	251.3	240.5	253.8	248.9	269.0
	SD	156.24	160.60	141.92	134.76	138.81	140.87
Week 6	N	108	122	121	82	89	93
	Mean change	165.1	149.3	6.8	160.6	159.5	18.6
	SD	173.95	169.20	120.18	180.05	166.66	151.03
	p-value ^a	< 0.001	< 0.001		< 0.001	< 0.001	
MDP During First IDC							
Study Baseline	N	120	130	131	103	97	110
	Mean	36.6	41.6	40.6	54.8	64.7	55.2
	SD	29.80	29.92	29.60	38.25	41.90	40.79
Week 6	N	29	35	95	33	35	76
	Mean change	-24.1	-22.1	10.7	-35.3	-42.7	-10.9
	SD	27.81	34.08	41.98	40.62	44.98	40.51
	p-value ^a	< 0.001	< 0.001		0.020	0.034	
Volume at First IDC							
Study Baseline	N	108	119	117	97	84	100
	Mean	173.8	170.1	183.1	183.7	198.2	215.2
	SD	120.46	119.76	119.96	101.79	123.39	129.97
Week 6	N	26	34	93	33	33	70
	Mean change	75.8	129.7	10.7	60.5	117.1	13.0
	SD	159.74	177.16	107.24	137.23	142.78	126.16
	p-value ^a	0.040	0.001		0.558	0.251	
I-QOL Total Summary Score							
Study Baseline	N	120	130	131	103	97	110
	Mean	31.6	34.4	32.2	36.5	36.6	39.0
	SD	18.84	17.45	17.81	18.29	20.77	18.16
Week 6	N	112	128	126	91	92	100
	Mean change	36.0	29.6	13.7	21.0	20.7	8.0
	SD	26.94	27.35	19.45	23.40	23.72	18.14
	p-value ^a	< 0.001	< 0.001		< 0.001	0.001	

MCC = maximum cystometric capacity; MDP = maximum detrusor pressure; IDC = involuntary detrusor contraction; I-QOL = Incontinence Quality of Life; SD = standard deviation

^a P-values for between-groups comparison (BOTOX[®] versus placebo) at each visit are based on ANCOVA model with the respective baseline efficacy measure (ie, MCC, MDP during first IDC, volume at first IDC, or I-QOL total summary score) as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

Supportive Efficacy Studies (511, 518 and 094)

Single Dose Study (511)

Design

This study was a small (n=59) Phase 2 feasibility study exploring the efficacy of a single dose of ID Botox for the treatment of NDO. It employed a multi centre, double blind, randomised, placebo controlled, parallel group design that was very similar to the first treatment cycle of the subsequent pivotal studies. The three randomised treatments were similar to the pivotal studies: patients received Botox 200 U, Botox 300 U or placebo in a 1:1:1 ratio. The target population was patients with MS or SCI who were designated by their clinician as having urinary incontinence due to 'detrusor hyperreflexia', a term equivalent to NDO. Patients had to have \geq six weeks of urinary incontinence and the underlying neurological condition had to have been stable for six months. As in the pivotal studies, patients had to have had an inadequate response to oral anticholinergics. *Unlike* the pivotal studies, all patients were using CIC at baseline to empty the bladder in the attempt to manage urinary incontinence. As such, this represents an easier population to treat than that recruited to the pivotal studies; no patient risked significant urinary retention or the commencement of CIC.

Following treatment, all patients were assessed at Weeks 2, 6, 12, 18 and 24. The primary efficacy measure was the same as in the pivotal studies, the frequency of urinary incontinence episodes, but this was expressed on a daily rather than weekly basis. Note that the primary efficacy variable was *not* specified in the protocol, but was instead chosen prior to completion of the study. Also, no time point was designated as primary, allowing the study multiple chances to achieve statistically significant differences between treatment groups. This would not be acceptable in a pivotal study and, along with the small size of this study, limits its overall relevance.

Secondary efficacy measurements were also similar to the pivotal studies and included the I-QOL, a well established quality of life tool called the SF-36 (not a secondary end point in the pivotal studies),⁶ and standard urodynamic parameters: MCC, MDP during first IDC, and detrusor compliance.

Statistical Analysis Plan

This study was a parallel group superiority study, comparing two Botox doses to placebo. The primary method of analysis was a comparison of the change in mean frequency of daily incontinence episodes at all visits between each Botox group (200 U and 300 U) and the placebo group in a pair wise fashion using an analysis of variance (ANOVA) model with factors for treatment and investigator. The primary objective was to show that either of the active doses was superior to placebo in reducing daily incontinence frequency, and the null hypothesis was tested at the 0.05 significance level.

Sample size was justified by the sponsor as follows:

"Sample size in this study was estimated using empirical data from physicians. In order to detect a between group difference of three episodes in change from baseline in daily

⁶ The short form 36 health survey (SF-36) is a multipurpose survey with only 36 questions. It yields an eight scale profile of functional health and wellbeing scores as well as psychometrically based physical and mental health summary measures and a preference based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. See <www.sf-36.org>.

frequency of incontinence episodes, 18 analysable patients per treatment group were considered to be needed. This estimate was based on an assumption of a two sided alpha level of 0.05, an 80% power and a standard deviation of three incontinence episodes (using anecdotal data from investigators)."

These assumptions were broadly appropriate, and the group sizes exceeded 18, but nonetheless the study failed to show consistent efficacy across multiple time points. As reported below, the mean treatment effect was somewhat smaller than the anticipated reduction of three episodes per day.

Results

The three treatment groups were reasonably well matched at baseline. The vast majority of patients (53/59) had SCI rather than MS, reflecting the requirement that patients use CIC at baseline.

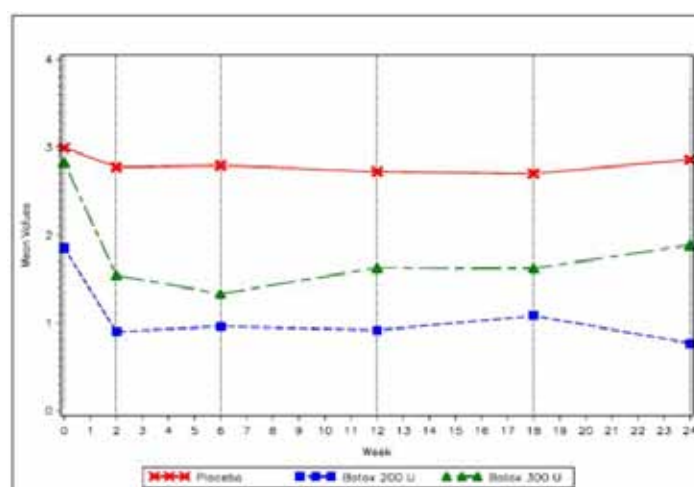
All but two patients completed the study; one dropped out of the 200 U group because of lack of efficacy, and another from the 200 U group because of an AE.

For the primary endpoint, the improvement in incontinence frequency was greater in both Botox groups than in the placebo group, and this difference occasionally reached statistical significance, as shown in the table below. (The difference relative to placebo was significant in the 300 U group at Weeks 2 and 6 and in the 200 U group at Week 24.) The magnitude of the treatment effect appeared similar at the two active doses, and was maintained across the 24 week study, but the study was not adequately powered for the demonstration of a statistical difference at all time points.

Across the different time points, the mean daily decreases from baseline during the 24 week study period ranged from -0.9 to -1.5 in the 300 U group and from -0.8 to -1.1 in the 200U Botox group; the mean decrease observed in the placebo group was -0.1 to -0.3 episodes per day.

There were also significant ($p \leq 0.05$) *within* group decreases from baseline in mean daily frequency of incontinence at all visits within the 300 U group, and at Weeks 2, 6 and 24 within the 200 U group, but no significant changes in the placebo group (Figure 12)

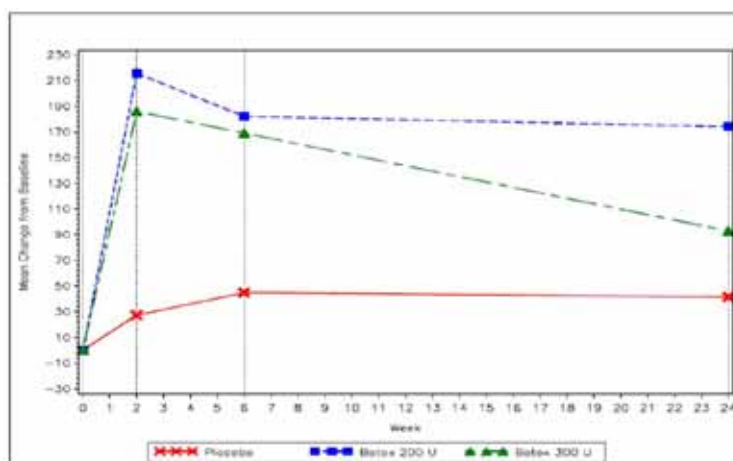
Figure 12: Mean daily frequency of involuntary losses of urine: mean values (using mean of non missing values to replace missing values; ITT).



Secondary endpoints also favoured active treatment at either dose. The mean changes from baseline MCC in the active groups were significantly greater than in the placebo group at all time points except Week 24 in the 300 U group (Figure 13). There were

significant *within* group increases in the mean MCC for both active treatment groups at all time points at which this was measured (Weeks 2, 6 and 24) but there were no significant changes in MCC for the placebo group.

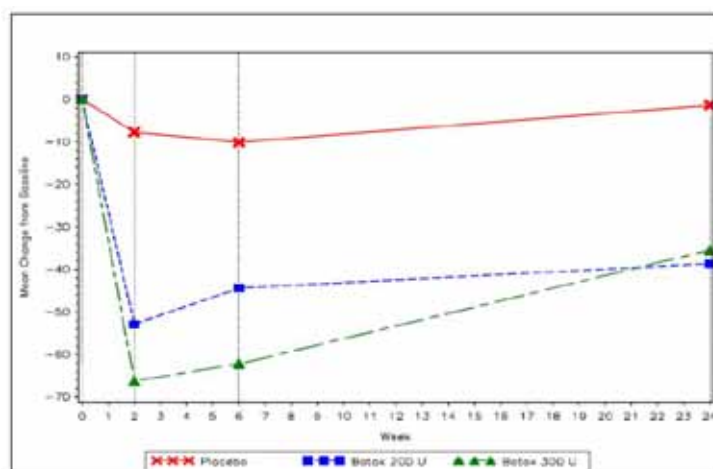
Figure 13: Maximum cystometric capacity (mL): Mean changes from baseline at each scheduled visit (using observed cases; ITT).



There were also greater increases in mean 'reflex detrusor volume' (corresponding to 'volume at first IDC', the term used in the pivotal studies) in the active treatment groups compared with the placebo group. A higher proportion of patients (~55%) in the active treatment groups experienced no IDC, compared to a lower proportion in the placebo group (~10%).

Significant decreases in the maximum detrusor pressure (at MCC and during IDC) were observed at all post treatment time points in the active groups, with smaller changes observed in the placebo group (Figure 14). Changes in detrusor compliance were variable and there were no convincing differences between treatment groups, with the 300 U group not significantly different from placebo, and the 200 U group showing an increased compliance that was only significant relative to placebo when analysed as a percentage change.

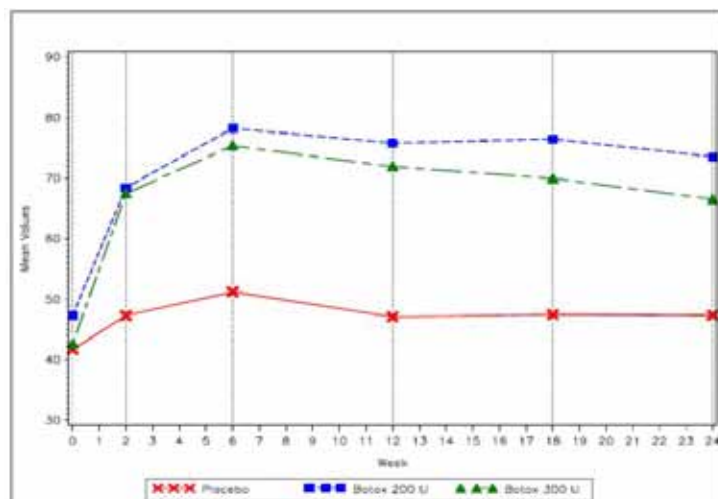
Figure 14: Maximum detrusor pressure during bladder contraction (cmH₂O): mean changes from baseline at each scheduled visit (using observed cases; ITT).



Patients in both active groups showed statistically significant improvements from baseline in their I-QOL scores at all time points and in all domains (Figure 15). There were few significant changes in scores in any of the domains on the SF-36 Health Survey, reflecting

the fact that this instrument was not specific to the problem being treated and these patients almost certainly had other significant quality of life issues related to their SCI.

Figure 15: I-QOL total scores: mean values at each scheduled visit (using observed cases; ITT).



For all of these endpoints (including MCC, MDP and I-QOL), both doses showed a similar efficacy, as shown in the figures and tables above. This justifies the subsequent decision to assess these doses in the pivotal studies, and supports the eventual decision to recommend the 200 U dose for general use.

Overall Summary of Study 511

This small (n=59) feasibility study primarily recruited patients with SCI suffering from NDO, and treated them with ID injections of Botox 200 U, Botox 300 U or placebo. Although it was underpowered, and only assessed a single dose with follow up for just 24 weeks, it showed a significant treatment effect for both doses for the primary endpoint (at some but not all time points) and for most secondary endpoints, including MCC, MDP and I-QOL. No overall difference in efficacy was observed between the two active dose groups. It thus supports the more definitive pivotal studies that reassessed the same doses in a larger population of SCI and MS patients, for up to two doses over a longer time period.

Dose Ranging Study (518)

Design

Study 518 (n=74) was ongoing at the time of submission but results from the primary analysis were available. It is a multicentre, double blind, randomised, placebo controlled, Phase 2 study of the efficacy and safety of up to two doses of ID Botox for NDO not adequately controlled with anticholinergics. The study was designed to explore the dose response relationship of ID Botox for doses up to and including the lower dose used in the pivotal studies (200 U). Patients received Botox (50, 100, or 200 U) or placebo in a parallel group design, at a ratio of 1:1:1:1. The second dose, if required, was open label Botox at 200 U in all patients.

As in the pivotal studies, patients were eligible if they had urinary incontinence (≥ 14 episodes/week) due to NDO for \geq three months prior to screening. *Unlike* the pivotal studies, MS patients were excluded: the NDO had to result from a SCI (at T1 level or lower, \geq six months prior to screening). (The sponsor chose to limit the patient population to produce more homogenous results and thus increase the power to compare doses.)

Patients were eligible to receive a second, open label treatment with 200 U Botox if they fulfilled all retreatment criteria, which included: a < 30% reduction in incontinence frequency compared to baseline, a patient request for retreatment, and an interval of at least 12 weeks since the first dose.

After treatment, patients were assessed at Weeks 2, 6 and 12, and every 6 weeks thereafter until they requested retreatment or left the study. Each patient was to remain in the study until 12 weeks after their second treatment or, if no retreatment was received, until 78 weeks after randomisation. Patient enrolment was terminated prematurely because of poor recruitment, but the study will continue until all enrolled patients have completed the study.

The primary endpoint was the frequency of incontinence, expressed as episodes per week. The primary time point at which this was to be assessed was 6 weeks post treatment, as in the pivotal studies.

Statistical Analysis Plan

This study was primarily a dose response study. The primary efficacy variable (incontinence frequency) was analysed in relation to dose levels using a linear regression approach at Week 6 of the first treatment. Baseline incontinence and stratification factor (concurrent anti cholinergic use or not) were used as covariates. The dose-response relationship was evaluated by testing the slope of the regression line. The null hypothesis was that there was no dose dependent response in the primary efficacy variable at the primary time point, 6 weeks. Statistical *p* values less than or equal to 0.05 were claimed as significant.

The originally intended sample size of 40 per group was estimated to provide 65% power to detect a slope from zero at a two sided 0.05 significance level given the assumption that there would be a linear relationship in the number of weekly urinary incontinence episodes among the dose groups. The standard deviation for urinary incontinence episodes was assumed to be 15 episodes and the mean difference between 200 U and placebo groups was assumed to be 7.5 episodes.

Of secondary importance, this study was also a superiority study, attempting to show superiority of Botox at various doses over placebo. An ANCOVA model, including the treatment group (categorical variable) as the main effect and baseline and stratification factor as covariates, was performed at all treatment cycle 1 time points for each Botox dose versus placebo. For within group comparisons, which were of tertiary importance, a paired t-test was performed.

Overall, the analysis methods were appropriate but the study was underpowered. A sample size of 40 per group was determined empirically, and when recruitment proved difficult the sponsors settled for groups less than half this size.

Results

This study was underpowered, and failed to reach its primary endpoint at the primary 6 week time point. It did, however, show numerical superiority of the 200 U dose over lower doses for most endpoints including the primary endpoint. Relative to placebo, significant reductions in incontinence frequency were only observed in the 200 U group, and only at some time points (at Weeks 30, 36 and 54).

Non significant dose dependent decreases in incontinence frequency were observed in all active treatment groups, however, and the magnitude of change increased with increasing dose. At the Week 6 time point, the mean reductions in incontinence frequency were -15.8,

-14.1, and -7.7 mLs in the 200, 100 and 50 U groups, respectively, compared to -8.5 in the placebo group.

The linear dose-response relationship for change in incontinence frequency was statistically significant ($p < 0.05$) at weeks 18, 30, 36, 42, 48 and 54, but the relationship did not reach statistical significance at the primary time point (Week 6, $p = 0.091$). A statistically significant *log* dose response was also seen at Weeks 42, 48 and 54.

Increases in MCC were observed within all treatment groups including placebo at Week 6. A broad trend in favour of higher doses was observed but the dose response analysis did not achieve statistical significance (linear slope, $p = 0.170$; log slope, $p = 0.446$). This was the only major parameter for which the changes were greater in the 100 U group (mean 220.1 mL increase) than the 200 U group (mean 183.7 mL). The standard deviations for this parameter were quite high, exceeding the mean in most groups, further weakening the power of the analysis.

MDP during first IDC showed a clear dose dependent decrease at Week 6, and for this parameter a statistically significant linear dose response was identified ($p = 0.034$). Relative to placebo, the two highest doses (200 U and 100 U) each showed significantly higher decreases from baseline for MDP, but the magnitude of the change was numerically greater for 200U (-33.0 versus -29.4 cmH₂O).

The volume at first IDC increased from baseline in all treatment groups at Week 6 and a broad dose response was observed but did not reach statistical significance (linear dose response, slope $p = 0.081$; log dose response slope, $p = 0.244$).

Compared to placebo, significant increases in mean volume per void were only observed in the 200 U group (at all time points to Week 54). A significant linear dose-response was observed for the majority of time points, and a significant log dose-response relationship was observed for most time points after Week 18.

A responder analysis also suggested superiority of the 200 U dose. The proportion of patients who were treatment responders (defined as $\geq 50\%$ reduction in urinary incontinence at Week 6) was highest in the 200 U group. The proportion of patients showing reductions at other thresholds ($\geq 75\%$, and 100%) also favoured the higher dose (Table 18).

Table 18: Number (proportion) of patients with ≥ 50 , ≥ 75 and 100% reduction from baseline in weekly frequency of urinary incontinence episodes (Treatment 1, mITT population).

Timepoint	Threshold	BOTOX®			Placebo (N=16)
		200 U (N=17)	100 U (N=21)	50 U (N=19)	
Week 2	$\geq 50\%$	11/15 (73.3%)	7/18 (38.9%)	5/17 (29.4%)	4/15 (26.7%)
	$\geq 75\%$	8/15 (53.3%)	4/18 (22.2%)	1/17 (5.9%)	1/15 (6.7%)
	100%	3/15 (20.0%)	2/18 (11.1%)	1/17 (5.9%)	1/15 (6.7%)
Week 6	$\geq 50\%$	8/13 (61.5%)	10/20 (50.0%)	8/16 (50.0%)	6/14 (42.9%)
	$\geq 75\%$	7/13 (53.8%)	7/20 (35.0%)	2/16 (12.5%)	2/14 (14.3%)
	100%	3/13 (23.1%)	3/20 (15.0%)	1/16 (6.3%)	1/14 (7.1%)
Week 12	$\geq 50\%$	8/13 (61.5%)	7/16 (43.8%)	3/11 (27.3%)	6/15 (40.0%)
	$\geq 75\%$	5/13 (38.5%)	5/16 (31.3%)	2/11 (18.2%)	1/15 (6.7%)
	100%	4/13 (30.8%)	3/16 (18.8%)	1/11 (9.1%)	1/15 (6.7%)
Week 18	$\geq 50\%$	10/11 (90.9%)	7/12 (58.3%)	7/14 (50.0%)	5/11 (45.5%)
	$\geq 75\%$	7/11 (63.6%)	6/12 (50.0%)	4/14 (28.6%)	2/11 (18.2%)
	100%	5/11 (45.5%)	1/12 (8.3%)	1/14 (7.1%)	1/11 (9.1%)

Overall, active treatment did not result in any significant changes in the weekly frequency of voiding by catheterisation or spontaneous voiding, but those patients that were using CIC at baseline were asked not to change CIC frequency.

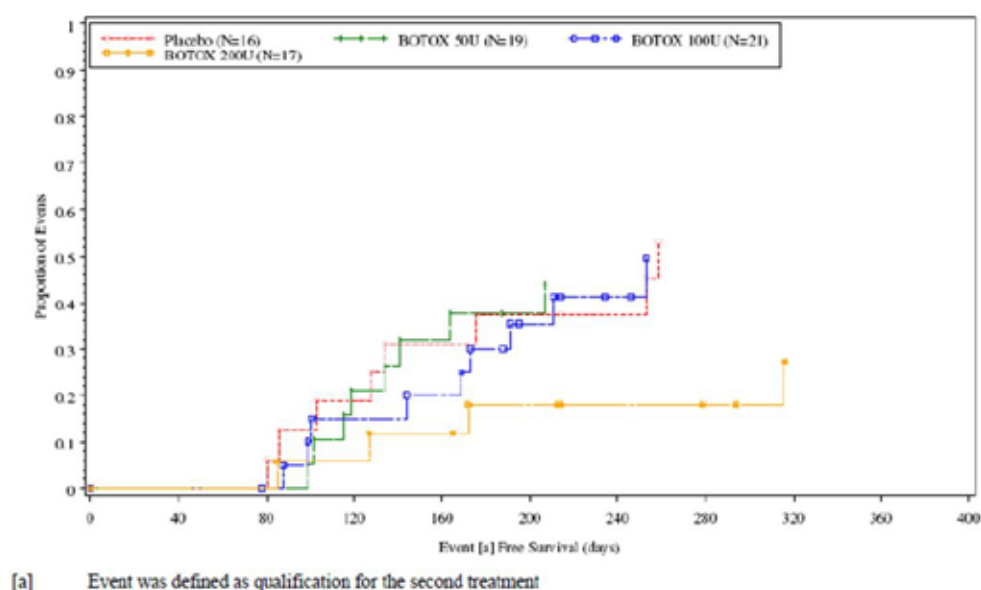
Retreatment

Only a small number of patients (n=28) received retreatment, and all of these received open label Botox 200 U. Most of these (25/28, 89%) had received placebo, Botox 50 U or Botox 100 U for their first dose. Some efficacy was observed after retreatment with Botox 200 U when compared with study or cycle baseline, as shown in the tables below, but the patient numbers were low; as a result, between group comparisons were not attempted.

Duration of effect

Of particular importance for an invasive treatment, patients receiving Botox 200 U had the longest duration of effect. This was evident in the Kaplan-Meier plot of time to qualification for retreatment (at which point, by definition, they had <30% reduction from baseline incontinence) (Figure 16).

Figure 16: Time between randomisation day and qualification for Treatment 2: Kaplan Meier curve on duration of effect (Study 191622-518, mITT population: responders).



Comparison with other studies

Given that Study 518 failed to reach its primary endpoint, it is useful to compare the treatment effect observed in this study with that seen in the pivotal studies, particularly in the SCI subgroup. The efficacy in the 200 U group of this study was broadly comparable to that seen in the pivotal studies for most endpoints, but the reduction in incontinence frequency was numerically inferior. The comparison suggests that the main problem with this study was its lack of statistical power.

Overall Summary of Study 518

As a small dose ranging study, Study 518 had just enough statistical power to show a significant dose-response relationship between placebo, 50 U, 100 U and 200 U for most endpoints, and the results were numerically superior in the 200 U group for most endpoints (except MCC). It was not powered to show significant superiority of 200 U over 100 U, but visual inspection of the results including the Kaplan-Meier plots of time to qualification for retreatment strongly suggest that only 200 U was capable of producing a clinically useful effect for a clinically useful period of time. Although 100 U had *some* efficacy, and reached significance at Week 6 for MDP, the time to retreatment for 100 U was broadly similar to placebo through most of the plot.

Extension Study (094)

Design

This study is an ongoing, partially blinded extension study recruiting patients from either of the two pivotal studies (515 and 516). It does not include a placebo group. Patients will receive the same dose they were assigned in the preceding study (200 U or 300 U); for former placebo recipients, this is the dose assigned for the second, active treatment, regardless of whether a second treatment was given. Patients will be followed for an additional three years. Dose blinding was used to preserve blinding in the pivotal studies but was ceased once the preceding pivotal studies were completed. Only interim results are available.

Eligibility criteria were essentially the same as in the pivotal studies. A maximum of six months between studies was permitted.

The efficacy endpoints were similar to the previous studies, but only a three day bladder diary was collected, and incontinence frequency was expressed as a daily frequency instead of a weekly frequency. Urodynamic assessments were not performed.

Statistical Analysis Plan

This study lacked a placebo control group, and thus was primarily observational and descriptive. The primary efficacy variable was the daily incontinence frequency at Week 6 after each treatment. The primary efficacy analysis was to summarise the daily frequency of urinary incontinence episodes according to (a) study treatment cycle, and (b) by Botox treatment cycle, with the latter accounting for previous treatment cycles in the pivotal studies. An ANCOVA model was used, with initial study baseline as covariate and treatment sequence, aetiology (MS or SCI), concurrent anticholinergic therapy and investigator as factors, to assess the change from baseline in incontinence frequency.

Because it lacked a clear control group, and was an open label extension study, power considerations are not relevant.

Results

After a second, third or fourth treatment cycle with ID Botox, a significant reduction in urinary incontinence frequency was observed at either dose, and was broadly similar to that observed in the pivotal studies. Note that the daily incontinence frequencies in Study 094 need to be multiplied by seven when comparing the magnitude of the changes with the weekly incontinence frequencies of the pivotal studies.

The I-QOL was also significantly improved, and the volume per void was also significantly increased for cycles 2-4. There were very few patients receiving their first active treatment cycle in this study, as most had already been treated in the pivotal studies, so analysis of cycle 1 in this study generally did not show a significant treatment effect. The sponsor also performed analyses in which the extension and pivotal data were pooled, allowing an assessment across multiple cycles. These analyses showed a persistent treatment effect across at least three cycles, but patient numbers were very low by the fourth cycle. Most parameters showed an apparent improvement in efficacy with later treatments, with progressively greater reductions in incontinence and improving responder rates, but this could simply reflect the fact that patients who responded well were more likely to agree to repeat treatment.

Conclusion

This partially blinded extension study showed a broadly similar treatment effect with repeat dosing as had already been demonstrated in the pivotal studies, but firm conclusions cannot be drawn because of the lack of a placebo group and the non random selection of patients willing to undergo repeat treatment. The mean *daily* decrease from the initial study baseline (the baseline in Study 515 or 516) ranged from -5.4 to -3.0, equivalent to a weekly decrease of -37.8 to -21.0, and these *within group* decreases were statistically significant for treatment cycles 2 and 3.

Improvements in secondary efficacy parameters were also observed over repeated treatment, including increases in volume per void and decreases in the frequency of spontaneous voids.

Dose Ranging Study in Idiopathic Overactive Bladder (IOAB) (077)

Design

This relatively large, dose ranging Phase 2 study (n=313) was designed to evaluate the safety and efficacy of a single ID Botox treatment, at each of five doses (300, 200, 150, 100 and 50 U), relative to placebo, in the treatment of patients with IOAB.

In contrast to the pivotal studies, patients were *excluded* from participating in the study if they had urge incontinence due to any known neurological reason, so this study *does not* directly address the target indication (and was therefore not included in the Clinical Summary of Efficacy or Clinical Summary of Safety). Patients were also excluded if they had a predominance of stress incontinence, or if they used CIC to manage urinary incontinence. Patients had to have been inadequately controlled on anticholinergic therapy.

The requirement that patients had to be essentially undiagnosed with respect to the cause of their urge incontinence might be expected to lead to an inhomogeneous patient population and include some patients where psychological factors played a role in their bladder symptom; on the other hand it does assess the broader population of 'idiopathic' incontinent patients that were explicitly not targeted in the pivotal trials. If Botox were to be used outside the context of NDO, where the pivotal studies showed evidence of efficacy, then this study is the best assessment to date of the likely efficacy in that broader population.

It had a multicentre, double blind, randomised, placebo controlled, parallel group design, and patients were assigned to one of the six treatments (including placebo) in a ratio of 1:1:1:1:1:1.

Treatment was given with 20 injections of 0.5 mL, whereas in the pivotal studies it was 30 injections of 1 mL.

Total study duration per patient was 36 weeks post treatment.

The primary endpoint was incontinence frequency (episodes of urinary urge incontinence per week) at baseline, and then at follow up, with the primary efficacy endpoint at Week 12.

Secondary endpoints included the total number of episodes of micturition (both by voluntary urination and by catheterisation), nocturia, and the presence of urgency (recorded as 'yes' or 'no') associated with each micturition or nocturia. Urodynamic parameters were measured during the screening period and at Weeks 12 and 36, including: volume at first IDC; MDP during first IDC; MCC; end fill pressure (EFP) measured at MCC or the pressure prior to terminal IDC; detrusor compliance (DC) and PVR urine volume.

These endpoints generally match those chosen for the pivotal NDO studies, but because patients were not offered a second dose, there is no information available on the time to retreatment.

Statistical Analysis Plan

The study was analysed as a superiority study, with the primary hypothesis being that at least one dose of Botox would be more effective than placebo in reducing weekly frequency of urinary urge incontinence.

The hypothesis was tested using an ANCOVA model with treatment group and investigator as factors and baseline frequency as a covariate. A two sided test based on pair wise

contrasts from the ANCOVA model was used, with a p value ≤ 0.05 considered statistically significant. No adjustment of significance levels was made for multiplicity of comparisons.

The sponsor estimated that, with 42 patients per treatment group, the power to detect between group differences in mean change from baseline was 80% for a difference of 5 episodes per week (for 4, 5 or 6 episodes per week, the power was 61, 80, or 92%, respectively). This calculation assumed a common standard deviation of eight episodes and was based on a two samples t-test in mean change from baseline. These assumptions were reasonable, and recruitment was better than this, but the power of the study was subsequently undermined by a powerful placebo response that dwarfed the treatment effect, and the placebo subtracted treatment effect was much less than anticipated.

Results

There were no statistically significant differences between groups for any of the baseline demographic characteristics. The disease characteristics were also similar, but there was a higher baseline incontinence frequency in the placebo group.

For the primary endpoint, incontinence frequency, the placebo effect was profound and swamped any treatment effect: a significant *within group* reduction was observed in all six treatment groups, *including placebo*, as early as Week 2, and this was statistically significant at all time points and in all treatment groups ($p < 0.001$). The maximum post treatment decreases in mean incontinence frequency occurred at Week 6 for almost all treatment groups (except the 300 U group, which showed maximal decrease at Week 18), and the reductions were maintained in all treatment groups for at least 18 weeks post treatment. There was no apparent dose response relationship.

For the proposed treatment dose of 200 U, the mean reduction in incontinence frequency was -19.6 at Week 12, the primary time point, compared to -17.4 in the placebo group. This is not a clinically meaningful difference: patients had roughly 2 episodes of incontinence less with active treatment, over the course of a week, when the baseline incontinence was 24-33 episodes. At the time point favoured in the pivotal studies (six weeks), the difference was similarly minor: a reduction of 20.0 episodes was observed in the 200 U group, compared to 18.2 in the placebo group, a treatment effect of less than 2 episodes. This is not a reduction that many patients would consider worthwhile, especially given that the treatment involves an invasive procedure with some attendant risk.

The treatment effect for the 200 U group relative to placebo did reach statistical significance by ANCOVA (Tables 19-20). The difference became significant at Week 6 and stayed significant to Week 36. For other doses, a significant significance was achieved at a range of time points from Week 2 to Week 36; even the 50U dose, which showed no convincing efficacy in the other dose ranging study (518), seemed to be different from placebo. Given that the absolute differences between groups was small, and the placebo group differed from the other groups in baseline urinary incontinence, it is difficult to draw any firm conclusions. Of note, there was apparently no statistical correction for the use of multiple comparisons.

Table 19: Weekly frequency of urge urinary incontinence (UII) episodes: baseline and change from baseline (ITT population with imputation).

Timepoint Parameter		BOTOX®					Placebo (N=44)
		300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline	N	55	53	49	54	57	44
Mean (SD)		26.8 (20.84)	24.1 (17.63)	28.3 (26.28)	27.8 (22.72)	30.3 (18.98)	32.5 (20.24)
Week 2	N	55	53	49	54	57	44
Mean (SD)		-18.6 (20.93)	-16.8 (13.96)	-20.8 * (14.93)	-18.6 (21.12)	-20.0 (14.97)	-17.3 (16.69)
Week 6	N	55	53	49	54	57	44
Mean (SD)		-18.8 (25.29)	-20.0 ** (12.21)	-23.4 ** (16.49)	-19.9 (19.69)	-21.2 (17.17)	-18.2 (18.56)
Week 12	N	55	53	49	54	57	44
Mean (SD)		-19.4 * (25.71)	-19.6 ** (12.15)	-23.0 ** (15.75)	-18.4 (20.22)	-20.7 * (17.80)	-17.4 (18.16)
Week 18	N	55	53	49	54	57	44
Mean (SD)		-19.7 *** (26.24)	-19.4 *** (13.55)	-21.7 *** (17.06)	-19.9 ** (18.03)	-20.4 ** (17.52)	-15.8 (18.32)
Week 24	N	55	53	49	54	57	44
Mean (SD)		-19.0 * (25.17)	-20.0 ** (14.67)	-22.7 ** (17.49)	-19.2 * (18.67)	-18.9 (17.95)	-17.2 (17.29)
Week 30	N	55	53	49	54	57	44
Mean (SD)		-17.1 (22.54)	-18.6 * (13.46)	-21.7 * (18.03)	-18.5 (18.44)	-17.5 (17.18)	-17.5 (17.23)
Week 36	N	55	53	49	54	57	44
Mean (SD)		-17.3 (21.95)	-18.7 * (13.25)	-21.9 * (18.70)	-18.5 (18.21)	-17.9 (16.94)	-17.9 (17.72)

SD = standard deviation

* p < 0.05; ** p < 0.01, *** p < 0.001 (p-values from pair wise contrasts between Botox and placebo groups for post treatment visits are from an ANCOVA model with factors for treatment group and investigator, using baseline as a covariate)

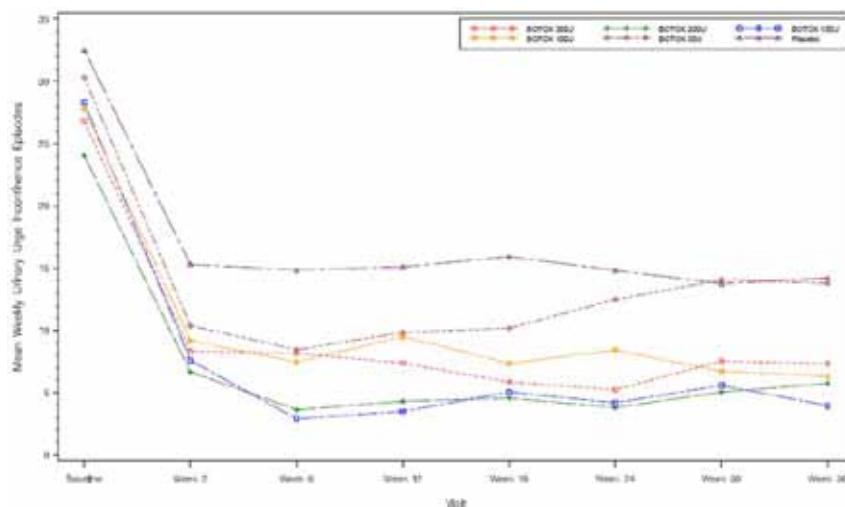
Table 20: Incidence of responders at Week 12 with 50%, 75% and 100% reduction in urge urinary incontinence (UII) episodes from baseline.

Characteristic	Attribute	BOTOX®					Placebo (N=44)
		300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Patients with 50% reduction in UII episodes from baseline	N (%)	47 (83.9%)	42 (79.2%)	38 (77.6%)	38 (70.4%)	41 (71.9%)	23 (52.3%)
Patients with 75% reduction in UII episodes from baseline	N (%)	43 (76.8%)	37 (69.8%)	36 (73.5%)	30 (55.6%)	33 (57.9%)	16 (36.4%)
Patients with 100% reduction in UII episodes from baseline	N (%)	32 (57.1%)	27 (50.9%)	20 (40.8%)	20 (37.0%)	17 (29.8%)	7 (15.9%)

UII = urinary urge incontinence

The same results are shown in Figure 17. It is important to note that, although the curve for placebo appears higher than all the active treatment curves, it is also higher at baseline; if the curves were equalised at baseline and expressed as absolute changes, then they would overlap. Also, the flatness of the curves from Week 6 to Week 36 is not suggestive of a convincing treatment effect given that Botox, used for other applications, usually shows a waning of efficacy after three months.

Figure 17: Mean weekly urge urinary incontinence (UUI) episodes by visit for all groups (ITT population).



Secondary endpoints were similarly disappointing, and were in general difficult to interpret. There was an apparently significant treatment effect on volume at IDC, as shown in the table below, but it was only significant at Week 36, when the effect of the Botox should have been becoming less, rather than more evident. There was no consistent effect on peak detrusor pressure, either within groups or relative to baseline. For MCC, the 300 U dose showed a significant effect, but the 200 U dose merely showed a favourable trend. No significant treatment effect was seen for EFP, but significant results were observed for detrusor compliance (Tables 21-25).

Table 21: Volume at first IDC (mL) – Baseline and change from baseline (ITT population)

Timepoint Parameter		BOTOX®					Placebo (N=44)
		300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline	N	39	39	32	42	44	31
Mean (SD)		167.4 (118.55)	179.5 (136.19)	156.6 (109.12)	135.7 (97.79)	158.1 (109.95)	169.5 (103.37)
Week 12	N	23	21	20	25	31	24
Mean (SD)		100.8 (100.00)	72.6 (87.69)	67.1 (149.35)	82.5 (137.48)	44.7 (99.30)	42.8 (179.43)
Week 36	N	29	25	22	31	28	22
Mean (SD)		81.8 ** (191.52)	49.6 * (126.76)	62.5 * (137.49)	58.2 (96.06)	36.6 (138.90)	-35.1 (116.24)

Note: data are presented only for those patients who recorded an IDC during urodynamic testing at baseline, week 12 and week 36

SD = standard deviation

* $p < 0.05$; ** $p < 0.01$ (p-values from pairwise contrasts between BOTOX® and placebo groups for post-treatment visits from an ANCOVA model with factors for treatment group and investigator, using baseline as a covariate).

Table 22: Peak detrusor pressure during first IDC (cmH₂O) – Baseline and change from baseline (ITT population).

Timepoint Parameter	BOTOX®					Placebo (N=44)
	300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline N	38	39	30	43	44	32
Mean (SD)	23.8 (20.63)	21.7 (18.26)	23.8 (18.84)	22.5 (19.22)	22.5 (15.27)	24.3 (18.40)
Week 12 N	21	22	19	27	32	24
Mean (SD)	-1.0 (30.06)	4.6 (24.48)	-5.3 (21.23)	-0.9 (17.95)	3.6 (21.14)	-1.1 (20.57)
Week 36 N	29	25	21	30	29	22
Mean (SD)	5.5 (23.33)	1.2 (16.64)	0.8 (16.61)	5.4 (17.29)	0.0 (20.39)	-2.6 (32.02)

SD = standard deviation

Table 23: Maximum cystometric capacity (mL) – Baseline and change from baseline (ITT population).

Timepoint Parameter	BOTOX®					Placebo (N=44)
	300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline N	52	49	41	52	54	40
Mean (SD)	271.7 (140.69)	280.1 (141.03)	258.4 (133.95)	255.0 (148.84)	262.9 (137.55)	267.1 (160.33)
Week 12 N	45	42	36	42	53	32
Mean (SD)	130.8 ** (129.72)	91.5 (128.60)	101.7 (126.89)	71.0 (128.60)	50.0 (119.81)	49.5 (146.81)
Week 36 N	46	41	30	45	45	29
Mean (SD)	59.3 * (139.84)	48.2 (152.84)	49.8 (132.59)	38.4 (141.93)	21.0 (139.16)	12.5 (201.01)

SD = standard deviation

* p < 0.05; ** p < 0.01 (p-values from pairwise contrasts between BOTOX® and placebo groups for post-treatment visits from an ANCOVA model with factors for treatment group and investigator, using baseline as a covariate)

Table 24: End fill pressure at MCC (cmH₂O) – Baseline and change from baseline (ITT population).

Timepoint Parameter	BOTOX®					Placebo (N=44)
	300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline N	52	49	41	52	54	39
Mean (SD)	6.4 (7.19)	5.9 (5.57)	6.7 (4.77)	7.1 (7.97)	7.3 (6.18)	5.4 (5.67)
Week 12 N	45	42	37	42	53	30
Mean (SD)	-0.6 (8.82)	-0.3 (4.87)	0.9 (8.90)	-0.6 (8.20)	0.3 (6.76)	1.4 (5.83)
Week 36 N	46	41	29	45	45	27
Mean (SD)	1.2 (10.04)	2.2 (14.12)	3.0 (8.62)	0.3 (10.91)	0.0 (9.51)	-0.7 (7.83)

SD = standard deviation

Table 25: Detrusor compliance (mL/cmH₂O) – Baseline and change from baseline (ITT population).

Timepoint Parameter	BOTOX®					Placebo (N=44)
	300 U (N=56)	200 U (N=53)	150 U (N=49)	100 U (N=54)	50 U (N=57)	
Baseline N	51	49	41	52	54	39
Mean (SD)	87.5 (94.04)	100.7 (126.61)	85.2 (114.81)	77.7 (93.17)	59.6 * (61.46)	101.2 (104.73)
Week 12 N	45	42	36	42	53	30
Mean (SD)	53.0 * (173.80)	81.7 ** (188.54)	13.6 (132.53)	63.0 * (135.56)	42.7 (128.61)	-22.8 (87.68)
Week 36 N	45	40	30	45	44	26
Mean (SD)	37.6 (136.86)	41.6 * (187.05)	1.6 (157.39)	16.1 (114.79)	37.1 (110.63)	-23.2 (113.76)

SD = standard deviation

* p < 0.05; ** p < 0.001 (p-values from pairwise contrasts between BOTOX® and placebo groups for post-treatment visits from an ANCOVA model with factors for treatment group and investigator, using baseline as a covariate)

For the quality of life assessments, the overall results were positive. For the I-QOL, statistically significant improvements in the mean change from baseline in Total I-QOL Scores were observed between the 300, 200, 150 and 100 U groups and the placebo group at all post treatment visits through Week 36 ($p \leq 0.036$). At the primary assessment time point of Week 12, the mean increases in the I-QOL scores ranged from 29.8 in the 50 U group to 39.7 in the 300 U group, compared to a mean increase of 17.9 in the placebo group. Qualitatively similar changes were seen in other quality of life measures: SF-36 health survey⁶ and King's Health Questionnaire⁷ (data not shown in this report).

Conclusion

In this population with poorly characterised incontinence, the placebo effect was so profound it disguised any Botox effect, and whether Botox has any useful efficacy for IOAB is thus unclear. A significant treatment effect was demonstrated by ANCOVA, but the magnitude of the difference between the proposed Botox dose and placebo was only two episodes of incontinence per week, which is not clinically meaningful.

Study in Patients with Respiratory Compromise (082)

This small study (n=34) was specifically designed to assess the safety of up to two doses of ID Botox in patients with neuromuscular respiratory impairment. As in the pivotal studies, it employed a multicentre, double blind, randomised, placebo controlled, parallel group design, and assessed the safety and efficacy of two doses of Botox (200 U and 300 U) in comparison to placebo. The eligibility criteria were similar to the pivotal studies, except that patients had to have neurological respiratory impairment in addition to NDO.

Respiratory impairment ranged from mild to severe, and was defined using American Thoracic Society (ATS) criteria. Patients were required to have a forced vital capacity (FVC) between 50% and 80% of the predicted value, using a published predictive method.⁸

All patients had SCI or MS, and had urinary incontinence that had not been adequately controlled with anticholinergic therapy. Anticholinergic therapy had to be kept stable throughout the study, and could not be initiated during the study. The level of

⁷ Kelleher CJ, et al. (1997) A new questionnaire to assess the quality of life of urinary incontinent women. *Br. J. Obstet. Gynaecol.* 104: 1374-1379.

⁸ Crapo RO, et al. (1981) Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am. Rev. Respir. Dis.* 123: 659-664.

incontinence was similar to the pivotal studies (≥ 4 episodes of urinary incontinence over 3 days, compared to ≥ 14 episodes over 7 days in the pivotal studies). SCI patients had to have a stable neurological injury between cervical level 5 (C5) and cervical level 8 (C8), inclusively, which is a higher level than patients in the pivotal studies, and one more likely to be associated with respiratory compromise.

Only the first dose was placebo controlled. As in the pivotal studies, patients were randomised to receive Botox 200 U, 300 U or placebo for their first dose, in a 1:1:1 ratio, and the placebo group was further randomised to receive Botox 200 U or 300 U in a 1:1 ratio for their second dose, if required.

The study lasted 52 weeks for each patient. A minimum follow up of 12 weeks for the second dose was ensured by restricting eligibility for a second dose to the period from 12-40 weeks. To qualify for retreatment, patients had to request retreatment and report at least 2 incontinence episodes in 3 days; an interval of 12-40 weeks had to have elapsed since the first treatment.

In addition to standard efficacy endpoints (frequency of urinary incontinence, frequency of voiding and standard urodynamic parameters), patients were monitored with the following pulmonary function tests, as this was the primary objective of the study:

- Maximum inspiratory pressure (MIP)
- Maximum expiratory pressure (MEP)
- FVC (percent predicted and absolute value)
- Forced expiratory volume in 1 second (FEV1) (% predicted and absolute)
- FEV1/FVC ratio
- Oxyhaemoglobin saturation (SpO2 %)

Statistical Analysis Plan

The efficacy data for this study was analysed as appropriate for a superiority study, but efficacy was of secondary importance to the safety analysis and no attempt was made to achieve adequate power for the efficacy analysis. For cycle 1, a comparison between each Botox group and placebo was performed at each applicable follow up visit using an ANCOVA model with baseline value as covariate and treatment group, aetiology at entry into the study (either SCI or MS), and investigator as factors. A significance level of <0.05 was used. Subsequent cycles were not subjected to between group comparisons.

Safety analyses focussed on pulmonary function, and an attempt was made to demonstrate non inferiority for important respiratory parameters including MIP, MEP, FVC, FEV1, and the derived variable FEV1/FVC ratio. For each variable of interest, a two sided 95% confidence interval (CI) for the difference in means was calculated. The study as submitted was clearly small and underpowered. Furthermore, pulmonary function would be expected to be quite heterogenous in this clinical population, making demonstration of a difference difficult. The sponsor did not define what would constitute a clinically meaningful difference in means, and instead wrote:

“For each respiratory assessment, a non inferiority test can be performed to compare each Botox group and the placebo group with a null hypothesis $-\leq -\Delta BPH : \mu \mu 0$ versus an alternative hypothesis $-> -\Delta BPH : \mu \mu 1$ where $B \mu$ is the mean change for the Botox group, $P \mu$ is the mean change for the placebo group, and Δ is a non

In view of this, formal power calculations are not relevant and a conclusion of non inferiority could not be made. The analysis is essentially observational and descriptive.

Efficacy Results

Within group changes were observed in urinary incontinence frequency for all groups including placebo. There was a favourable trend in favour of active treatment, with mean three day incontinence totals decreasing by 11.2 and 12.1 in the 300 U and 200 U groups, respectively, at Week 6, compared to a decrease of only 4.1 in the placebo group (Tables 26-28). This did not achieve significance as patient numbers were low.

There were increases in MCC and decreases in MDP, with the 200 U group showing a significant increase in MCC relative to placebo.

Table 26: Number of urinary incontinence episodes (total from three day diary) – Study baseline and change from study baseline (treatment cycle 1, ITT population).

Timepoint	Parameter	BOTOX®		Placebo (N = 10)	300 U BOTOX® vs Placebo p-value ^b Difference ^c	200 U BOTOX® vs Placebo p-value ^b Difference ^c
		300 U (N = 12)	200 U (N = 12)			
Study baseline	N	11	12	9		
	Mean	14.9	14.1	9.9		
	(SD)	(5.41)	(10.40)	(7.08)		
Post-treatment 1 Week 2	N	11	11	9	0.315	0.123
	Mean	-7.0	-8.5	-2.7	-3.3	-4.5
	(SD)	(8.15)	(9.25)	(7.94)		
Week 6	P-value ^a	0.017	0.012	0.343		
	N	9	9	9	0.210	0.249
	Mean	-11.2	-12.1	-4.1	-4.6	-4.5
Week 12	(SD)	(6.30)	(8.05)	(4.51)		
	P-value ^a	< 0.001	0.002	0.026		
	N	7	9	8	0.885	0.419
	Mean	-9.3	-10.4	-6.9	0.5	-2.5
	(SD)	(7.20)	(11.98)	(8.34)		
	P-value ^a	0.014	0.031	0.052		

SD = standard deviation

^a P-values for within-group changes from study baseline are from paired t-tests.

^b P-values for between-group comparison at each visit is based on an ANCOVA model with study baseline value as covariate and treatment group, etiology at entry into study, and investigator as factors.

^c Difference is between BOTOX® and placebo (BOTOX® minus placebo) using least square means.

Table 27: Maximum cystometric capacity (mL) – Baseline and change from study baseline (treatment cycle 1, ITT population).

Timepoint	Parameter	BOTOX®		Placebo (N = 10)	300 U BOTOX® vs Placebo p-value ^b Difference ^c	200 U BOTOX® vs Placebo p-value ^b Difference ^c
		300 U (N = 12)	200 U (N = 12)			
Study baseline	N	12	12	10		
	Mean	212.3	185.2	301.7		
	(SD)	(174.20)	(71.51)	(190.58)		
Week 6 post-treatment 1	N	11	9	9	0.678	0.006
	Mean	38.5	217.0	-87.0	24.7	253.7
	(SD)	(229.47)	(114.35)	(138.15)		
	P-value ^a	0.591	< 0.001	0.096		

SD = standard deviation

^a P-values for within-group changes from study baseline are from paired t-tests.

^b P-values for between-group comparison at each visit is based on an ANCOVA model with study baseline value as covariate and treatment group, etiology at entry into study, and investigator as factors.

^c Difference is between BOTOX® and placebo (BOTOX® minus placebo) using least square means.

Table 28: Maximum detrusor pressure at first IDC (cmH₂O) – Baseline and change from baseline (treatment cycle 1, ITT population).

Timepoint	Parameter	BOTOX [®]		Placebo (N = 10)	300 U BOTOX [®] vs Placebo p-value ^b Difference ^c	200 U BOTOX [®] vs Placebo p-value ^b Difference ^c
		300 U (N = 12)	200 U (N = 12)			
Baseline	N	12	12	10		
	Mean	45.3	31.5	39.9		
	(SD)	(23.31)	(23.18)	(20.24)		
Week 6 post-treatment 1	N	7	3	7	0.445	0.091
	Mean	-3.7	-18.7	11.0	11.8	-48.5
	(SD)	(30.28)	(33.65)	(26.63)		
	P-value ^a	0.757	0.438	0.316		

SD = standard deviation

Note: The factors of etiology and investigator were confounded. Therefore the individual treatment group least square means were non-estimable. However for the treatment differences, least square means, CIs, and p-values could still be determined.

^a P-values for within-group changes from study baseline are from paired t-tests.^b P-values for between-group comparison at each visit is based on an ANCOVA model with study baseline value as covariate and treatment group, etiology at entry into study, and investigator as factors.^c Difference is between BOTOX[®] and placebo (BOTOX[®] minus placebo) using least square means.

Safety Results

The safety results for this study are presented in the Safety Section.

Dose Considerations Across All Studies

In the pivotal studies, most efficacy endpoints showed very similar results across the two active dose groups, as summarised in Table 29. Given that AEs were higher in the 300 U group, as discussed in the Safety Section, the 200 U appears to offer a better risk-benefit balance. Doses lower than 200 U were considerably less effective in the dose ranging Study 518, with a duration of action that resembled placebo, but this study was underpowered. It did show a significant dose trend across doses to 200 U, but did not specifically show a significant benefit of 200 U over 100 U. On balance, the efficacy evidence favours the proposed dose of 200 U.

Table 29: Change from study baseline in select efficacy measures for treatment cycle 1 in the 300 U and 200 U Botox dose groups (placebo controlled pivotal study ITT population).

Timepoint	Attribute	Weekly Frequency of Urinary Incontinence Episodes		Volume per Void (mL)		I-QOL Total Summary Score		MCC (mL)		MDP (cmH ₂ O) during First IDC	
		BOTOX®		BOTOX®		BOTOX®					
		300 U (N = 223)	200 U (N = 227)	300 U (N = 223)	200 U (N = 227)	300 U (N = 223)	200 U (N = 227)	300 U (N = 223)	200 U (N = 227)	300 U (N = 223)	200 U (N = 227)
Week 2	N	223	227	190	198	NA	NA	NA	NA	NA	NA
	Mean change	-17.4	-17.7	75.2	60.2	NA	NA	NA	NA	NA	NA
	SD	22.09	20.45	124.74	116.0	NA	NA	NA	NA	NA	NA
	p-value ^a	0.591		NA	NA	NA	NA	NA	NA	NA	NA
Week 6	N	223	227	193	199	203	220	190	211	62	70
	Mean change	-21.3	-21.3	121.2	108.4	29.25	25.89	163.1	153.6	-30.1	-32.4
	SD	21.03	21.60	136.39	135.87	26.429	26.202	176.15	167.81	35.39	40.94
	p-value ^a	0.267		NA	NA	0.076		0.243		0.730	
Week 12	N	207	223	185	192	198	213	NA	NA	NA	NA
	Mean change	-21.9	-20.6	115.8	96.7	30.25	28.89	NA	NA	NA	NA
	SD	18.64	20.99	125.70	116.28	27.089	25.942	NA	NA	NA	NA
	p-value ^a	0.133		NA	NA	0.376		NA	NA	NA	NA

IDC = involuntary detrusor contraction; I-QOL = Incontinence Quality of Life Instrument; MCC = maximum cystometric capacity; MDP = peak (amplitude) detrusor pressure during first IDC; NA = not applicable or not available; SD = standard deviation.

^a P-values for between-group comparison of 300 U and 200 U BOTOX® at each visit were based on an ANCOVA model with baseline parameter (weekly frequency of urinary incontinence episodes, mean volume per void, I-QOL total summary score, MCC or MDP during first IDC) as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors.

Overall Summary of Clinical Efficacy

The pivotal studies achieved their primary endpoints and all of their secondary endpoints. Results were similar across the two studies. The magnitude of the observed benefit for either 200 U or 300 U was clinically meaningful, with reductions in incontinence frequency of about 21 episodes per week at Week 6 and Week 12, compared to reductions of only 10 in the placebo group, from a baseline of 31-32 episodes per week. About 37-40% of Botox recipients had a 100% reduction in incontinence, compared to only 9% of placebo recipients.

MCC increased by 163.1 and 153.6 in the pooled 300 U and 200 U groups, respectively, compared to only 11.9 in the placebo group, and maximum detrusor pressure was decreased by 30-32 cmH₂O from a baseline of 45-52 cmH₂O, compared to a trivial mean increase in the placebo group of 1 cmH₂O.

The median duration of effect, based on time to return to an incontinence level within 50% of baseline, was 294-301 days in the active groups, compared to 165 days in the placebo group. The median time to request retreatment was 265-269 days in the active groups, compared to 92 days with placebo.

Similar results were obtained with repeat dosing in the pivotal studies and in an extension study, but this was not placebo controlled.

In the pivotal studies, 300 U and 200 U showed similar efficacy. A dose ranging study showed a trend suggesting superiority of 200 U over lower doses. Other minor studies were underpowered but were broadly consistent with the pivotal studies.

A study in IOAB, by contrast, showed only minor evidence of efficacy, highlighting the fact that the current submission only supports the more narrow indication of NDO.

Safety

Introduction

Botox already has a well established role in the clinical treatment of a variety of disorders including blepharospasm, spasticity and dystonia. As such, its safety profile is reasonably well characterised. Most of the safety issues related to Botox relate directly to its mode of action, with excess weakness in treated muscles or spread to muscles near the intended target being the primary concern. For instance, excess facial weakness may follow treatment for blepharospasm, and neck weakness or dysphagia may follow treatment of cervical dystonia. Systemic spread of the toxin appears to be rare but would pose a serious safety risk if it occurred, and cases of possible spread have been reported in the literature.⁹ The sponsor specifically addressed this by looking for evidence of systemic spread in the AE profile. In addition, a safety study is underway specifically assessing the use of ID Botox patients with neuromuscular compromise of respiration; these are the patients who would be at highest risk if Botox were to spread systemically.

In the context of ID Botox, the primary safety concern is that the drug would be expected to cause bladder weakness and thus impair bladder emptying. Poor bladder emptying could in turn present as acute urinary retention, as a chronically over distended bladder with 'overflow' incontinence, and as an increased risk of urinary tract infection due to the failure of the normal bladder flushing mechanisms and the persistence of a pool of contaminated urine between voids.

Note that poor bladder emptying could also negate some of the efficacy of ID Botox, in the sense that, for patients not using a catheter, it is the difference between the PVR and the bladder's holding capacity that is available for urine storage between voids. A treatment that increased holding capacity by 100 mL and also increased PVR by 100 mL would not enable the patient to store any more urine between voids but would instead simply increase the risk of urinary tract infection. (For the treatment of urge incontinence, there might be efficacy gains anyway, on non volumetric grounds, because of reduce urgency or reduced pressure.) Thus, although the sponsor discussed changes in PVR solely in the context of safety, it also has an effect on efficacy.

Given that ID Botox is administered via an invasive procedure, a number of procedural complications might be expected such as trauma, haematuria, periprocedural urinary infection, and autonomic dysreflexia in patients with SCI.

Exposure

For their integrated safety analysis, the sponsor pooled data for five of the seven studies (Studies 515, 516, 094, 511 and 518). They excluded Study 082 because it involved a specific population of patients with respiratory impairment. They also excluded Study 077, which studied patients with IOAB rather than NDO. These excluded studies are considered separately below.

Exposure in the included studies consists of 809 patients, of which 537 patients received Botox (235 received 300 U, 262 received 200 U and 40 received <200 U) for their first treatment cycle. Another 272 patients received placebo during the first treatment. The 40

⁹ Dutton JJ. (1996) Botulinum-A toxin in the treatment of craniocervical muscle spasms: short- and long-term, local and systemic effects. *Surv. Ophthalmol.* 41: 51-65; Bhatia KP, et al. (1999) Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. *J. Neurol. Neurosurg. Psychiatry* 67: 90-93; Coban A, et al. (2010) Iatrogenic botulism after botulinum toxin type A injections. *Clin. Neuropharmacol.* 33: 158-160.

patients who received Botox doses <200 U were enrolled in the smaller of the two dose ranging studies (Study 518).

A total of 462 patients (462/809, 57.1%) received a second treatment (200 U or 300 U), some of whom had received placebo in the first cycle. Although this second dose provides some useful safety data relevant to repeat dosing, none of it was placebo controlled.

Adverse Events

AEs were analysed by two methods: across the whole duration of the first treatment cycle, and over the first 12 weeks after treatment. The problem with using the whole treatment cycle is that Botox recipients had a longer median interval between first and second dose, and were therefore destined to have more AEs simply by virtue of the longer monitoring period. Comparing the treatments over 12 weeks corrects for this bias, but could potentially fail to capture delayed AEs.

AEs were more common in the Botox groups overall, but the difference was less marked when only the first 12 weeks were considered (AEs in first 12 weeks were 64.7%, 61.5%, 50.0% and 52.9% in the 300 U, 200 U, <200 U and placebo groups, respectively). Relative to placebo, an excess of AEs was observed for the following disorders: urinary tract infection, urinary retention, haematuria, bladder pain, dysuria, constipation and fatigue (Tables 30-31). AEs considered by the investigator to be 'treatment related' are shown in Table 32 (first cycle) and Table 33 (first 12 weeks); these tables do not necessarily capture all events in which Botox played a causal role, and clearly capture some events in which Botox played no role. Of note, some of the placebo AEs could still be related to the invasive procedure.

Reviewing the incidence of AEs over later cycles did not show any new problems, regardless of whether all AEs or just 'treatment related' AEs were considered.

Table 30: Adverse events occurring in the $\geq 3\%$ and more than one patient in any treatment group (placebo controlled study safety population; treatment cycle 1).

System Organ Class Preferred Term	300 U BOTOX® (N = 235)	200 U BOTOX® (N = 262)	< 200 U BOTOX® (N = 40)	Placebo (N = 272)
Overall	187 (79.6%)	211 (80.5%)	24 (60.0%)	196 (72.1%)
Infections and infestations	151 (64.3%)	160 (61.1%)	17 (42.5%)	128 (47.1%)
Urinary tract infection	125 (53.2%)	129 (49.2%)	17 (42.5%)	97 (35.7%)
Nasopharyngitis	12 (5.1%)	10 (3.8%)	0 (0.0%)	7 (2.6%)
Upper respiratory tract infection	8 (3.4%)	6 (2.3%)	0 (0.0%)	5 (1.8%)
Cystitis	7 (3.0%)	6 (2.3%)	0 (0.0%)	4 (1.5%)
Bronchitis	7 (3.0%)	4 (1.5%)	0 (0.0%)	2 (0.7%)
Vulvovaginal mycotic infection ^a	5 (3.4%)	7 (4.9%)	0 (0.0%)	3 (2.3%)
Renal and urinary disorders	80 (34.0%)	89 (34.0%)	6 (15.0%)	58 (21.3%)
Urinary retention	50 (21.3%)	45 (17.2%)	0 (0.0%)	8 (2.9%)
Haematuria	16 (6.8%)	13 (5.0%)	2 (5.0%)	9 (3.3%)
Bladder pain	10 (4.3%)	3 (1.1%)	0 (0.0%)	2 (0.7%)
Dysuria	9 (3.8%)	11 (4.2%)	3 (7.5%)	11 (4.0%)
Nephrolithiasis	2 (0.9%)	9 (3.4%)	1 (2.5%)	5 (1.8%)
Nervous system disorders	39 (16.6%)	38 (14.5%)	0 (0.0%)	23 (8.5%)
MS relapse ^b	12 (5.1%)	5 (1.9%)	0 (0.0%)	6 (2.2%)
Headache	9 (3.8%)	8 (3.1%)	0 (0.0%)	7 (2.6%)
Gastrointestinal disorders	37 (15.7%)	42 (16.0%)	3 (7.5%)	37 (13.6%)
Diarrhoea	13 (5.5%)	11 (4.2%)	0 (0.0%)	10 (3.7%)
Constipation	11 (4.7%)	11 (4.2%)	0 (0.0%)	7 (2.6%)
Nausea	11 (4.7%)	9 (3.4%)	0 (0.0%)	3 (1.1%)
Hyperchlorhydria	0 (0.0%)	1 (0.4%)	3 (7.5%)	2 (0.7%)
Musculoskeletal and connective tissue disorders	35 (14.9%)	43 (16.4%)	1 (2.5%)	34 (12.5%)
Muscular weakness	13 (5.5%)	10 (3.8%)	0 (0.0%)	5 (1.8%)
Muscle spasm	7 (3.0%)	6 (2.3%)	0 (0.0%)	2 (0.7%)
Back pain	5 (2.1%)	9 (3.4%)	0 (0.0%)	4 (1.5%)
General disorders and administration site conditions	22 (9.4%)	47 (17.9%)	3 (7.5%)	28 (10.3%)
Fatigue	7 (3.0%)	16 (6.1%)	0 (0.0%)	7 (2.6%)
Pyrexia	6 (2.6%)	16 (6.1%)	1 (2.5%)	11 (4.0%)
Injury, poisoning, and procedural complications	21 (8.9%)	39 (14.9%)	4 (10.0%)	22 (8.1%)
Fall	2 (0.9%)	8 (3.1%)	0 (0.0%)	2 (0.7%)
Post procedural haematuria	1 (0.4%)	3 (1.1%)	3 (7.5%)	3 (1.1%)
Skin and subcutaneous tissue disorders	16 (6.8%)	18 (6.9%)	2 (5.0%)	18 (6.6%)
Decubitus ulcer	5 (2.1%)	8 (3.1%)	1 (2.5%)	4 (1.5%)
Vascular disorders	12 (5.1%)	13 (5.0%)	0 (0.0%)	5 (1.8%)
Hypertension	8 (3.4%)	7 (2.7%)	0 (0.0%)	1 (0.4%)
Psychiatric disorders	11 (4.7%)	18 (6.9%)	1 (2.5%)	10 (3.7%)
Insomnia	2 (0.9%)	8 (3.1%)	0 (0.0%)	1 (0.4%)

MS = multiple sclerosis

Note: All adverse events are presented, regardless of relationship to treatment. All adverse events include any adverse event that occurred during the first treatment cycle. Within each system organ class, PTs are sorted by descending frequencies of treatment groups from left to right. Within each PT, a patient is counted at most once. Studies include 191622-511, -515, -516, and -518.

^a Percentages based on the female population.

^b MS exacerbations were to have been reported as individual signs and symptoms, however the over-arching term MS exacerbation (PT, MS relapse) was recorded for a total of 23 patients (18 SAEs, 5 non-serious) in addition to or instead of their signs/symptoms of the exacerbation. MS exacerbation analysis was done using a dedicated MS exacerbation CRF page

Table 31: Adverse events occurring in the $\geq 3\%$ and more than one patient in any treatment group (placebo controlled study safety population; first 12 weeks of treatment cycle 1).

System Organ Class Preferred Term	300 U BOTOX® (N = 235)	200 U BOTOX® (N = 262)	< 200 U BOTOX® (N = 40)	Placebo (N = 272)
Overall	152 (64.7%)	161 (61.5%)	20 (50.0%)	144 (52.9%)
Infections and infestations	89 (37.9%)	82 (31.3%)	15 (37.5%)	72 (26.5%)
Urinary tract infection	70 (29.8%)	64 (24.4%)	14 (35.0%)	47 (17.3%)
Upper respiratory tract infection	7 (3.0%)	3 (1.1%)	0 (0.0%)	4 (1.5%)
Renal and urinary disorders	75 (31.9%)	71 (27.1%)	4 (10.0%)	41 (15.1%)
Urinary retention	49 (20.9%)	45 (17.2%)	0 (0.0%)	8 (2.9%)
Haematuria	14 (6.0%)	10 (3.8%)	2 (5.0%)	8 (2.9%)
Bladder pain	8 (3.4%)	2 (0.8%)	0 (0.0%)	2 (0.7%)
Dysuria	6 (2.6%)	6 (2.3%)	2 (5.0%)	11 (4.0%)
Gastrointestinal disorders	26 (11.1%)	21 (8.0%)	3 (7.5%)	25 (9.2%)
Constipation	10 (4.3%)	4 (1.5%)	0 (0.0%)	4 (1.5%)
Diarrhoea	7 (3.0%)	4 (1.5%)	0 (0.0%)	6 (2.2%)
Hyperchlorhydria	0 (0.0%)	1 (0.4%)	3 (7.5%)	1 (0.4%)
General disorders and administration site conditions	12 (5.1%)	30 (11.5%)	3 (7.5%)	17 (6.3%)
Fatigue	5 (2.1%)	10 (3.8%)	0 (0.0%)	3 (1.1%)
Pyrexia	2 (0.9%)	11 (4.2%)	1 (2.5%)	8 (2.9%)

Note: All adverse events are represented, regardless of relationship to treatment. All adverse events include any adverse event that occurred during the first treatment cycle. Within each system organ class, PTs are sorted by descending frequencies of treatment groups from left to right. Within each PT, a patient is counted at most once. Studies include 191622-511, -515, -516, and -518.

Table 32: Overall treatment related adverse events occurring in the $\geq 3\%$ and more than one patient in any treatment group (placebo controlled study safety population; treatment cycle 1).

System Organ Class Preferred Term	300 U BOTOX® (N = 235)	200 U BOTOX® (N = 262)	< 200 U BOTOX® (N = 40)	Placebo (N = 272)
Overall	81 (34.5%)	84 (32.1%)	12 (30.0%)	44 (16.2%)
Renal and urinary disorders	65 (27.7%)	65 (24.8%)	3 (7.5%)	25 (9.2%)
Urinary retention	48 (20.4%)	45 (17.2%)	0 (0.0%)	7 (2.6%)
Haematuria	11 (4.7%)	9 (3.4%)	1 (2.5%)	5 (1.8%)
Dysuria	4 (1.7%)	6 (2.3%)	2 (5.0%)	5 (1.8%)
Infections and infestations	16 (6.8%)	22 (8.4%)	11 (27.5%)	13 (4.8%)
Urinary tract infection	15 (6.4%)	19 (7.3%)	10 (25.0%)	12 (4.4%)
Injury, poisoning, and procedural complications	8 (3.4%)	8 (3.1%)	4 (10.0%)	6 (2.2%)
Post-procedural haematuria	1 (0.4%)	3 (1.1%)	3 (7.5%)	3 (1.1%)

Note: Treatment-related adverse events include the study drug related or injection procedure related adverse event that occurred during the first treatment cycle. Within each system organ class, PTs are sorted by descending frequencies of treatment groups from left to right. Within each PT, a patient is counted at most once. Studies include 191622-511, -515, -516, and -518.

Table 33: Overall treatment related adverse events occurring in the $\geq 3\%$ and more than one patient in any treatment group (placebo controlled study safety population; first 12 weeks of treatment cycle 1).

System Organ Class Preferred Term	300 U BOTOX® (N = 235)	200 U BOTOX® (N = 262)	< 200 U BOTOX® (N = 40)	Placebo (N = 272)
Overall	79 (33.6%)	81 (30.9%)	11 (27.5%)	41 (15.1%)
Renal and urinary disorders	64 (27.2%)	65 (24.8%)	3 (7.5%)	25 (9.2%)
Urinary retention	47 (20.0%)	45 (17.2%)	0 (0.0%)	7 (2.6%)
Haematuria	11 (4.7%)	9 (3.4%)	1 (2.5%)	5 (1.8%)
Infections and infestations	12 (5.1%)	18 (6.9%)	10 (25.0%)	10 (3.7%)
Urinary tract infection	11 (4.7%)	15 (5.7%)	9 (22.5%)	9 (3.3%)

Note: Treatment-related adverse events include the study drug related or injection procedure related adverse event that occurred during the first treatment cycle. Within each system organ class, PTs are sorted by descending frequencies of treatment groups from left to right. Within each PT, a patient is counted at most once. Studies include 191622-511, -515, -516, and -518.

“Adverse Drug Reactions” were defined as AEs with a $\geq 1\%$ overall incidence rate, and either had a $\geq 1\%$ difference between the Botox 200U group and the placebo group or an apparent dose-response trend. These are shown in Tables 34-35.

Table 34: Botox adverse drug reactions (placebo controlled study safety population; first 12 weeks of treatment cycle 1).

System Organ Class Preferred Term	200 U BOTOX® (N = 262)	Placebo (N = 272)
Infections and infestations		
Urinary tract infection	24.4%	17.3%
Renal and urinary disorders		
Urinary retention	17.2%	2.9%
General disorders and administration site conditions		
Fatigue	3.8%	1.1%
Psychiatric disorders		
Insomnia	1.5%	0.0%

Table 35: Botox injection procedure related adverse drug reactions (placebo controlled study safety population; first 12 weeks of treatment cycle 1).

System Organ Class Preferred Term	200 U BOTOX® (N = 262)	Placebo (N = 272)
Renal and urinary disorders		
Haematuria	3.8%	2.9%
Dysuria	2.3%	4.0%
Injury, poisoning, and procedural complications		
Autonomic dysreflexia	1.5%	0.4%

Adverse Urological Effects

Intrinsic to its mode of action, ID Botox weakens the bladder with the likely result that bladder emptying is impaired. By whatever means this potential problem was assessed, including the incidence of acute urinary retention, the rates of uptake of catheterisation in patients who were not originally using CIC at baseline, and post void residual volumes measured during urodynamic studies, recipients of active treatment showed poorer bladder emptying than placebo recipients. This is not so much a complication of treatment as an integral part of the therapeutic approach, shifting the bladder dynamics away from urgent over-activity to potential under activity. Some patients might find this trade off acceptable, especially given that under activity can be managed with catheterisation, whereas overactivity is often more difficult to manage. One important downside of such a shift is an increased risk of urinary tract infections, related to the presence of a stagnant urine pool that is inadequately flushed or, in catheterised patients, the presence of a foreign body that can introduce or harbour bacteria.

Considering the PVR, a clear increase was seen in both active groups by Week 2, with the 300U group showing a mean increase of 176.0 mL, the 200 U group showing a mean increase of 94.1 mL, and the placebo group essentially showing no change (+3.3 mL). This difference was highly significant ($p < 0.001$, see Table 36). Compared to the changes in MCC reported as an efficacy benefit (Table 37), it can be seen that, in broad terms, most of the increased capacity of the bladder was volume that could not be voluntarily voided, and was therefore not available for urine storage in non catheterised patients. For the pooled 300 U group in the pivotal studies, MCC increased by 163.1 mL, and for the pooled 300 U group in the safety analysis, the PVR increased by a slightly larger amount, 176.0 mL (note that the two populations overlap, but are not identical, as the PVR values are derived from patients not using CIC at baseline). The net change in available holding capacity of the bladder is therefore minimal (or comes out as a net loss, if those two figures are taken at

face value), unless the patient is prepared to undergo catheterisation to ensure emptying. The results in the 200 U group were somewhat better, but even in that group the increased mean MCC (153.6 mL) is less impressive once it has been 'discounted' by the mean increase in PVR (94.1 mL).

Note that the sponsor's analysis did not include any attempt to relate these two volumes to each other, but instead reported MCC in the efficacy section and the PVR in the Safety section. In effect, this inflates the apparent clinical efficacy of the drug and represents a selective interpretation of the overall change in urodynamics achieved with Botox.

Table 36: Change from baseline in post void residual volume (placebo controlled study safety population not using CIC at baseline; treatment cycle 1).

Timepoint	300 U BOTOX® (N = 100)	200 U BOTOX® (N = 108)	200 U BOTOX® (N = 17)	Placebo (N = 104)	P-value ^b
Baseline					0.311
N	91	103	17	99	
Mean ± SD	57.9 ± 50.49	62.9 ± 51.37	61.8 ± 50.45	57.3 ± 55.44	
Median	50.0	54.0	50.0	45.0	
Min, Max	0, 198	0, 200	0, 172	0, 190	
Tx 1; Week 2					< 0.001
N	83	98	12	88	
Mean ± SD	176.0 ± 256.87	94.1 ± 170.83	3.9 ± 47.82	3.3 ± 55.69	
Median	105.0	41.5	-3.0	0.0	
Min, Max	-140, 1200	-200, 955	-72, 110	-156, 200	
P-value ^a	< 0.001	< 0.001	0.953	0.920	

Max = maximum; Min = minimum; SD = standard deviation; Tx = treatment

Note: Data were collected from studies 191622-515, 516, and -518.

^a Wilcoxon signed rank tests were performed.

^b P-value is from the Wilcoxon rank sum test for all BOTOX® dose groups and placebo comparisons.

Table 37: Maximum cystometric capacity (mL) – Baseline and change from baseline at Week 6 in treatment cycle 1 (ITT population).

Timepoint	Attribute	191622-515			191622-516			191622-515/516 Pooled		
		BOTOX®			BOTOX®			BOTOX®		
		300 U (N = 132)	200 U (N = 135)	Placebo (N = 149)	300 U (N = 91)	200 U (N = 92)	Placebo (N = 92)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	132	135	149	91	92	92	223	227	241
	Mean	255.8	252.3	256.0	246.8	247.3	249.4	252.2	250.2	253.5
	SD	144.99	154.37	143.83	149.06	147.61	139.29	146.40	151.35	141.86
Week 6	N	107	123	129	83	88	85	190	211	214
	Mean change	167.7	151.2	15.5	157.2	157.0	6.5	163.1	153.6	11.9
	SD	169.56	170.59	127.31	185.18	164.75	144.77	176.15	167.81	134.25
	p-value ^a	< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001	

SD = standard deviation

^a P-values for between-group comparison (versus placebo) at each visit are based on ANCOVA model with baseline MCC as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

For each level of residual urine volume, a higher proportion of Botox recipients exhibited it than did placebo recipients. There is a clear relationship between post void residual volume and the risk of urinary infection, and various volumes cut offs have been proposed as clinically significant (ranging from 150-200mL).¹⁰ Considering those with ≥ 200mL of residual urine, a level at which significant concerns would be raised regarding the risk of urinary tract infections, about a third of Botox recipients (44.2% of the 300 U group and 29.3% of the 200 U group), had this much urine in their bladder after a voluntary void, compared to only 3.4% of placebo recipients. PVRs above 400 mL were seen in 9.1% of

¹⁰ Brookman-May S, et al. (2010) Association between residual urinary volume and urinary tract infection: prospective trial in 225 male patients. *Urology A*. 49: 1163-1168.

patients receiving the proposed Botox dose of 200 U and in an even higher proportion (23.3%) of the 300 U group, compared to no placebo recipients.

The elevated PVR associated with Botox not only degrades potential efficacy gains made in the bladder's holding capacity, but increases the risk of urinary tract infections. This effect was minor in patients using CIC at baseline, where the UTI rate was mildly elevated in both active groups compared to placebo (UTI incidence: 300 U group, 29.2%; 200 U, 22% versus placebo, 20.7%), but it was much more marked in the group who were *not* using CIC at baseline (42.6% and 40.4% versus 11.9%, respectively, for those who subsequently commenced CIC; 26.1% and 21.3% versus 16.4%, for those who continued not to use CIC). Note that these figures only apply to the first 12 weeks of the first cycle.

Table 38 shows that *commencing* CIC posed an increased risk of UTI over and above that seen with the baseline use of CIC, and above that seen in patients who remained free of CIC. This could reflect that CIC was initiated too late in many cases, after a UTI had already occurred because of the increased residual urine. In fact, in those who failed to commence CIC, but had PVR volumes ≥ 200 mL, the UTI rate was similar to those who did commence CIC, indicating that a large part of the increased risk came not from the introduction of a foreign body into the urinary system but to the increased PVR that necessitated the catheterisation. It is possible that a more vigorous surveillance program, monitoring PVR in every patient more frequently, could have led to the initiation of CIC earlier in some cases and thereby avoided some UTIs.

Table 38: Summary of UTI rates by pre and post treatment CIC status and post void residual urine volume during the complete treatment cycle 1 (placebo controlled safety population).

CIC Status		300 U BOTOX®	200 U BOTOX®	Placebo
Pre-treatment	Post-treatment			
Using CIC	Using CIC ^a	54.9% (62/113)	51.5% (68/132)	47.1% (66/140)
Not using CIC	Using CIC	63.0% (34/54)	53.2% (25/47)	28.6% (12/42)
	Not using CIC	52.2% (24/46)	47.5% (29/61)	24.6% (15/61)
	Not using CIC and PVR urine ≥ 200 mL	71.4% (15/21)	68.0% (17/25)	40.0% (2/5)
	Not using CIC and PVR urine < 200 mL	36.0% (9/25)	33.3% (12/36)	23.2% (13/56)

CIC = clean intermittent catheterization; PVR = post-void residual

^a Patients who were using CIC pre-treatment continued to use it post-treatment

Although the commencement of CIC is an appropriate response to poor bladder emptying, and can actually increase the available holding capacity of the bladder by facilitating more complete emptying, it is something that many patients would prefer to avoid. As shown in Table 39, a higher proportion of Botox recipients had to commence CIC than placebo recipients. At Week 12, only 10.1% of placebo recipients had commenced CIC, compared to about 35.9% of the 300U group and 25.5% of the 200 U group (considering the subgroup who were not already using CIC at baseline).

Table 39: Proportion of patients using CIC post treatment by baseline CIC status (placebo controlled study safety population; treatment cycle 1).

Patients Using CIC at Baseline ('CIC Yes')				
Timepoint	300 U BOTOX® (N = 114)	200 U BOTOX® (N = 132)	< 200 U BOTOX® (N = 23)	Placebo (N = 146)
Tx 1; Week 2	103/106 (97.2%)	125/126 (99.2%)	20/20 (100%)	134/137 (97.8%)
Tx 1; Week 6	103/106 (97.2%)	123/125 (98.4%)	21/21 (100%)	133/136 (97.8%)
Tx 1; Week 12	101/106 (95.3%)	122/124 (98.4%)	17/17 (100%)	132/135 (97.8%)
At any time during treatment cycle 1	112/114 (98.2%)	132/132 (100.0%)	21/23 (91.3%)	140/146 (95.9%)
Patients Not Using CIC at Baseline ('CIC No')				
Timepoint	300 U BOTOX® (N = 100)	200 U BOTOX® (N = 108)	< 200 U BOTOX® (N = 17)	Placebo (N = 104)
Tx 1; Week 2	19/94 (20.2%)	16/105 (15.2%)	1/16 (6.3%)	6/98 (6.1%)
Tx 1; Week 6	36/95 (37.9%)	26/103 (25.2%)	1/16 (6.3%)	6/98 (6.1%)
Tx 1; Week 12	33/92 (35.9%)	26/102 (25.5%)	2/14 (14.3%)	10/99 (10.1%)
At any time during treatment cycle 1	46/100 (46.0%)	42/108 (38.9%)	4/17 (23.5%)	18/104 (17.3%)

CIC = clean intermittent catheterization; Tx = treatment

Note: Catheterization information and baseline voiding pattern was based on patient bladder diary data. The percentage is calculated as number of patients performing catheterization/number of patients at each visit. Data were collected from studies 191622-515, 516, -518.

When the changes in PVR are viewed across multiple treatment cycles, no new issues emerge, but there was no placebo controlled data beyond the first treatment cycle. The PVR remained high with the second treatment, and patient numbers after that were too small to allow meaningful analysis. There is no strong indication that cumulative toxicity occurs with repeat dosing but the results should be interpreted with caution. Patients with severe problems related to urinary retention or increased UTIs would be less likely to ask for a repeat treatment, so the population assessed in later treatment cycles are a selected group. The methodological requirement that patients undergo a documented relapse in their incontinence prior to qualifying for a second treatment would protect them somewhat from the risks of over treatment. It remains possible that, in routine clinical practice, patients outside a trial setting might receive multiple Botox treatments at pre determined intervals, such as three monthly, with a cumulative deleterious effect on bladder emptying leading to even higher rates of UTIs and CIC usage than observed in the pivotal studies. The PI should warn against this.

Serious Adverse Events

Serious AEs were relatively rare, and did not differ significantly between treatment groups. Even for urinary tract infections, where a causal role of Botox seems relatively likely in the overall incidence of this AE, the active groups did not show an excess of this problem as a *serious* AE. The only two cases of pyelonephritis, and the only case of urosepsis, occurred in the placebo group.

AEs leading to discontinuation showed no overall pattern, being highest in the <200 U group (2.5%), then the 300 U group (1/3%), the placebo group (0.7%) and lowest in the 200 U group (0.4%), as shown in Table 40.

Table 40: All adverse events leading to study discontinuation (placebo controlled study safety population; first 12 weeks of treatment cycle 1).

System Organ Class Preferred Term	300 U BOTOX* (N = 235)	200 U BOTOX* (N = 262)	< 200 U BOTOX* (N = 40)	Placebo (N = 272)
Overall	3 (1.3%)	1 (0.4%)	1 (2.5%)	2 (0.7%)
Renal and urinary disorders	2 (0.9%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Bladder pain	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Calculus bladder	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urethral haemorrhage	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Breast cancer	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)
Sudden death	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)
Surgical and medical procedures	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Abortion induced ^a	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Infections and infestations	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Influenza	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

* Percentages are based on the female population.

Potential Systemic Effects

Occasional reports of possible systemic effects of Botox have been reported in the literature following local use of Botox for a variety of conditions.⁹

The current PI sheet for Botox acknowledges this issue as follows:

“Postmarketing safety data from Botox and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin, have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression.”

The application of ID Botox would be expected to raise similar concerns.

Several AE preferred terms were prospectively flagged as potentially indicative of systemic spread of toxin, based on their occurrence during the clinical syndrome of botulism. AEs occurring within the pooled safety population were correlated with these terms and the results are tabulated below. Urinary retention was the most common AE seen in this analysis, but in the context of ID treatment is clearly indicative of a local effect.

The incidence of muscular weakness was the next most common AE in this category, and was more common in Botox recipients (5.5% and 3.8% in the 300 U and 200 U groups, respectively) than placebo recipients (1.8%). This finding showed marked variation by aetiology: in the MS subpopulation muscular weakness was reported in 10.3% (12/117), 7.6%, (10/132), and 3.8% (5/133) of the MS patients in the 300 U and 200 U and placebo groups, respectively, during treatment cycle 1.¹¹

A review of individual cases of weakness did not usually reveal a clear aetiological role of Botox: the weakness often appeared many weeks after the Botox treatment (or in one case

¹¹ Lower limb muscular weakness was almost certainly quite severe at baseline in many SCI patients, making this group relatively less likely to report lower limb weakness as an AE, but they would be expected to notice clinically significant upper limb weakness.

lasted for just four hours on the day of the procedure, resolving spontaneously) which does not closely match the known pharmacology of Botox.

The sponsor rejected the possibility of Botox playing a role in causing the weakness, with the claim:

“As is known, ambulation difficulties due to lower extremity weakness are one of the hallmark symptoms in MS patients. The majority of MS cases reviewed were reported as weakness of the lower extremities. Based on individual review, and in the absence of a clear trend or pattern, none of the above cases were found to be due to distant spread of toxin as they were considered to be confounded by the underlying disease of MS.”

Although it is indeed likely that the MS contributed to the reports of weakness, the excess of muscular weakness in the active groups, with an even higher excess at 300 U compared to 200 U, suggests that Botox might have played a causal role in some cases. One possibility is that some patients experienced systemic weakness during urinary tract infections, which exacerbated their existing neuromuscular deficits; another is that the pro inflammatory effects of UTIs, which were more common with active treatment, lead to exacerbations of MS and then weakness. A more serious possibility is that toxin spread locally from injection sites to the psoas muscles, which pass through the pelvis; weakness of these muscles could present as ambulatory difficulties. In fact, this evaluator cannot dismiss the possibility that this was the explanation for at least some cases of muscular weakness in MS patients.

By Fisher’s exact test, a comparison of the incidence of muscle weakness in the pooled Botox group (4.3%) compared to the pooled placebo group (1.8%) was not statistically significant ($p=0.101$, from the Integrated Summary of Safety, ISS) but there is only a 10% possibility that such a difference could arise by chance, and the possibility of a true causal relationship is strengthened by the observed dose trend, which was not subjected to statistical analysis. Against this, the Botox recipients had a longer period of monitoring because of their longer first treatment cycle. Considering just the first 12 weeks of treatment, there was no apparent dose trend (incidence of muscular weakness: Botox 300 U, 1.7%; Botox 200 U, 1.5%; Botox <200 U, 0.0%; all Botox 1.5%; placebo 1.8%; $p=0.770$).

Constipation was also more common in active treatment groups, though this could potentially indicate local spread of toxin from the bladder to the nearby rectum, rather than true systemic spread. It was reported in 4.7%, 4.2% and 2.6% of the 300 U, 200 U and placebo groups, respectively, over the course of the first treatment cycle. Time to onset was varied and ranged from 2 days to 365 days, but 65% reported an onset within 12 weeks of treatment. The excess was not simply due to the increased monitoring time in the active groups, because it was reported as an AE in 4.3%, 1.5% and 1.5% of the 300 U, 200 U and placebo groups, respectively, within the first 12 weeks of treatment. Note that, for this AE, there was no difference between the proposed dose of 200 U and placebo, whereas there was an excess in the higher dose group.

All other AEs potentially indicative of systemic spread occurred only rarely, and seemed unlikely to indicate systemic spread of toxin. All of them are within the spectrum of problems observed in neurological patients, and in none of them was there a dose-response trend (Table 41).

Table 41: Patients reporting adverse events potentially associated with effects remote to the site of injection.

Placebo-controlled Study Safety Population (Treatment Cycle 1)				
Adverse Event (Preferred Term)	300 U BOTOX® (N = 235)	200 U BOTOX® (N = 262)	< 200 U BOTOX® (N = 40)	Placebo (N = 272)
Urinary retention	50 (21.3%)	45 (17.2%)	0 (0.0%)	8 (2.9%)
Muscular weakness	13 (5.5%)	10 (3.8%)	0 (0.0%)	5 (1.8%)
Constipation	11 (4.7%)	11 (4.2%)	0 (0.0%)	7 (2.6%)
Vision blurred	2 (0.9%)	3 (1.1%)	0 (0.0%)	0 (0.0%)
Diplopia	1 (0.4%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
Dyspnoea	1 (0.4%)	1 (0.4%)	0 (0.0%)	4 (1.5%)
Dysarthria	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
Dysphonia	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Respiratory failure	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
BOTOX®-treated Safety Population (Across All Treatment Cycles)				
Adverse Event (Preferred Term)	300 U BOTOX® (N = 318)	200 U BOTOX® (N = 362)	< 200 U BOTOX® (N = 40)	
Urinary retention	67 (21.1%)	65 (18.0%)	1 (2.5%)	
Muscular weakness	21 (6.6%)	22 (6.1%)	0 (0.0%)	
Constipation	15 (4.7%)	15 (4.1%)	0 (0.0%)	
Vision blurred	2 (0.6%)	3 (0.8%)	0 (0.0%)	
Dyspnoea	1 (0.3%)	1 (0.3%)	0 (0.0%)	
Diplopia	1 (0.3%)	3 (0.8%)	0 (0.0%)	
Dysarthria	1 (0.3%)	1 (0.3%)	0 (0.0%)	
Hyporeflexia	1 (0.3%)	0 (0.0%)	0 (0.0%)	
Speech disorder	1 (0.3%)	0 (0.0%)	0 (0.0%)	
Dysphonia	0 (0.0%)	1 (0.3%)	0 (0.0%)	
Respiratory failure	0 (0.0%)	1 (0.3%)	0 (0.0%)	

Procedural Complications

A small number of AEs appeared to be related to the ID injection procedure itself. These included autonomic hyper reflexia, haematuria and bladder pain. For the doses of 300 U and 200 U, the incidence of any AE flagged as a procedural complication was 3.3-3.5%. The incidence reached 10% in the <200 U group, but this was based on low patient numbers and may include non procedural injuries.

Autonomic dysreflexia refers to excessive autonomic (especially sympathetic) activity, which results from aberrant reflexes in patients with neurological dysfunction, especially of the spinal cord. It can be triggered by trauma or infection that would normally cause only a mild sympathetic response, and is often characterised by hypertension and tachycardia. Across the pooled safety population, autonomic dysreflexia was reported as an AE in 1.7% (4/235) of patients in the 300 U group, 1.5% (4/262) in the 200 U group and 0.4% (1/272) in the placebo group during treatment cycle 1. (Note that, in this situation, even events in the placebo group could be due to the procedure.) All of the events resolved without sequelae.

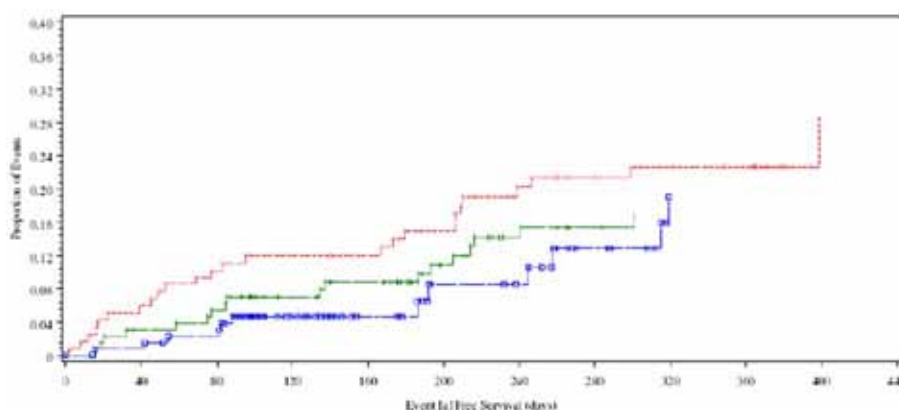
Haematuria was observed soon after the procedure in a small number of patients (see table above) but resolved. The overall incidence of haematuria, including haematuria occurring well after the procedure, was 6.8%, 5.0%, 5.0% and 3.3% in the 300 U, 200 U, <200U and placebo populations, respectively. Bladder pain, including delayed pain, appeared to be more common when active drug was injected, occurring in 4.3%, 1.1%, 0.0% and 0.7% of the 300 U, 200 U, <200 U and placebo populations, respectively. Procedural pain was reported less commonly.

Effect on Multiple Sclerosis Relapses

ID administration of Botox is not expected to have a direct effect on the underlying disease in MS patients, but it is easy to imagine indirect effects, such as an increased number of urinary tract infections leading to immunological stimulation and subsequent MS relapses. It is also possible that urinary retention due to Botox could be misdiagnosed as an MS relapse, though there was no evidence that this occurred. If Botox caused lower limb weakness in some patients (as suggested in the incidence of AEs related to 'muscular weakness'), then this could also be diagnosed as an MS relapse.

Visual inspection of Kaplan-Meier plots for time to first MS relapse suggest that Botox does indeed increase the risk of an MS relapse, but statistical modelling did not show a significant effect (Figure 18 and Table 42). The proportion of patients with at least one relapse was 21.4%, 14.0% and 9.2% in the 300 U, 200 U and placebo groups, respectively, over the course of the first treatment cycle. Given that this treatment cycle was longer for the active groups, it is more appropriate to consider the annualised relapse rates, which were 0.29, 0.23 and 0.20 in the same three dose groups, respectively. Thus, in the absence of better data, it seems likely that there is a slightly increased risk of an MS relapse with Botox treatment, though this is not confirmed statistically and the causal relationship, if there is one, remains unclear.

Figure 18: Plot of time of first MS exacerbation after Treatment 1 based on Kaplan Meier estimates (pooled Studies 515 and 516).



Red line: 300 U Botox (N=117)

Green line: 200 U Botox (N=129)

Blue line: Placebo (N=130)

(a) Event is defined as the number of days from first treatment date to first MS exacerbation. For the censored patients, the time to onset of MS exacerbation is calculated as the time from the date of first injection of study medication to the last day on treatment cycle 1 or study exit date if the patient who exits the study during treatment cycle 1.

Table 42: MS exacerbation event rates (placebo controlled treatment cycle 1).

	300 U BOTOX® (N = 117)	200 U BOTOX® (N = 129)	Placebo (N=130)
Patients with MS Exacerbation			
No	92 (78.6%)	111 (86.0%)	118 (90.8%)
Yes	25 (21.4%)	18 (14.0%)	12 (9.2%)
Number of MS Exacerbations			
1	20 (17.1%)	13 (10.1%)	10 (7.7%)
2	4 (3.4%)	4 (3.1%)	1 (0.8%)
3	1 (0.9%)	1 (0.8%)	1 (0.8%)
> 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total Number of MS Exacerbations	31	24	15
Poisson regression ^a			
Model 1	0.817	0.771	
Model 2	0.673	0.596	
Model 3	0.702	0.630	
Event Rate per Patient Year			
Based on All MS Patients			
Total Exposure in Patient Years	108.0	106.4	73.2
Event Rate	0.29	0.23	0.20
Based on Only Patients with MS Exacerbation			
Total Exposure in Patient Years	22.6	16.6	9.3
Event Rate	1.37	1.45	1.62

MS = multiple sclerosis

Note: Table shows MS patients who experienced a multiple sclerosis exacerbation event. Data were collected from studies 191622-515 and -516.

^a P-value from Poisson regression on the number of MS exacerbation events is performed for pairwise comparison between each of the BOTOX® treatment groups and the placebo group. Model 1: no overdispersion correction; model 2: deviance-type overdispersion correction; model 3: Pearson-type overdispersion correction

Laboratory Monitoring

Patients were monitored with a range of routine laboratory tests including electrolytes, liver function tests and full blood examination. With the exception of changes associated with UTIs, the sponsor claimed that there were no clear trends suggesting that Botox had any effect on these parameters. The Summary of Clinical Safety referred to tables in the ISS that supposedly supported this claim, but the ISS was not originally part of the digital submission. Subsequent review of the shift tables for haematology and biochemistry monitoring did not reveal any concerning trends.

Antitoxin Antibodies

Most patients in the major studies (total n=608, Botox treated n=514, Botox treated in pivotal studies, n=477) were monitored for the development of antitoxin antibodies. With the exception of three patients in whom cross reacting antibodies were detected prior to treatment, no patient developed antitoxin antibodies. Of the three patients with pre existing antibodies, only two received Botox; both of these patients received placebo for the first treatment cycle and Botox for the second. In terms of efficacy, one of these patients showed no response to placebo or Botox, and the other showed an apparent response to both placebo and Botox, so it is unclear whether the antibodies had any pharmacodynamic effect. (The PI refers to 475 patients in the pivotal studies, not 477, because the patients with pre existing antibodies have been excluded; this seems appropriate.)

Deaths

Six deaths occurred in the pooled safety population including Study 082 and Study 077 (one in the 300 U group, two in the 200 U group, two in the <200 U group, and one in the placebo group). The sponsor provided narrative summaries of each death and these did not suggest that Botox had played any causal role; most of the deaths occurred well after

treatment and the mechanism of death was not consistent with the known pharmacology of Botox.

Safety in Study 082 (Patients with Respiratory Compromise)

Five patients in this small study (n=34) experienced respiratory AEs, one of which was considered by the investigator to be treatment related. This event occurred in a patient in the 200 U group who experienced a severe decrease in pulmonary function tests during treatment cycle 1. The event started on Day 43 post treatment and lasted for 7 days, resolving without apparent sequelae. The time course is not particularly suggestive of a Botox complication and other factors related to the patient's underlying neurological condition may have played a role. Two events of 'dyspnoea' occurred in the placebo group, and the placebo group showed the highest overall incidence of AEs.

Overall, there were no significant changes in pulmonary function, and no difference between groups for the major respiratory parameters (Table 43). A larger study would be required to determine with confidence whether ID Botox can cause respiratory compromise but the evidence available at the time of submission is generally reassuring.

Table 43: Forced vital capacity (L) – Baseline and percent change from baseline (Treatment 1 – Safety population with LOCF imputation, nonparametric analyses).

Timepoint	Parameter	BOTOX ^a		Placebo (N = 10)	p-value ^b for 300 U BOTOX ^a vs placebo	p-value ^b for 200 U BOTOX ^a vs placebo
		300 U (N = 12)	200 U (N = 12)			
Study baseline	N	12	12	10		
	Median	2.790	2.415	2.905		
Week 2	N	12	12	10		
	Median	-3.476	-4.583	-5.656		
	Difference ^b (95% CI) ^c	1.792 (-3.8322, 7.9876)	1.093 (-3.1152, 6.8128)		0.581	0.581
	p-value ^d	0.151	0.102	0.010		
Week 6	N	12	12	10		
	Median	-5.484	-5.230	-3.040		
	Difference ^b (95% CI) ^c	-3.944 (-10.9467, 3.8223)	-3.060 (-12.8904, 3.9676)		0.318	0.334
	p-value ^d	0.027	0.147	0.570		
Week 12	N	7	10	7		
	Median	-1.190	-0.409	0.000		
	Difference ^b (95% CI) ^c	-4.640 (-12.1605, 4.9021)	-0.617 (-7.7581, 6.5789)		0.224	0.810
	p-value ^d	0.016	0.625	0.438		

CI = confidence interval

A positive change from baseline indicates improvement.

^a p-values for between-group differences at each visit are from Wilcoxon rank-sum test.

^b Differences are active treatment minus placebo using the Hodges-Lehmann estimates.

^c 95% CIs for the differences (active treatment minus placebo) are constructed on the Hodges-Lehmann estimates.

^d p-values for within-group changes from study baseline are from Wilcoxon signed-rank tests.

Safety in Study 077 (Patients with IOAB)

Study 077 was not integrated into the safety analysis, but results in this study were consistent with those seen in the larger pooled safety population. In particular, as shown in Table 44, there was a dose dependent increase in the overall rate of AEs, and urinary retention and UTIs were more common at higher doses, greatly exceeding the rates seen in the placebo group.

Table 44: Treatment related adverse events occurring in ≥ 2 patients by primary SOC and preferred term (safety population).

System Organ Class Preferred term	BOTOX [®]					Placebo (N=43)
	300 U (N=55)	200 U (N=52)	150 U (N=50)	100 U (N=55)	50 U (N=56)	
Overall	22 (40.0%)	20 (38.5%)	20 (40.0%)	20 (36.4%)	17 (30.4%)	8 (18.6%)
Renal & urinary disorders	15 (27.3%)	13 (25.0%)	14 (28.0%)	13 (23.6%)	11 (19.6%)	4 (9.3%)
Urinary retention	13 (23.6%)	11 (21.2%)	13 (26.0%)	10 (18.2%)	5 (8.9%)	1 (2.3%)
Urethritis noninfective	2 (3.6%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bladder pain	2 (3.6%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	1 (1.8%)	1 (2.3%)
Dysuria	0 (0.0%)	1 (1.9%)	2 (4.0%)	0 (0.0%)	3 (5.4%)	1 (2.3%)
Urinary hesitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)
Pollakiuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	2 (3.6%)	0 (0.0%)
Infections & infestations	7 (12.7%)	11 (21.2%)	6 (12.0%)	7 (12.7%)	3 (5.4%)	1 (2.3%)
Urinary tract infection	7 (12.7%)	9 (17.3%)	6 (12.0%)	6 (10.9%)	3 (5.4%)	1 (2.3%)
Influenza	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	1 (1.8%)	4 (7.7%)	4 (8.0%)	2 (3.6%)	4 (7.1%)	0 (0.0%)
Residual urine volume *	1 (1.8%)	4 (7.7%)	3 (6.0%)	1 (1.8%)	3 (5.4%)	0 (0.0%)
Gastrointestinal disorders	1 (1.8%)	1 (1.9%)	1 (2.0%)	3 (5.5%)	4 (7.1%)	3 (7.0%)
Abdominal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	2 (3.6%)	2 (4.7%)

* Note that 1 patient in each of the 200 U and 100 U BOTOX[®] groups also experienced adverse events of residual urine that mapped to the Renal and urinary disorders SOC

The PVR assessment in this study were consistent with the findings in the general safety population, in that the 200 U group showed a mean increase of 107.6 mL at Week 2, and 82.1 mL at Week 6, compared to mean changes within 1 mL in the placebo group. The difference relative to placebo was statistically significant.

Comments on the Risk Management Plan

The sponsor's RMP was reviewed in the context of the submitted data.

With respect to the broad use of Botox for its full range of conditions, no new safety signals emerged from the submitted studies and the RMP appears appropriate.

With respect to the use of Botox in NDO, the RMP identifies two potential problems: urinary tract infections and urinary retention. For UTIs, the sponsor's risk minimisation strategy is stated as:

"This identified safety concern is proposed to be addressed in the Summary of Product Characteristics (SPC) upon approval with the following instructions: (a) for the use of prophylactic antibiotics to be administered 1-3 days pre treatment, on treatment day, and 1-3 days post treatment; (b) Acute urinary tract infection as a contraindication for treatment with ID Botox for NDO."

This recommendation deals with UTIs directly related to the injection procedure itself, but not to UTIs related to impaired bladder emptying and an increased need for catheterisation. As discussed below in relation to the proposed PI, there is also a need to inform patients that they may have UTIs as a result of impaired bladder emptying, and patients should be monitored for elevated PVR. The RMP should reflect the increased risk of UTIs via this additional mechanism.

With respect to impaired bladder emptying, the recommendation is:

"This identified safety concern is proposed to be addressed in the SPC upon approval with the following instructions:

In non catheterising patients that the PVR be assessed within 2 weeks post treatment and periodically as medically appropriate up to 12 weeks; and that patients be instructed to contact their physician if they experience difficulties in voiding as

catheterisation may be require. Continuing assessment of urinary retention rates in the ongoing long term follow up study (Study 094) and the ongoing Phase 3 study in patients with respiratory compromise (Study 082) [are recommended]."

This recommendation is appropriate.

Overall Summary of Safety

The overall safety profile of Botox appears acceptable, but it should be used in caution with patients in whom worsening weakness could have serious consequences. The literature already contains some cases of apparent systemic spread of toxin when Botox has been used for a variety of indications. In the submitted studies, there was an excess of weakness in recipients of Botox relative to placebo, but not when treatment groups were observed over comparable time periods. Similarly, although there was an increased number of relapses in Botox recipients, and Kaplan-Meier curves of MS relapses suggested that these were more common with Botox, there was no convincing change in MS annualised relapse rate.

For the new proposed indication of NDO, specific concerns arise related to poor bladder emptying. Compared to placebo recipients, patients receiving Botox 200 U had an increased incidence of urinary retention (17.2% versus 2.9%) and urinary tract infections (24.4% versus 17.3%) in the first 12 weeks after treatment. PVR values were significantly increased, and offset some of the gains in the bladder's holding capacity. A higher proportion of Botox recipients started catheterisation (25.5% versus 10.1% by Week 12), and Botox should only be considered in patients who are prepared to initiate catheterisation as a direct result of their Botox treatment. Of note, initiation of catheterisation did not have an adverse impact on patients' quality of life as assessed by the I-QOL. Most of these urological complications were increased in the 300 U group relative to the 200 U group, despite an overall similarity between the two doses on efficacy measures, justifying the choice of 200 U as the recommended dose.

Constipation was increased in patients who received 300 U, possibly reflecting some local spread of toxin, but the incidence of constipation was similar in the 200 U and placebo groups.

The procedure itself was generally well tolerated, but caused haematuria or procedural pain in some patients, and autonomic dysreflexia was observed in susceptible patients.

First Round Evaluation of Clinical Data

First Round Risk-Benefit Balance

The efficacy benefits of ID Botox consist of a reduction in incontinence episodes, and an improvement in bladder pressures. For patients using catheterisation, there is a clear increase in the holding capacity of the bladder as reflected by the maximum cystometric capacity, though this benefit is considerably offset in non-catheterised patients by an increase in the post void residual volume.

The magnitude of the observed benefit in the pivotal studies was clinically meaningful, with reductions in incontinence frequency of about 21 episodes per week at Week 6 and Week 12, compared to reductions of only 10 in the placebo group, from a baseline of 31-32 episodes per week. Furthermore, about 37-40% of Botox recipients achieved the highly desirable state of being "dry", with a 100% reduction in incontinence, compared to only 9% of placebo recipients.

Maximum cystometric capacity increased by 153.6 mL in the pooled 200 U groups, compared to only 11.9 mL in the placebo group, and MDP was decreased by 30-32 cmH₂O from a baseline of 45-52 cmH₂O, compared to a trivial mean increase in the placebo group

of 1 cmH₂O. This might be expected to reduce the risk of reflux nephropathy, though such an effect was not directly demonstrated, and the increased risk of UTIs in the placebo group might offset the potential benefit, because any urine that did reflux would have a higher chance of being infected.

The median duration of effect, based on time to return to an incontinence level within 50% of baseline, was 294-301 days in the active groups, compared to 165 days in the placebo group. The median time to request retreatment was 265-269 days in the active groups, compared to 92 days with placebo. This interval between treatments is likely to meet with a reasonable patient acceptance, and means that the risk of procedural complications will only be faced 1-2 times per year. Patients are likely to find this acceptable if they have a notable improvement in their continence, and if the response is unsatisfactory they are unlikely to pursue further treatments.

The first cost of this efficacy benefit is a fairly small procedural risk: 3-4% procedural complications were observed, but no serious procedural complications. There is also a small theoretical risk of systemic spread of Botox, which could be very serious if it occurred, but no convincing evidence of this emerged in the pivotal studies. Some patients will experience local spread and an increased incidence of constipation was observed with treatment at 300 U, but this risk appears minor with the proposed dose of 200 U. In the first 12 weeks after treatment, it was observed in 4.3%, 1.5% and 1.5% of the 300 U, 200 U and placebo groups, respectively.

The main risk of treatment is that bladder emptying is likely to be weakened by Botox. This is not an unforeseen complication but intrinsically related to its mode of action. This is much less of an issue for patients who are already using an intermittent catheter because they have a means of achieving almost full drainage despite detrusor weakness. On the other hand, for patients not using a catheter prior to Botox treatment, this is an important issue that will need to be discussed in detail and they should not proceed with the treatment unless they are prepared to initiate catheterisation. A significant proportion of patients will need to commence catheterisation following Botox as a direct result of treatment, over and above those patients who would need to commence it as part of their underlying neurological illness. Considering the subgroup in the pivotal studies who were not already using CIC at baseline, only 10.1% of placebo recipients had commenced CIC at Week 12, compared to about 35.9% of the 300 U group and 25.5% of the 200 U group. However, commencement of catheterisation was not associated with an impaired quality of life as assessed with quality of life instruments. This is not surprising for anyone who has treated such patients. For many patients with urge incontinence, even outside the setting of Botox treatment, commencement of catheterisation can in fact restore a sense of control over bladder function, and give patients a means of emptying their bladder fully at a convenient time. If the commencement of catheterisation is accompanied by significantly improved continence, as in the pivotal studies, most patients are likely to see this as an acceptable trade off.

The other downside of impaired bladder emptying is that the risk of urinary tract infections increases whenever a stagnant pool of urine remains in the bladder to provide a safe haven for bacteria, instead of being flushed away with voiding. The risk of urinary tract infections was increased by Botox in the pivotal studies, particularly in patients who commenced catheterisation, or who had elevated post void residuals and failed to commence catheterisation. In the pivotal studies, the risk of infections for those who were already using a catheter at baseline was only mildly elevated in both active groups compared to placebo (UTI incidence: 300 U group, 29.2%; 200 U, 22% versus placebo, 20.7%), but it was much more marked in the group who were *not* using CIC at baseline (42.6% and 40.4% versus 11.9%, respectively, for those who subsequently commenced

CIC; 26.1% and 21.3% versus 16.4%, for those who continued not to use CIC). The risk of UTIs might be even higher outside a trial setting, particularly if clinicians fail to monitor for elevated PVRs.

A significant weakness of the submitted data was a lack of placebo controlled data beyond the first treatment cycle, and the risk-benefit of subsequent treatments is thus uncertain. Uncontrolled data in extension studies did not raise any new concerns, however. For many other indications, serial Botox has been used for multiple cycles without evidence of new safety issues.

In summary, Botox treatment is associated with a clear reduction in incontinence episodes, a chance of achieving the “dry” status, but also a clear risk of impaired bladder emptying, requiring commencement of catheterisation and an increased risk of UTIs. The balance of risk and benefit will vary for individual patients, but appears favourable overall, and on average quality of life appeared improved in patients treated with Botox, even in those commencing catheterisation.

First Round List of Questions

It was not clear, from the submitted data, how much the continence gains due to Botox were offset by continence losses during Botox induced UTIs, because bladder diaries were not used during UTIs.

Please comment on this issue and perform an explicit sensitivity analysis on the data to determine to what extent this modifies your conclusions. If it is assumed, pessimistically, that incontinence during UTIs was always equal to the worst incontinence levels observed in the entire population, does the primary efficacy variable (incontinence episodes per week) still show a significant treatment effect?

The analysis of MCC in isolation from PRV overestimates the benefit in bladder-holding capacity for any patient unable or unwilling to empty the bladder with a catheter.

Please:

- Re-do all efficacy analyses in the pivotal studies (515 & 516) involving the single parameter MCC. In these reanalyses, the latter parameter MCC is to be supplemented with the parameter MCC-PVR, that is, the arithmetic difference between the MCC and the PVR;
- Present the results of these reanalyses in tabulated form and explain in detail all working;
- Compare and contrast the results of the original analyses (that is, those based on the parameter MCC) with those of the reanalyses (that is, those based on the parameter MCC-PVR). The comparison must focus on the clinical significance of any results.

First Round Conditions of Registration

The following conditions of registration are proposed:

- The sponsor is required to supply as evaluable data, within the context of a category 1 application, the final study report for the extension Study 094. This report is to be supplied to the TGA as soon as possible after the completion of the study.
- The sponsor is required to supply as evaluable data, within the context of a category 1 application, the final study report for the respiratory safety Study 082. This report is to be supplied to the TGA as soon as possible after the completion of the study.

- The sponsor is required to inform the TGA if the ongoing study program for the indication of idiopathic overactive bladder is abandoned or modified in any way with the reasons for any such changes. The sponsor is also required to submit all final study reports of Phase 3 studies for this indication, whether completed or terminated early for any reason, even if the study results are negative. All such data is to be submitted as evaluable data, within the context of a category 1 application and is to be submitted as soon as possible once the final study report becomes available.

First Round Conclusions and Recommendations

Conclusions

- In the setting of the second line treatment of neurogenic detrusor overactivity, ID Botox (200 U in divided injections) significantly reduced the frequency of urinary urge incontinence, compared to placebo.
- Botox improved most urodynamic parameters associated with detrusor overactivity, including maximum cystometric capacity and maximum detrusor pressure, but it increased post void residual volumes.
- Botox improved incontinence related quality of life.
- Botox increased the risk of urinary retention and urinary tract infection, and caused some patients to take up catheterisation.
- Botox carries a low but poorly defined risk of causing weakness at sites distant from the bladder.
- Results were broadly consistent across aetiological subgroups, and efficacy was demonstrated in patients with MS or SCI, in males and in females, and in patients using or not using anticholinergic agents at baseline.
- The efficacy and safety of repeat doses remains poorly characterised, because placebo-controlled data is unavailable, but the existing *uncontrolled* evidence is broadly reassuring.
- Botox did not have acceptable efficacy in a study of idiopathic overactive bladder.
- The submitted studies raised some minor methodological concerns, including the failure to count episodes of incontinence during urinary tract infections.
- The proposed PI was broadly acceptable but contained some potentially misleading sections.

Recommendations

- It was not clear, from the submitted data, how much the continence gains due to Botox were offset by continence losses during Botox induced UTIs, because bladder diaries were not used during UTIs. The sponsor should be asked to comment on this issue and to perform an explicit sensitivity analysis on the data to determine to what extent this modifies their conclusions.
- The sponsor should be asked to analyse the efficacy parameter MCC-PVR, as described in the List of Questions.
- Provided that the sponsor's response to the above items are satisfactory, Botox 200 U should be approved for the second line treatment of neurogenic detrusor overactivity.

- Conditions of such registration are outlined above.
- The PI should be revised along the lines suggested.
- Botox should *not* be approved for the treatment of overactive bladder in other contexts, unless further data is submitted that demonstrates efficacy in this population.

Second Round Evaluation of Clinical Data

In a second round of evaluation, the sponsor responded to nine questions posed by the TGA. This second round was conducted in two stages, because the sponsor's initial responses to the first two questions did not include the requested additional analyses, and were therefore not considered adequate. After further discussion, the sponsor has resubmitted analyses that fully address the original concerns. The discussion below therefore refers to the 'Initial' and 'Final' responses to these two questions.

Question 1: Effect of UTIs on Gains in Urinary Continence

"It was not clear, from the submitted data, how much the continence gains due to Botox were offset by continence losses during Botox induced UTIs, because bladder diaries were not used during UTIs. Please comment on this issue and perform an explicit sensitivity analysis on the data to determine to what extent this modifies your conclusions."

Original Rationale Behind the Question

The primary efficacy variable for the pivotal studies was the number of episodes of incontinence per week as recorded in a patient diary. Patients were asked *not* to fill out their diaries during symptomatic UTIs, presumably on the grounds that their incontinence frequency at this time was not reflective of their true underlying incontinence. Indeed, it seems likely that urge incontinence was increased during symptomatic UTIs, because urinary urgency, along with dysuria, is one of the hallmarks of a UTI even in a population without neurogenic detrusor overactivity. Although efficacy data during symptomatic UTIs is therefore likely to have been confounded by the effects of infection, this is a real, rather than spurious effect, and analysis of incontinence episodes at this time is a legitimate part of assessing the patient's overall urological status. There appear to be no good grounds for censoring such data, though there might be defensible grounds for analysing it separately.

UTIs were significantly more common in Botox recipients, which is likely to reflect the fact that Botox impairs bladder emptying. Botox recipients are therefore potentially more likely to suffer UTI induced incontinence – though it is also possible that the Botox induced relaxation of the bladder lessened this expected effect of infection. Unfortunately, because this data was censored, we have no evidence one way or another.

The original concern was that the beneficial reductions in the frequency of incontinence reported in the submission and the PI are overstated because not all incontinence was recorded. Some was censored, and this censoring was greatest in the active group. This could lead to bias in two ways:

1. Incontinence frequency is recorded as episodes divided by time. If the censored *time* was kept in the denominator but the censored *episodes* were not counted in the numerator, then this would spuriously reduce the recorded incontinence frequency, and the effect would be greatest in the active group. ***The sponsor should confirm that they did not handle the data in this way.***
2. If recipients of active therapy had more incontinence associated with UTIs, but less incontinence at other times, then it is the overall balance between these positive

and negative effects that is important. Censoring the negative effects could disguise the nature of this balance. For instance, if a patient had two good weeks in which her incontinence was reduced by active treatment by 5 episodes per week, and then she had a UTI induced by Botox and had 20 extra episodes in that week, she would have had an overall *increase* of 10 episodes relative to the untreated state. The sponsor's method of analysis would only count her good weeks. Even if the incontinence associated with UTIs was offset by the gains, such censorship could still lead to an exaggerated assessment of efficacy

Given that the appropriate data was not collected, it is difficult to determine whether such bias was significant. A sensitivity analysis could, however, be performed by assigning *notional* incontinence values during censored diary days and seeing the effect of this new, fictional data on the estimated efficacy benefit.

In such a sensitivity analysis, reassurance about the potential for bias could come in either of two forms:

1. It could be demonstrated that, even when censored days are assigned a pessimistic but realistic number of notional incontinence episodes, the primary efficacy outcome remains clinically and statistically significant.
2. It could be demonstrated that the number of notional incontinence episodes that would have to be assigned to negate the efficacy effect is unrealistically pessimistic.

Note that the concern is not that the studies have produced an entirely spurious treatment effect, but that the primary efficacy variable has been subjected to bias. The issue at stake is whether regulatory authorities like the TGA should accept a study design that introduces an avoidable bias into data collection for the primary efficacy variable.

Sponsor's Initial Response

The sponsor began by noting that "The protocol stated that patient bladder diary was not to be collected during a *symptomatic* urinary tract infection (UTI)... Since the AE of UTI was not based on it being a symptomatic UTI, it cannot be confirmed that diaries were not completed at the time of a UTI adverse event."

This merely means that not all UTIs were censored. The question could have been phrased more explicitly, in terms of 'symptomatic' UTIs, but the question clearly refers to patients not filling out diaries, which implies that it is symptomatic UTIs that are being discussed. The UTIs that *were* associated with censoring – the symptomatic ones – are the very ones most likely to have been associated with increased incontinence.

The sponsor then presents two analyses: a subgroup analysis based on the presence or absence of a UTI adverse event, using the primary (still censored) efficacy variable, and a similar subgroup analysis using the secondary I-QOL variable.

The sponsor writes:

"The higher rate of the adverse event of UTI in the Botox groups compared to the placebo group during the first 12 weeks post treatment was apparent in those patients who were not using CIC prior to treatment. An analysis has therefore been performed in this subset of patients to assess the change in urinary incontinence in the first 12 weeks post treatment in patients who either (a) did not have an adverse event of UTI within this first 12 week period, or (b) who did have an adverse event of UTI within the 12 week period. The results are summarised in Table 45 (below); the median change in weekly urinary incontinence episodes is presented in addition to the mean in view of the small number of patients per treatment group due to the subsetting. This analysis

shows that the magnitude of reduction in urinary incontinence was consistently higher in the Botox treatment groups compared to the placebo group, regardless of whether an AE of UTI was reported post treatment.”

Table 45: Weekly urinary incontinence episodes in first 12 weeks of treatment cycle 1 by UTI status in patients who were not using CIC prior to treatment – Baseline and change from baseline (ITT population without LOCF imputation).

Time point	Attribute	No UTI Post-treatment ^b (Studies 515/516 pooled)			UTI Post-treatment ^b (Studies 515/516 pooled)		
		BOTON ^a			BOTON ^a		
		300 U (N = 67)	200 U (N = 73)	Placebo (N = 87)	300 U (N = 35)	200 U (N = 32)	Placebo (N = 13)
Baseline	N	67	73	87	35	32	13
	Mean \pm SD	33.1 \pm 21.85	39.4 \pm 26.12	34.5 \pm 24.87	28.2 \pm 12.61	31.3 \pm 16.83	38.6 \pm 35.38
	Median	27.0	28.0	26.0	25.0	25.5	24.0
Week 2	N	59	70	81	33	30	13
	Mean Change	-18.5	-21.1	-14.1	-15.8	-18.2	-8.4
	Median Change	-17.0	-19.0	-11.0	-15.0	-15.5	-6.0
	p-value *	0.216	0.347		0.358	0.553	
Week 6	N	63	68	83	31	31	11
	Mean Change	-24.1	-23.1	-14.8	-18.9	-21.3	-16.6
	Median Change	-21.0	-20.0	-12.0	-19.0	-19.0	-7.0
	p-value *	0.002	0.122		0.018	0.032	
Week 12	N	57	66	78	31	30	12
	Mean Change	-21.4	-22.7	-13.8	-20.4	-22.8	-15.9
	Median Change	-19.0	-20.0	-8.5	-19.0	-20.5	-8.5
	p-value *	0.007	0.027		0.213	0.280	

CIC = clean intermittent catheterisation; ITT = intent-to-treat; LOCF = last observation carried forward; UTI = urinary tract infection

* Pairwise comparison versus placebo is based on an ANCOVA model with baseline weekly frequency of urinary incontinence episodes as covariate and treatment group, aetiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors.

^b UTI status based on the adverse event of UTI with start date within first 12 weeks of treatment cycle 1

Overall, it is clear that, using the *censored* primary efficacy variable, the occurrence of a UTI adverse event did not prevent active treatment from achieving a statistically significant reduction in incontinence frequency for at least one time point (Week 6), and a favourable trend at other time points. The magnitude of the benefit appeared similar to that seen in non UTI patients.

This is not a surprising result, and would be expected *even if the potential bias being flagged as a concern was real and substantial*. Even if a symptomatic UTI caused a *massive* increase in incontinence, this would not be detected by any analysis that specifically censored data collection during that increased incontinence. A Botox recipient who had an improvement in one week, followed by a UTI and an associated deterioration in the next week, and then recovered with improvement in the third week, would enter this subgroup analysis in the UTI subgroup, but *only the good weeks would be counted*. Only if the UTI continued to produce increased incontinence *after* the patient had apparently recovered (and therefore resumed filling out the diary), would this type of analysis be expected to find an impact on efficacy. Furthermore, inclusion of *asymptomatic* UTIs in this analysis dilutes the effect being sought. It is the UTIs leading to censoring that are of interest, not all UTIs.

The sponsor also presented an analysis of I-QOL, stating:

“An additional analysis has been performed on the I-QOL total summary score by post treatment UTI status using the same subpopulations described for the analysis performed for urinary incontinence. This analysis also confirms the lack of impact of UTI on I-QOL (Table 46) as the magnitude of increase in I-QOL was consistently higher in the Botox treatment groups compared to placebo, irrespective of post treatment UTI status. The I-QOL score provides indirect support for an improvement in incontinence regardless of UTI status, since a decrease in incontinence would be expected to strongly correlate with improvements in I-QOL scores.”

Table 46: I-QOL total summary score in first 12 weeks of treatment cycle 1 by UTI status in patients who were not using CIC prior to treatment – Baseline and change from baseline (ITT population without LOCF imputation).

Time point	Attribute	No UTI Post-treatment ^b (Studies: S15/S16 pooled)			UTI Post-treatment ^b (Studies: S15/S16 pooled)		
		BOTOX ^a			BOTOX ^a		
		300 U (N = 67)	200 U (N = 73)	Placebo (N = 87)	300 U (N = 35)	200 U (N = 32)	Placebo (N = 13)
Baseline	N	67	73	87	35	32	13
	Mean ± SD	33.76 ± 19.53	32.63 ± 20.06	30.49 ± 15.35	31.33 ± 19.35	33.47 ± 15.43	39.17 ± 24.97
	Median	33.00	29.50	27.30	27.30	33.15	29.50
Week 6	N	61	70	83	32	32	13
	Mean Change	32.59	22.69	15.01	32.36	27.12	5.95
	Median Change	34.10	15.60	9.00	34.70	21.60	5.70
	p-value *	<0.001	0.023		0.163	0.04	
Week 12	N	59	68	84	34	32	12
	Mean Change	34.74	27.25	11.49	36.20	32.75	10.88
	Median Change	36.40	25.60	7.90	37.50	26.75	7.35
	p-value *	<0.001	<0.001		0.196	0.249	

CIC = clean intermittent catheterisation; I-QOL = Incontinence quality of life; ITT = intent-to-treat; LOCF = last observation carried forward; UTI = urinary tract infection

* pairwise comparison versus placebo is based on an ANCOVA model with baseline weekly frequency of urinary incontinence episode as covariate and treatment group, aetiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors.

This argument is a reasonable defence of the internal validity of the pivotal studies, but it is somewhat irrelevant to the question being asked. It does not directly address the concern that numerical estimates of incontinence frequency might have been biased by diary censoring, although it does suggest that any biasing was not of such a magnitude that the entire treatment effect is likely to be spurious.

The I-QOL results shows that patients with at least one UTI clearly *thought* their incontinence was better, and this subjective assessment presumably extends across censored periods; even though incontinence at this time was not recorded in their diary, patients are likely to have factored in the increased UTIs and any associated incontinence. The balance between the incontinence gains from Botox and the negative effects of Botox induced UTIs, at least according to patients, seems positive. The concerns about some numerical bias in the primary endpoint remain.

Finally, the sponsor refers to secondary efficacy variables that were not subject to censorship:

“Additional evidence of efficacy regardless of UTI status comes from the urodynamic assessments; these assessments were performed regardless of the presence of a symptomatic UTI. Thus, as presented in the original submission, significant

improvements in urodynamic parameters were observed following Botox treatment. Large and significant increases in MCC were demonstrated and a high proportion of patients did not have an IDC following Botox treatment."

This observation is generally reassuring, though it is hard to know if patients experiencing a UTI sometimes chose to reschedule their urodynamic studies because of the UTI. At any rate, these are merely secondary efficacy variables. The concern is that the primary efficacy variable was subject to bias, not that the entire treatment effect was spurious.

Adequacy of the Response

The sponsor has not acknowledged the original concern at all, and the analysis submitted in response does not directly address the question asked. It is still unclear what effect diary censorship has had on the magnitude of the observed treatment effect for the primary efficacy variable. Concerns about censored data cannot be addressed by any subgroup analysis that uses the suspect data.

Residual Issues

The original question remains valid. Even though the numerical effect of the censorship might be small, the sponsor has been asked to perform a sensitivity analysis to allow regulatory authorities and clinicians to estimate the impact of that bias. They have not performed such an analysis. The sponsor should also confirm that censored diary time was excluded from the denominator in calculating incontinence frequency.

Sponsor's Final Response

The sponsor subsequently proposed:

"a sensitivity analysis on the Week 6 urinary incontinence data. For patients who have a UTI onset date during the week 6 visit window and do not have a complete 7 day diary, their week 6 urinary incontinence (UI) value will be replaced by their baseline weekly UI value. For the patients not reporting a UTI during the week 6 window, this analysis will be performed using observed data without LOCF imputation."

The TGA responded as follows:

"The evaluator has asked that Allergan increase the robustness of the sensitivity analysis by including one analysis with imputation of baseline incontinence, one with a 50% increase from baseline, and another with a 100% increase from baseline and examine the effects of such imputations on therapeutic effect."

The sponsor complied with this request, and the data is shown in Table 47.

Table 47: Weekly urinary incontinence at Week 6 including patients who had a UTI during Week 6 and missing diary days with imputation of baseline, 50% increase from baseline, and 100% increase from baseline in pooled data (Studies 515 and 516, ITT population).

Attribute	191622-515/516 Pooled		
	BOTOX ^a		
	300U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Imputation of baseline			
N	203	217	223
Mean change	-22.2	-21.0	-10.8
LS mean change	-23.0	-19.6	-10.8
Difference vs. placebo	-12.15	-8.83	
p-value ^a	< 0.001	< 0.001	
Imputation of 50% increase from baseline			
N	203	217	223
Mean change	-21.6	-20.8	-10.5
LS mean change	-22.6	-19.3	-10.5
Difference vs. placebo	-12.07	-8.83	
p-value ^a	< 0.001	< 0.001	
Imputation of 100% increase from baseline			
N	203	217	223
Mean change	-21.0	-20.6	-10.2
LS mean change	-22.2	-19.0	-10.2
Difference vs. placebo	-11.99	-8.83	
p-value ^a	< 0.001	< 0.001	

LS=least square; LOCF=last observation carried forward

Note: For patients not reporting a UTI, the observed data was used without LOCF

a P-values for between-group comparison (versus placebo) at each visit are based on ANCOVA model with baseline value as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

The number of patients affected by diary censoring was only 17, as reported by the sponsor:

“There were 75 patients who reported a UTI within the Week 6 analysis window (day 30 to day 64). Among these 75 patients, 58 had the full seven day diary data, 11 patients had partial diary data (3 to 6 days), one patient had two or less days of diary data, and five patients had no diary data. Therefore a total of 17 patients’ data (eight patients from the 300 U group, four patients from the 200 U group and five from the placebo group) were imputed as per the reviewer’s request and the results are summarised in Table 47.”

The sponsor also confirmed that the censored diary days were handled correctly in terms of their non contribution to both the numerator and the denominator in all calculations of incontinence frequency.

This final response is reassuring. Even using the most pessimistic imputation method (which assumes that patients had a doubling of baseline incontinence during diary days that were incomplete because of UTIs), the treatment effect was statistically significant ($p < 0.001$ in both dose groups). Also, the treatment effect inferred by this pessimistic method had a magnitude that is likely to be clinically useful and meaningful to the patients if it is reproduced in actual practice: recipients of the proposed 200 U dose had a mean reduction of 20.6 incontinence episodes per week, compared to a reduction of only 10.2 in the placebo group. This is very similar to that observed in the initial primary analysis with standard LOCF imputation.

In conclusion, this methodological issue did not produce significant bias and the sensitivity analysis confirms the robustness of the claimed treatment effect. The difference between

the sensitivity analysis and the original analysis is so small that the PI does not need to address it.

Question 2: Reanalysis of MCC in Pivotal Studies

"Please:

- a. Redo all efficacy analyses in the pivotal studies (Studies 515 and 516) involving the single parameter MCC (maximum cystometric capacity). In these reanalyses, the latter parameter MCC is to be replaced by the parameter MCC-PVR, that is, the arithmetic difference between the MCC and the PVR.*
- b. Present the results of these reanalyses in tabulated form and explain in detail all working.*
- c. Compare and contrast the results of the original analyses, that is, those based on the parameter MCC with those of the reanalyses, that is, those based on the parameter MCC -PVR. The comparison must focus on the clinical significance of any results." (Note that one draft version of this question used the term 'cystoscopic' in place of 'cystometric'.)*

Original Rationale Behind the Question

ID Botox reduces bladder muscle activity, with resulting benefits in improved urinary continence, decreased urgency and increased holding capacity. This benefit comes at the expense of a variable degree of detrusor weakness and underactivity, leading to worsened bladder emptying and an increased risk of UTIs, as discussed in detail in the first round evaluation. In the pivotal studies, the sponsor performed urodynamic studies to document the increased holding capacity of the bladder, as reflected in the MCC, and they performed ultrasound of the bladder to document adequacy of bladder emptying, as reflected in the PVR. Both volumes increased with active treatment.

For patients who achieve nearly total emptying with the help of clean intermittent catheterisation, the PVR is of somewhat academic interest, because the *post catheterisation residual volume* is more relevant, and is likely to be very low. For patients not using a catheter, however, the PVR is very important. The residual volume not only influences the risk of UTIs, it offsets the gains in holding capacity. For instance, if the MCC increases by 150 mL, and the PVR also increases by 150 mL, the amount of urine that can be stored between voids is essentially unchanged: the dynamic range of the bladder is merely moved to higher volumes. Given that the increase in MCC was discussed extensively in the efficacy section of the submission, it would have been appropriate to consider it in relation to the PVR, and hence to consider to what extent the increased bladder capacity was actually voidable, and hence available for new storage between voids. Instead, the sponsor neglected these considerations entirely, and only presented the PVR in the safety section.

The original, first round evaluation addressed this issue by comparing the group means for MCC and PVR, as follows:

"Considering the PVR, a clear increase was seen in both active groups by Week 2, with the 300 U group showing a mean increase of 176.0 mL, the 200 U group showing a mean increase of 94.1 mL, and the placebo group essentially showing no change (+3.3 mL). This difference was highly significant ($p < 0.001$). Compared to the changes in MCC reported as an efficacy benefit [...], it can be seen that, in broad terms, most of the increased capacity of the bladder was volume that could not be voluntarily voided, and was therefore not available for urine storage in non catheterised patients. For the pooled 300 U group in the pivotal studies, MCC increased by 163.1 mL, and for the

pooled 300 U group in the safety analysis, the PVR increased by a slightly larger amount, 176.0 mL (note that the two populations overlap, but are not identical, as the PVR values are derived from patients not using CIC at baseline). The net change in available holding capacity of the bladder is therefore minimal (or comes out as a net loss, if those two figures are taken at face value), unless the patient is prepared to undergo catheterisation to ensure emptying. The results in the 200 U group were somewhat better, but even in that group the increased mean MCC (153.6 mL) is less impressive once it has been 'discounted' by the mean increase in PVR (94.1 mL)."

This simplistic analysis suggests that, for the higher dose, *available storage in the bladder was actually reduced by Botox* – something that would never be guessed by reading the sponsor's own discussion of the efficacy results. Such an analysis is clearly suboptimal, however, because what is important is how these two volumes relate to each other in individual patients. For this reason, the sponsor was asked to compare the change in MCC to the changes in PVR on a per patient basis. Obviously, because these parameters were measured by different techniques at somewhat different times, this is an indirect assessment of the actual reserve of the bladder, but it is better than no estimate at all.

Sponsor's Response

The sponsor refused to perform the requested analysis, arguing that it was impossible:

"As described in the study protocols, the methodology used for the urodynamic assessments, which included the determination of the MCC, required that the patient's bladder was emptied via the catheter at the start of the urodynamic procedure, prior to the initiation of bladder filling. Since the patient's bladder was emptied prior to the start of the urodynamic assessment, the infused volume used to determine MCC is therefore the actual MCC.

PVR urine volume was not measured and therefore not captured at the end of the urodynamic assessment. Therefore, the requested calculation of MCC minus PVR cannot be performed. Even if PVR was recorded on the same day visit as the urodynamic assessment was performed, this was independent of the urodynamic assessment and cannot be linked to the urodynamic assessment. The PVR was measured via ultrasound and was not measured in the context of the urodynamic assessment."

Note that the sponsor is not merely suggesting that the analysis of MCC minus PVR is likely to be flawed, because the two parameters were collected by different methods on different days, but that the calculation "cannot be performed". That is, despite having an MCC for each patient and a PVR for each patient, they are unable or unwilling to subtract one from the other.

Their final comment suggests that they might not have understood the question at all:

"The sponsor would like to point out that the MCC data presented in the submission reflects the true MCC and is not influenced by any PVR urine the patient may have had in their bladder prior to the urodynamic procedure as the patient's bladder was emptied at the start of urodynamics."

The concern was not that the MCC had been mismeasured in any way. The concern was that the MCC is not a true reflection of available storage capacity in the patient's day-to-day life unless the patient starts each voiding cycle with an empty bladder, which cannot always be guaranteed. Without a catheter, a patient starts the voiding cycle with a volume of urine already in their bladder (the PVR) and can only add a limited volume (V , where $V = \text{MCC} - \text{PVR}$) until reaching the full state (the MCC). It is V that determines how often a

patient needs to empty the bladder, not the MCC, and it is an estimate of V that was requested.

Adequacy of the Response

This response is totally inadequate. The sponsor is free to point out the potential flaws in such an analysis, but to say that it cannot be performed is nonsensical. They have individual patient values for MCC and for PVR, so it must be possible to calculate MCC-PVR. Their response is like saying a body mass index cannot be calculated or even estimated because the patient's height was measured on one day and the patient's weight on another.

It is true, of course, that the PVR would *ideally* be measured on the same day and with similar technology as the MCC, to allow a more direct comparison, but a PVR measured by ultrasound, in the same general time period as the urodynamic studies, has direct bearing on what bladder emptying *would have been*, had it actually been measured on the day of the urodynamic studies. (And, conversely, the notional MCC on the day of the ultrasound is likely to be quite similar to, or at least highly correlated with, the actual MCC recorded on the day of the urodynamic studies). The whole point of measuring these parameters, in both the clinical and trial setting, is that they give a measure of lasting significance despite some day to day variability. Clinicians routinely order these tests, see the patient 1-2 weeks after the test, and make decisions based on the results. There would be no point in ordering the tests if their validity expired completely at the end of the day, and they would be meaningless as secondary efficacy variables if they did not reflect the patient's urodynamic status for an extended, clinically meaningful period.

Residual Issues

Following the initial response to this question, the original question remained unanswered.

Sponsor's Final Response

The sponsor eventually agreed to provide the requested analysis in a second stage of the Round 2 evaluation. They presented it as follows:

"Per the request of the TGA, a separate MCC analysis has now been conducted (MCC – PVR) in the subset of patients who were not performing CIC both at baseline and at Week 6 post treatment. The results from this analysis are presented in Table 48 alongside the results from the original analysis of MCC in the overall ITT population (all patients). As can be seen, the improvement in this 'modified' MCC (V, where V = MCC-PVR) is not as large as in the overall study population. However, it should be noted that the numbers of patients for whom both an MCC and PVR is available both at baseline and Week 6 are smaller than that for which the overall sample size was planned. In addition, the standard deviations for these 'modified' MCC data are far larger than in the overall study population. Hence, the comparison of Botox 200 U and placebo is not statistically significant in this 'modified' MCC population compared to the overall study population."

This data appears in Table 48.

Table 48: ‘Modified’ MCC (MCC minus PVR urine volume [mL]) versus MCC in overall ITT population – Baseline and change from baseline at Week 6 in treatment cycle 1 (pooled data, Studies 515 and 516).

Timepoint	Attribute	191622-515/516 Pooled MCC – PVR (Only Patients who were not Performing CIC at Baseline ^b)			191622-515/516 Pooled MCC (Overall ITT Population - All Patients)		
		BOTOX ^a			BOTOX ^a		
		300U (N = 71)	200 U (N = 90)	Placebo (N = 83)	300 U (N = 223)	200 U (N = 227)	Placebo (N = 241)
Baseline	N	71	90	83	223	227	241
	Mean	199.0	175.6	165.6	252.2	250.2	253.5
	SD	173.43	167.31	162.03	146.40	151.35	141.86
Week 6	N	71	90	83	190	211	214
	Mean change	46.4	29.1	-13.0	163.1	153.6	11.9
	SD	242.36	204.56	120.62	176.15	167.81	134.25
	LS Mean difference vs placebo	97.81	44.46		150.65	133.55	
	p-value ^a	0.010	0.191		< 0.001	< 0.001	

SD = standard deviation; LS=least square; CIC=clean intermittent catheterization; MCC=maximum cystometric capacity

^a P-values for between-group comparison (versus placebo) at each visit are based on ANCOVA model with baseline MCC as covariate, and treatment group, etiology at entry into study, concurrent anticholinergic therapy at screening, and investigator as factors

^b Only patients who had MCC and PVR data at both baseline and week 6 were analysed

As expected from inspection of the group mean MCC and PVR values in the First Round submission, and discussed previously, the increase in the MCC did *not* accurately reflect the functional storage capacity of the bladder in non catheterised patients.

For the 90 patients in the 200 U group who were not performing CIC at baseline, the mean increase in the “modified” MCC (that is, MCC-PVR) was only 29.1 mL from a baseline of 175.6 mL. It was not statistically different from the mean decrease in storage capacity seen in placebo patients (13.0 mL, p=0.191), but the analysis was not adequately powered. More importantly, this is not a clinically meaningful increase. For patients in whom the MCC and PVR both increased by a similar amount following Botox, the functional storage capacity of the bladder has not been usefully increased and the volume changes merely increase the risk of UTIs. For most patients, the ability to store another 29.1 mL between voids would not be worth the risks of an invasive procedure and the increased risk of UTIs. (These risks *are* offset by gains in continence, however.)

In the 300 U group, the mean increase in “modified” MCC was moderately better (46.4 mL), and this was significantly different to placebo (p=0.010), but this dose is not being proposed for registration and is unsuitable because of the increased risk of side effects associated with the higher dose.

The failure of the “modified” MCC to show a significant and worthwhile benefit does not by itself invalidate the efficacy of Botox for NDO. First, catheterised patients are not affected by this finding, because they achieve near total emptying of the bladder and can enjoy the full increase in MCC as available storage. Second, Botox produced gains in continence and quality of life, which were observed in all major subgroups including patients who were not using CIC at baseline.

What this analysis shows is that the gains in MCC do not reflect available bladder storage capacity. Patients need to be advised that, although Botox is likely to help their incontinence frequency, they cannot expect to store much more urine in their bladder between voids unless they use a catheter to achieve emptying. The unimpressive gains in functional storage capacity (for non catheterised patients) should be mentioned in the PI, in place of the current discussion that, by omission, falsely implies that the increased MCC is available in spontaneously voiding patients.

The sponsor’s data (Table 48) would be suitable for inclusion in the PI, but a more descriptive term for MCC-PVR should be used in place of “modified MCC”. This volume

could be called the “Functional Reserve Capacity” or “Available Storage” or any other suitable term that indicates its relevance to non catheterised patients.

Question 3: RMP - Study 082 Timelines

“One of the additional pharmacovigilance activities for the risk of pyelonephritis is the ongoing studies (094 and 082). There is no estimated completion date for Study 082, and no estimated date for when the final study report will be provided for both studies. Please provide these timelines as they are necessary to inform post market monitoring and evaluation.”

Original Rationale Behind the Question

At the time of submission, two important supportive studies (Table 49) were ongoing, a long term extension study that will provide data on the long term efficacy and safety of Botox, and a safety study performed in a vulnerable population of patients with pre existing respiratory compromise.

Table 49: Ongoing studies at time of submission.

191622-094 Module 5.3.5.1, Report 191622-094	Phase 3 long-term extension	Patients completing 191622-515 or 191622-516 with no greater than a 6-month gap between studies	To evaluate the long-term safety and maintenance of efficacy of BOTOX®	Multiple treatments BOTOX® 300 U, 200 U 30 intradetrusor injections each of 1 mL	Interim analysis: 285 enrolled 155 received at least 1 treatment with BOTOX®	Up to 3 years	Ongoing: Interim
191622-082 Module 5.3.5.4, Report 191622-082	Phase 3 double-blind, randomized, placebo-controlled, parallel group	Patients with NDO resulting from MS (EDSS score 7.0 - 8.0) or SCI (injury between C5 and C8) who had not been adequately managed by anticholinergics with ≥4 episodes of UI/3 days during screening period and FVC between 50% and 80% of predicted	To evaluate the safety and efficacy of BOTOX® compared with placebo in patients with urinary incontinence due to NDO not adequately managed with anticholinergic therapy and had neurological respiratory impairment	Up to 2 treatments Tx 1: BOTOX® 300 U, 200 U, or placebo Tx 2: BOTOX® 300 U, 200 U 30 intradetrusor injections each of 1 mL	Interim analysis: 34 randomized: Tx 1: 24 BOTOX® 10 placebo Tx 2: 12 BOTOX®	52 weeks	Ongoing: Interim

This question (like the subsequent question, Question 4) asks for a timeline for completing these studies, as the results will affect post-marketing monitoring and evaluation.

Sponsor's Response

“The final clinical study report for Study 094 is planned to be available in the first quarter of 2014. Enrolment into Study 082 is very slow as there are only a limited number of appropriate patients that have NDO as well as the required neurological respiratory impairment.”

Adequacy of the Response

This addresses the question appropriately. Study 082 requires a very specific subset of patients and so recruitment difficulties are not surprising.

Residual Issues

None. The studies should be submitted for evaluation as soon as they are available.

Question 4: RMP - Study 082, Study 094 Completion Dates

“Please provide estimated dates for the completion of Study 082, and the finalisation of study reports for Study 094 and 082.”

This was covered by Question 3.

Question 5: RMP - Chronic Migraine Post Market UK Study

"A post market study for chronic migraine has been requested by the Medicines and Healthcare products Regulatory Agency (MHRA). The estimated target dates provided for protocol development and study timelines refer to time periods 'postapproval'. MHRA approval was given in July 2010. Please provide updated dates for this chronic migraine post market study (in the UK), including estimated dates for submission to the TGA of the final study report and MHRA evaluation."

Original Rationale Behind the Question

This study, which was not evaluated in the context of the NDO submission, will add to the safety database for Botox, and the timing of the study will affect post marketing monitoring.

Sponsor's Response

"Investigator enrolment has begun. The third quarter of 2011 is the target for the first patient to be enrolled. The estimated target date for the final study report is fourth quarter of 2014."

Adequacy of the Response

This answers the question.

Residual Issues

None.

Question 6: RMP – 200 U Vial Size Risks

"In Australia, Botox 200 U vials were recently approved (March 2011), and the recommended dose for treatment of neurogenic detrusor overactivity is 200 U. The global RMP provided identifies and addresses the risk of overdose associated with misuse of the 200 U vial. However, this is not included in the Australian section, and the proposed PI only refers to the 100 U vial."

Please provide further information on Australian specific measures, including an updated PI, to assess and address any risk associated with the use of 200 U vials in the Australian market."

Original Rationale Behind the Question

It is important that the PI accurately reflects the availability of different vial sizes, and that the risk of vial size mistakes is brought to the attention of clinicians.

Sponsor's Response

The 200 U vial was approved by the TGA on 23 February 2011, but is not yet marketed in Australia. If Allergan decides to market the 200 U vial, a Dear Healthcare Professional Letter will be sent to the physicians addressing the following key points:

- Notification that a 200 U vial size is now available, including colour illustrations of packaging
- Colour coded text on the packaging to differentiate between product sizes
- Caution to physicians to confirm the correct vial size and dose prior to injecting.

In addition, Allergan will discuss with all injectors the dilution technique using the information already existent in the Botox PI.

Adequacy of the Response

The suggested education plan is appropriate.

Residual Issues

None.

Question 7: RMP – Physician Education Programme

“A physician education programme and patient aids are proposed as additional risk minimisation activities “to adequately inform physicians (and patients) about the potential risk of spread reactions, appropriate injection techniques, dosing, and the lack of interchangeability by defined dose of botulinum toxin products”. However, from the information provided in the RMP, it is difficult to understand how this will occur in Australia.

Please provide further information on the physician education programme regarding how this will be developed and implemented in Australia. This should include, but not be restricted to, answering the following queries:

- a. Will the programme consist of both education materials and training, or just the materials?*
- b. How will the relevant healthcare professionals be identified and targeted, eg will relevant stakeholders be consulted?*
- c. Beyond using the PI and identified code of conduct, what process will be used to develop the materials and ensure they are relevant to providers/specialist in Australia (for example, conform and relevant to current practice guidelines)?*
- d. How will the success of the programme/activity be measured and presented? Ensuring compliance with the relevant code of conduct will not, to my knowledge, give any indication of the distribution, uptake or usefulness of the education programme.”*

Original Rationale Behind the Question

Botox use comes with substantial operator dependent risks, particularly in relation to dose and site of application. The best way to minimise the risk of distant spread is to educate physicians. Also, botulinum toxin products use different definitions of a standard unit, a counterintuitive arrangement that increases the risk of dosing errors, and so users need to be reminded that the different products are not interchangeable.

Sponsor’s Response

- (a) Allergan proposes injector training programmes as risk minimisation activities for Australia. If physicians are unable to attend training programmes, educational materials will be supplied to ensure these physicians are adequately educated on the potential risk of spread reactions, appropriate injection techniques, dosing, and the lack of interchangeability between botulinum toxin products.
- (b) The relevant healthcare professionals such as urologists for NDO will be identified in consultation with Advisory Board, Key Opinion Leaders, and relevant Certified Bodies.
- (c) Global physician training materials will be used and adapted according to Australian guidelines and Code of Conduct. The expertise of the Australian Advisory Board members will be utilised in the development and adaptation of these materials for use in Australia.

- (d) Success will be measured by Allergan sales representatives in a visit to the doctors to check the awareness of the information provided or any questions they may have. This includes discussion on potential spread of toxin events, lack of interchangeability, dosing recommendation and medication error.

Adequacy of the Response

Items (a), (b) and (c) are straightforward and address the question asked. The proposed education program appears to be comprehensive. The proposed monitoring of the education program, outlined in item (d) would rely heavily on the sales representative detecting and reporting problems. A more stringent monitoring program would involve formal quizzes of practitioners, and this could be linked with continuing medical education programs.

Residual Issues

It remains somewhat unclear whether potential flaws in physician knowledge will be adequately monitored. The proposed program relies on an employee of the sponsor to find and report problems.

Question 8: RMP – Patient Aids

“Please provide further information on patients aids regarding how they will be developed and used in Australia. This should include, but not be restricted to, answering the following queries:

(a) Is there a definite intention to utilise an additional aid product, or will the CMI be used for this purpose?

(b) If an aid will be developed, what processes will be utilised to ensure they are relevant and appropriate?

(c) How will the success of the aid be measured and presented? Ensuring compliance with the relevant code of conduct will not, to my knowledge, give any indication of the implementation and usefulness of the patient aid.”

Original Rationale Behind the Question

Patients need to be aware of potential symptoms of toxin spread so they can obtain timely assessment and treatment.

Sponsor’s Response

“(a) Allergan’s intention is to utilise the CMI as the single source of educating patients on possible spread of toxin.

The proposed CMI contains the following information under section 5 – Side Effects – Things which may occur – General.

‘In some cases, the effect of botulinum toxin may be observed beyond the site of injection and the following symptoms may occur:

- loss of strength and muscle weakness*
- drooping of the upper eyelid*
- double or blurred vision*
- trouble speaking or saying words clearly*
- constipation*
- aspiration pneumonia (serious lung infection)*

- *trouble swallowing or breathing, which can be life threatening.*

These symptoms can happen hours to weeks after injection and are more likely to occur in patients treated with high doses or who have underlying conditions that would predispose them to these symptoms.

Tell your doctor immediately or go to Accident and Emergency at your nearest hospital if you experience any of the above symptoms.'

Allergan believes the above wording adequately details the precautions and common adverse events associated with treatment of Botox; therefore an additional Patient Aid is not required. "

Items (b) and (c) are therefore not applicable.

Adequacy of the Response

The CMI is an appropriate means of communicating the necessary information. Given that patients are unlikely to be collecting their own Botox supplies from pharmacists, however, the onus will be on clinicians to pass on the CMI to patients.

Residual Issues

The sponsor should include, as part of their physician education program, clear advice that the CMI should be passed on to patients. Compliance with this advice should be audited.

Second Round Risk-Benefit Balance

Second round assessment of benefits

The sponsor's response to Question 1 (related to diary censoring during UTIs) was reassuring. This methodological issue turned out to produce no major bias, and a significant benefit was observed even with pessimistic imputation methods. The sponsor has also showed that, even in a subgroup with UTIs, patients felt that incontinence related QOL was improved by Botox overall.

The sponsor's response to Question 2 has confirmed the evaluator's suspicions that the available storage capacity in the bladder of non catheterised Botox recipients was only moderately increased, because Botox increased both the PVR and the MCC. This means that increased storage capacity cannot be considered a substantial benefit in this subgroup. (Increased storage was, however, achieved in catheterised patients.)

Patients and clinicians will primarily be interested in the effect of Botox on incontinence frequency, rather than MCC or storage capacity, so this issue is of secondary importance.

Second round assessment of risks

No new clinical information was submitted in response to questions. The risk of poor bladder emptying is integral to the use of Botox for NDO, but this can be managed with catheterisation.

Second round assessment of benefit-risk balance

The overall benefit-risk balance of Botox for NDO is favourable, and has not been substantially modified by the second round analyses.

For non catheterised patients, the mean increase in available storage capacity (MCC-PVR) has been revealed as quite small (29.1 mL), but this was already strongly suspected in the first round. This issue is not relevant for catheterised patients. Even in non catheterised patients, gains in continence are of more importance than gains in volume and outweigh the risks including increased urinary tract infections.

Second Round Recommendation Regarding Authorisation

Botox for NDO has a favourable risk-benefit balance, but causes impaired bladder emptying and increases the risk of UTI.

The sponsor's initial responses to Questions 1 and 2 were inadequate, but the final responses were satisfactory.

The PI needs to be updated along the lines suggested in the first and second rounds of this evaluation.

Once the PI is satisfactory, Botox should be authorised for the treatment of urinary incontinence related to NDO.

V. Pharmacovigilance findings

Risk Management Plan

The sponsor submitted a Risk Management Plan that was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 50.

Table 50: Ongoing Safety Concerns.

Important identified risks	Hypersensitivity Reactions
	Pre-existing neuromuscular disorders
	Immunogenicity, drug resistance, and antibody formation
	Dysphagia in cervical dystonia and in chronic migraine patients
	Worsening or intractable migraine/headache in chronic migraine treatment
	Distant spread of toxin
	Urinary tract infections in neurogenic detrusor overactivity patients
	Urinary retention in NDO patients
Important potential risks	Seizure
	Cardiovascular events
	Death
	Guillain-Barre Syndrome
	Pyelonephritis
	Potential medication error, overdose from misuse of 200 U vial
	Interaction with other neuromuscular junction acting agents
	Interaction with different botulinum toxin serotypes at the same time or within several months
Important missing information	Pregnancy
	Lactation
	Renal and hepatic impairment

The main changes in the safety specifications of RMP version 4.0 from the previous version (3.2) evaluated by the TGA are:

- General: Distant spread of toxin moving from potential to identified risk, death included as a potential risk,
- Headache/migraine indication: addition of worsening or intractable migraine in chronic treatment to identified risks, and
- NDO indication: addition of urinary tract infection and urinary retention to identified risks, and pyelonephritis to potential risks.

No safety concerns have been removed or downgraded in importance, and the clinical evaluation report agrees that no new safety signals had emerged in the submitted data for this indication. It is recommended that the next version of the RMP reflect the clinical evaluation comments regarding the relationship between risk of urinary tract infection and impaired bladder emptying (and increased need for catheterisation).

Pharmacovigilance Plan

Routine pharmacovigilance activities are proposed for all safety concerns.

For safety concerns specifically related to the additional indication of NDO, the sponsor identifies that:

- Urinary tract infection and urinary retention will be monitored with routine pharmacovigilance as the risk has been well characterised in clinical trials; and
- Additional activities are proposed for pyelonephritis.

Cases of pyelonephritis will continue to be observed in ongoing studies (094 and 082), and enhanced pharmacovigilance will occur through a targeted questionnaire follow up of all cases reported to the sponsor. The main objective of the use of this ongoing follow up in studies is to continue to assess the magnitude of risk and contributing factors of pyelonephritis. A brief overview of each study is provided below.

Study 094:

- Safety and Efficacy of Two Dose Levels of Botox in Patients with Urinary Incontinence Due to Neurogenic Detrusor Overactivity
- Multicentre, long term follow up
- 500 patients
- Estimated completion date March 2013, with the final clinical study report estimated to be available in early 2014.

Study 082:

- Safety and Efficacy Study of Botox Purified Neurotoxin Complex in Patients with Neurogenic Detrusor Overactivity and Neurological Respiratory Impairment
- Placebo controlled randomised study
- 135 patients through US, Canada, Australia and India
- No estimated completion date provided – enrolment has been slow for this study (<10 patients /year).

For non NDO specific safety concerns, enhanced pharmacovigilance is being conducted for:

- Dysphagia in cervical dystonia and in chronic migraine patients
- Worsening or intractable migraine/headache in chronic migraine treatment
- Distant spread of toxin, and
- GBS.

Since TGA's review of the previous RMP, the MHRA has requested an additional post marketing study for chronic migraine to be conducted within the UK to describe utilisation patterns and collect safety data in chronic migraine patients who use Botox. This

comprises the enhanced pharmacovigilance activity for the two safety concerns around chronic migraine. The protocol was agreed with the UK MHRA in October 2011, and third quarter of 2011 is target for enrolment of first patient. The estimated target date for the final study report is fourth quarter of 2014.

The enhanced pharmacovigilance activities for distant spread of toxin and GBS safety concerns are similar to those assessed and determined to be acceptable in the previous review of the RMP.

Death has been included as an additional potential safety risk. The RMP states that periodic safety update reports (PSURs) have presented analyses on death as an outcome, finding that the majority of deaths reported after treatment with Botox for adults reflect the underlying diseases in the population, such as neurological debility, malignancies, trauma and cardiovascular disease. Rare fatalities have occurred in paediatric patients, and the majority were in the severe disability category with significant co morbidities.

OPR reviewer comment:

During clinical trials involving 497 patients receiving Botox and 272 placebo, urinary retention and urinary tract infections were two of the most common treatment related adverse events reported. These are both identified as known risks and therefore at this stage it is considered acceptable that urinary tract infections and urinary retention are addressed through routine pharmacovigilance monitoring.

Further information will become available on the risk of and risk factors for pyelonephritis in the two ongoing studies. The RMP identifies that clinical trials did not identify an elevated risk when compared to placebo for pyelonephritis. In treatment groups of around 250 patients, there were one to two cases of pyelonephritis identified giving a prevalence estimate of 0 to 0.7%. The background rate of one episode of pyelonephritis per year in neurologic bladder patients is estimated to be around 1.7%, which equates to just over eight cases in 500 patients and just over two cases in 135 patients. It is possible that these ongoing studies will be able to detect an increased rate of pyelonephritis over the background rate.

For the additional potential risk of death, a review of the Australian Adverse Event Report Database identifies no cases of 'death' or 'death, maybe drug' associated with Botox use. Routine pharmacovigilance and PSUR updates are considered acceptable for this potential risk.

Risk Minimisation Activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor is proposing routine risk minimisation activities for all safety concerns, except GBS and renal and hepatic impairment which will have no activities.

Enhanced activities are attached to the identified risk of 'distant spread of toxin', specifically patient and physician education in Australia.

OPR reviewer comment:

For this indication, Botox is administered into the detrusor muscle via a cystoscope. Cystoscopies are routinely performed by urologists in Australia. Given their area of expertise reflects the main side effects of this indication for Botox, routine activities are considered appropriate for most safety concerns. There is no concern regarding the provision of additional activities around the risk of distant spread of toxin.

Potential for medication errors

In Australia, Botox has been available in only 100 U vials until March 2011 when 200 U vials were approved. The RMP addresses the risk of overdose associated with the misuse of the 200 U vial through labelling and packaging. However, this is not included in the Australian section, and proposed PI only refers to the 100U vial.

Different botulinum toxin A products utilise different systems of units; therefore, medication errors may occur if doses are not considered according to the specific manufacturers units.

PSURs include information on adverse events associated with medication errors. Accumulated information to date identify the following medication errors reported:

- Reconstitution with the wrong substance – leading to injection site pain, swelling, irritation, inflammation and drug ineffective;
- Inadvertent accidental splashing – into the eye or cheek of patient or professional – leading to pain, irritation or discomfort; and
- Storage error (temperature, expiration date) – leading to injection site pain and swelling.

There was one fatal case of anaphylaxis reported for a patient who died immediately after being injected with 100 U Botox inappropriately constituted with 5 mL of 1% lidocaine.

OPR reviewer comment:

Given the recent approval of 200 U vials in Australia, the risk of overdose associated with misuse of this vial does exist. The sponsor has provided additional information that the 200 U vial is not yet available in Australia, and have committed to sending a Dear Healthcare Professional Letter to physicians if it is marketed here. There is also wording being proposed in the Dosage and Administration section of the PI to prevent accidental overdose from the two dosage forms. This is acceptable, and the TGA should be informed if this decision is taken and be provided with the Dear Healthcare Professional Letter.

To address the risks associated with the interchangeability of different botulinum toxin A products (no standard dosage unit), the following wording was included in the PI (in bold typeface) and agreed to by the TGA in 2009:

'Due to the lack of an international unit, Botox is not therapeutically equivalent to the other botulinum toxin A preparation currently available on the Australian market. The potencies of Botox and the other botulinum toxin A preparation are based on different assay methods. In view of this lack of harmonisation of unit system for the botulinum toxins type A on the market, extreme caution is required if it should prove necessary to substitute the botulinum toxin A of one pharmaceutical company by another. The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.'

The reported AEs associated with medication errors appear to be minor and manageable, apart from the fatal case of anaphylaxis. The PI includes statements that specifically address safe storage, reconstitution and dilution instruction. Anaphylaxis is identified as a rare AE, and the recommended doses are clear in the dosage and administration section.

RMP: planned actions

Additional activities for the 'distant spread of toxin' risk are categorised into those focused on reducing the risk in clinical trials and those focused on post market use. In clinical trials, an investigator brochure and patient informed consent form are used that includes key safety information. This aspect has not been reviewed. In the post market setting, it is proposed that physician and patient programmes will occur.

The physician education programme will consist of injector training programmes, with educational materials (in the form of a letter) being available as an addition or alternative support. The objective of these are 'to adequately inform physicians about the potential risk of spread reactions, appropriate injection techniques, dosing, and the lack of interchangeability by defined dose of botulinum toxin products'. The programme will be directed at urologists for the NDO indication (and neurologists and pain specialists for chronic migraine), and will be identified through consultation with relevant bodies in Australia. The sponsor has stated that an Australian Advisory Board will be utilised to ensure the global materials are adapted appropriately for use in Australia, including the consideration of Australian guidelines. Success will be measured by sales representatives who will determine awareness of the information during their discussions with doctors.

The RMP discusses the use of patient aids 'to adequately and appropriately inform patients about the potential risk of distant spread of toxin reactions'. The sponsor has provided further information that the CMI will be the single source of patient education or information. The RMP will be updated to reflect this in the next version.

OPR reviewer comment:

There are no specific concerns regarding the proposed physician education programme, although the ability to measure success of the programme has not been addressed well.

The clinical evaluation report recommended that the RMP should also address the increased risk of UTI's from impaired bladder emptying and an increased need for catheterisation, and provides PI recommendations to assist in the management of this risk. The CMI currently identifies these adverse events in several places. No further recommendations are made regarding the PI and CMI for these risks.

In regard to the routine risk minimisation activities, the draft PI and CMI documents are considered satisfactory.

Summary of Recommendations

The OPR provides the following recommendations in the context that the submitted RMP is supportive to the application:

- The implementation of RMP version 4.0 (14 October 2010), and any subsequent updated versions, be implemented as a condition of registration;
- The next version of the RMP reflect the clinical evaluation comments regarding the relationship between risk of urinary tract infection and impaired bladder emptying and increased need for catheterisation. If the sponsor agrees with the recommendation, this will be followed up on submission of the next updated version of the RMP;
- The pharmacovigilance and risk minimisation plans are implemented as outlined in the RMP; and
- If the sponsor decides to market the 200 U vial of Botox in Australia, then the Dear Healthcare Professional Letter will be provided to the TGA (OPR).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Single dose and repeat dose toxicity studies were conducted in rats and/or monkeys to assess the toxicity to the bladder and to the tissues around and near the bladder. Systemic toxicity was also examined in these studies:

- There were no clinical signs or microscopic evidence of local toxicity to the smooth muscle of the bladder at single doses up to 25U/site in rats or repeat doses of 36 U/site in monkeys (3.7 times and 5 times, respectively, the clinical dose at an individual injection site).
- No adverse local effects were seen after a single intrauterine injection (6 U/site) or single doses of 20 U/site (3 times the clinical dose) in the proximal rectum and seminal vesicle of Cynomolgus monkeys.
- Intraprostatic injections of ≥ 24 U/site (3.6 times the clinical dose) were associated with an accumulation of amorphous material and formation of ejaculatory coagulum within the urethra causing bladder obstruction. A NOEL was not established for the prostate and seminal vesicle changes and there was no evidence of reversibility.
- Signs of systemic toxicity were seen following ID injections to both rats and Cynomolgus monkeys and included known toxic effects of Botox – respiratory distress, toes curled over, abnormal gait and/or ptosis with Botox related deaths at higher doses. Atrophy and necrosis of the skeletal musculature of the diaphragm was observed at necropsy. The ID doses causing systemic toxicity in both rats and monkeys were similar to previously reported IM doses causing systemic toxicity.

Nonclinical recommendations and conclusions:

- The lack of histological or any other local effects attributed to the injection of Botox into the detrusor muscle suggest that the risk of local toxicity is low in humans at the proposed MRHD. Furthermore, ID injections of Botox at the proposed MRHD (200 U) are not expected to pose any greater systemic toxicity risk than that expected with currently approved IM doses for other indications.
- A risk of urethral obstruction and bladder stone development exists in the event of accidental injection into the prostate.
- There are no nonclinical objections to the extension of indications for Botox to include the treatment of urinary incontinence in patients with neurogenic detrusor overactivity. Demonstration of efficacy will need to rely on clinical data.
- The PI document should be amended as indicated in the nonclinical evaluation report.

Clinical

The submission consists of seven clinical studies of Botox in the treatment of detrusor overactivity, including six studies of NDO and one of IOAB. No new pharmacokinetics and pharmacodynamics studies were presented.

The clinical evaluator has recommended that Botox for NDO has a favourable risk-benefit balance but causes impaired bladder emptying and increases the risk of UTIs. The sponsor's initial responses to questions posed by the clinical evaluator were judged inadequate by the evaluator but the sponsor's final responses were satisfactory. Finally, the clinical evaluator recommended that the PI needs to be updated along the lines suggested in the first and second round clinical evaluation reports and that once there is agreement that the PI is satisfactory, then Botox should be approved for the treatment of urinary incontinence related to NDO.

Pharmacology

Pharmacokinetics

No new pharmacokinetics data were submitted for evaluation.

Pharmacodynamics

The sponsor performed urodynamic monitoring within the pivotal efficacy studies and the relevant data are evaluated within the context of those studies.

Efficacy

Pivotal studies – Study 515 and Study 516

There were two pivotal efficacy studies, Study 515 (n=275) and Study 516 (n=416) and they shared a similar design, differing only in the level of urinary incontinence required before patients were eligible for a second Botox treatment. Patients received up to two randomised, double blind treatments, the first treatment being placebo controlled and the second dose controlled. Both studies followed up patients for one year plus additional time where needed to ensure that 12 weeks of follow up were available after the second treatment. Both pivotal studies recruited patients with urinary incontinence associated with NDO due to either MS or a SCI. A previous trial of anticholinergic agents for at least one month had to have failed. Patients were eligible regardless of whether they were still receiving anticholinergics at baseline or whether they performed intermittent self catheterisation but these concurrent bladder treatments had to be kept stable throughout the study. Patients with an in dwelling urinary catheter were not eligible.

For their first treatment, patients in both studies were randomised to saline placebo, Botox 200 U or Botox 300 U in a 1:1:1 ratio and they received these dosages as 30 x 1 mL injections administered under cystoscopic guidance into the detrusor muscle at an approximate depth of 2 mm. After a minimum of twelve weeks, regardless of their initial response to the first treatment, patients were eligible for retreatment upon request, provided that their incontinence was sufficiently severe at that stage. The severity thresholds for retreatment differed in the two studies, incontinence having to be still at least 50% of the baseline level in Study 515 and having to be at least 70% of the baseline level in Study 516, to warrant retreatment. The second treatment consisted of active therapy with either Botox 200 U or 300 U. Patients who had already received active treatment in the first cycle received the same dose in the second cycle and patients who had received placebo were randomised to receive either of the two active doses in a 1:1 ratio. In addition to their blinded, randomised treatment, patients also received empirical antibiotics for each of three days prior to and after the procedure.

Thus, placebo controlled data was only available for a single cycle. However, the Delegate would agree with the evaluator this was reasonable in the context of a study of at least a year's duration.

Both pivotal studies were analysed as superiority studies in comparison with placebo. The primary statistical analysis was an ANCOVA, using the baseline incontinence frequency as

covariate and the treatment group, neurological diagnosis (MS or SCI), concurrent anticholinergic therapy at screening and investigator as factors. The primary analysis was on the ITT population. Power assumptions and calculations appeared reasonable.

For both efficacy studies, the primary endpoint was the change in the mean number of incontinence episodes per week, identified from patient diaries. The same parameter was also subjected to a responder analysis (proportion of patients with 50% or 100% reduction from baseline incontinence). Importantly, the clinical evaluator identified early on that there was a bias potentially in favour of Botox for this endpoint, namely that patients were explicitly instructed not to collect bladder data if they were experiencing symptoms of a UTI. Thus, what was not clear was how much the continence gains due to Botox were offset by continence losses during periods of Botox induced UTIs. As we shall see the evaluator asked the sponsor to perform various sensitivity analyses to help clarify this issue.

Two urodynamic parameters, based on studies performed after six weeks of treatment, were assessed as secondary endpoints. These were the MCC and the MDP during the first involuntary detrusor contraction during filling. As correctly noted by the evaluator, it is the difference between the MCC and the PVR which determines how much urine can be added to the bladder between voids. If a treatment were to increase both the MCC and the PVR by the same volume, this would not actually lead to an increased capacity to store urine between voids. Thus consideration of the MCC in isolation could result in a spurious measure of efficacy. The clinical evaluator noted that the sponsor generally failed to acknowledge this point and PVR was not considered in the efficacy analysis but only in the safety analysis. Patients' QoL as measured by a specific incontinence related questionnaire was the other major secondary endpoint.

Tertiary endpoints included the volume per void as assessed from the patients' diaries, the volume at which the first involuntary detrusor contraction occurred, detrusor compliance and a range of QoL assessments.

Patients were reasonably well matched with regard to baseline demographic and disease characteristics. In Study 515, the placebo group had a higher proportion of males (49.0%) and the Botox 300 U group had a relatively lower proportion of males (32.6%), with the proportion in the Botox 200 U group lying in between these two values (40.7%). This imbalance was statistically significant ($p = 0.02$). There was also a statistically significant across group difference in the SCI patients for weekly frequency of catheterisation, with the highest frequency in the placebo group ($p = 0.026$). Also of note, only 43% of patients in Study 515 and 48% of patients in Study 516 were attempting to empty the bladder solely by voluntary voids at baseline. The majority of patients in each study were already using clean intermittent catheterisation either solely or as part of a mixed approach in combination with voluntary voiding.

In the larger of the two studies, Study 515, most patients, 329/416, 79.1%, completed the study while in Study 516, the rate of completion was 230/275, 83.6%.

Results for the primary endpoint, mean change in urinary incontinence frequency (episodes/week) are shown in Figure 5 and Table 6. From a baseline of about 30 incontinence episodes per week, Botox recipients showed a reduction of about 21-23 episodes, compared to a reduction in the placebo group of about 8-13 episodes across the different studies and time points. Both pivotal studies produced similar results, with a significant treatment effect for each study individually as well as in the pooled analysis. The difference between the two active dose groups was minor and did not show a consistent pattern across the two studies. Support for the primary analysis was given by the results for the responder analysis which showed that a 50% reduction in incontinence

was observed at Week 6 in 74.4% and 75.8% of the pooled 300 U and 200 U groups, respectively but only in 38.6% of the placebo group ($p < 0.001$).

Secondary endpoints also favoured both active groups over placebo, with MCC increasing by 163.1 and 153.6 mL at Week 6 in the pooled 300 U and 200 U groups, respectively, from a baseline of about 250 mL, compared to a mean increase of only 11.9 mL in the pooled placebo group. Results were similar in both dose groups and in each pivotal study considered separately ($p < 0.001$ for all comparisons versus placebo). The MDP was substantially reduced in the active treatment groups. From a baseline of 45-52 cmH₂O in the pooled pivotal studies, the pressure was reduced by a mean of 30-32 cmH₂O in the 300 U and 200 U groups, compared to minor increase of 1 cmH₂O in the placebo group (p value < 0.001 for either dose group versus placebo, both in the pooled analysis and for each study). There were improvements in I-QoL which were highly significant ($p < 0.001$) at Weeks 6 and 12, in both the pooled analysis and for each study.

Other minor endpoints were generally consistent with the major endpoints, except that the mean number of voids via clean intermittent catheterisation was not improved with active treatment but instead showed an adverse trend with active treatment, because a greater proportion of patients had poor urinary emptying and needed to void with the help of a catheter. As noted by the clinical evaluator, this is an expected and integral consequence of Botox treatment of NDO.

The duration of effect, as measured by the median time for *responding* patients to achieve less than or equal to a 50% reduction in urinary incontinence, was 301 days for the 300 U dose group and was 294 days for the 200 U dose group, compared to 165 days in the placebo group (pooled analysis). The duration of effect, as measured by the median time for *all* patients to achieve less than or equal to a 50% reduction in urinary incontinence, was 210 days for each active dose group, compared to one day in the placebo group (pooled analysis). For the more subjective measure of time to request for treatment, similar results were obtained. All relevant Kaplan-Meier curves showed that both active groups had a similar benefit over placebo.

Placebo-controlled data was only available for the first treatment cycle. Therefore, it is not possible to draw any firm conclusions about the efficacy of repeat doses of Botox.

Subgroup analyses were performed based on gender, aetiology of NDO (MS or SCI), concurrent use of anticholinergic agents, age and Botox naive status. All major endpoints including the primary endpoint of incontinence frequency were achieved for both MS patients and for SCI patients, apart from volume at the first involuntary detrusor contraction which merely showed a favourable trend. The primary endpoint was achieved in all major subgroups with the reduction of incontinence more pronounced in females than in males. Concurrent use of anticholinergics made very little difference to the magnitude of the treatment effect.

Supportive studies – Study 511, Study 518 and Study 094

Study 511

This was a small ($n=59$) Phase II feasibility study of the efficacy of a single dose of ID Botox for the treatment of NDO. It employed a multicentre, double blind, randomised, placebo controlled, parallel group design that was very similar to the first treatment cycle of the pivotal studies with patients randomised to receive Botox 200 U, Botox 300 U or placebo in a 1:1:1 ratio. The target population consisted of patients with MS or SCI who were designated by their clinician as having urinary incontinence due to 'detrusor hyperreflexia' (equivalent to NDO). Unlike the pivotal studies all patients were using clean intermittent catheterisation at baseline to empty the bladder. It was a parallel group

superiority study comparing each of the two Botox doses to placebo. The three treatment groups were reasonably well matched at baseline. The vast majority of patients (53/59) had SCI rather than MS, reflected by the fact that all patients were using clean intermittent catheterisation at baseline. All but two patients completed the study. There was one who dropped out of the 200 U group because of lack of efficacy and another from the 200 U group because of an adverse event. For the primary endpoint, the improvement in incontinence frequency was greater in both Botox groups than in the placebo group and this difference occasionally reached statistical significance. The magnitude of the treatment effect appeared similar at the two active doses and was maintained across the 24 week study. Secondary endpoints also favoured the active treatment at either dose.

Study 581

This study (n=74) was ongoing at the time of the submission but results from the primary analysis were available. It was a multicentre, double blind, randomised, placebo controlled, Phase II study of the efficacy and safety of up to two doses of ID Botox for NDO not adequately controlled with anticholinergics. The study was designed to explore the dose response relationship of ID Botox for doses up to and including the lower dose used in the pivotal studies (200 U). Patients received Botox 50, 100 or 200 U or placebo in a parallel group design, at a ratio of 1:1:1:1. The second dose, if required, was open label Botox at 200 U in all patients. The study was underpowered and failed to reach its primary endpoint at the Week 6 time point. It did, however, show numerical superiority of the 200 U dose over lower doses for most endpoints including the primary endpoint. Relative to placebo, significant reductions in incontinence frequency were only observed in the 200 U group and only at some time points (at weeks 30, 36 and 54). The magnitude of the decrease in incontinence frequency increased with increasing dose. Only a small number of patients (n = 28) received retreatment and all received open label Botox 200 U. Most of these (25/28, 89%) had received placebo, Botox 50 U or Botox 100 U for their first dose. Some efficacy was observed after retreatment with Botox 200 U when compared with study baseline but because the patient numbers were low, between group comparisons were not attempted. From the relevant Kaplan-Meier plot, patients receiving the 200 U dose had the longest duration of effect.

Extension study 094

This is an ongoing partially blinded extension study recruiting patients from either of the two pivotal studies (515 and 516). It does not include a placebo group and therefore is primarily observational and descriptive. Patients were to receive the same dose they were assigned in the preceding study, that is, either 200 U or 300 U. For patients who received placebo in the preceding study, the dose they were to be assigned was to be the dose assigned for the second, active treatment. After a 2nd, 3rd and 4th treatment cycle with ID Botox, a significant reduction in urinary incontinence was observed at either dose and was broadly similar to that observed in the pivotal studies. The I-QoL was significantly improved. Improvements in secondary efficacy parameters were also observed over repeated treatment, including increases in volume per void and decreases in the frequency of spontaneous voids.

Study 077

This study was a relatively large, dose ranging Phase II study (n=313) designed to evaluate the safety and efficacy of a single ID Botox treatment at each of five doses (300, 200, 150, 100 and 50 U), relative to placebo, in the treatment of patients with IOAB. In contrast to the pivotal studies, patients were excluded from participating in the study if they had urinary incontinence due to any known neurological reason. It had a multicentre, double blind, randomised, placebo controlled, parallel group design and patients were assigned to

one of the six treatments (including placebo) in a ration of 1:1:1:1:1:1. The study was analysed as a superiority study with the primary hypothesis being that at least one dose of Botox would be more effective than placebo in reducing the weekly frequency of urinary incontinence. As concluded by the clinical evaluator, in this population with poorly characterised incontinence, the placebo effect was so profound that it disguised any Botox effect. Whether Botox has any efficacy in the treatment of IOAB is unclear. The magnitude of the difference between the effects of the proposed Botox dose and placebo was only 2 episodes of incontinence per week, which is not clinically meaningful.

Study 082

This was a small study (n=34) involving up to two doses of ID Botox in patients with neuromuscular respiratory impairment. It employed a multicentre, double blind, randomised, placebo controlled, parallel group design and assessed safety and efficacy of two doses of Botox (200 U and 300 U) in comparison to placebo. As in the pivotal studies, patients were randomised to receive Botox 200 U, 300 U or placebo for their first dose, in a 1:1:1 ratio and the placebo group was further randomised after that first dose to receive Botox 200 U or 300 U in a 1:1 ratio for their second dose, if required. Within group changes were observed in urinary incontinence frequency for all groups including placebo. There was a trend in favour of active treatment, with mean three day incontinence totals decreasing by 11.2 and 12.1 in the 300 U and the 200 U groups, respectively, at Week 6, compared to a decrease of only 4.1 in the placebo group.

Dose considerations across all studies

On balance, the clinical evaluator was of the opinion that the efficacy evidence favoured the proposed dose of 200 U.

Safety

For their integrated safety analysis, the sponsor pooled data from five of the seven studies, namely Studies 515, 516, 094, 511 and 518. Study 082 was excluded because it involved only patients with neuromuscular respiratory impairment and Study 077, that in patients with idiopathic overactive bladder, was also excluded from the pooled analysis. The safety results of the latter two studies were reported separately.

Exposure in the pooled studies consisted of 809 patients of whom 537 received Botox, 235 having received 300 U, 262 having received 200 U and 40 having received less than 200 U for their first treatment cycle. Another 272 patients received placebo during the first treatment. A total of 462 patients (462/809, 57.1%) received a second treatment, 200 U or 300 U. None of the second dose treatment was placebo controlled.

AEs were more common in the Botox groups overall but the difference was less marked when only the first 12 weeks were considered. Relative to placebo, an excess of AEs was observed for the following: urinary tract infection, urinary retention, haematuria, bladder pain, dysuria, constipation and fatigue. Having reviewed the evidence of AEs over later cycles, the clinical evaluator was of the opinion that there was no evidence of any new or unexpected problems, regardless of whether all AEs or just 'treatment related' AEs were considered.

As noted by the clinical evaluator, *intrinsic to its mode of action* ID Botox weakens the bladder with the likely result that bladder emptying is impaired. By whatever means this problem was assessed, including the incidence of acute urinary retention, the rates of uptake of catheterisation in patients who were not using clean intermittent catheterisation at baseline and post void residual volumes measured during urodynamic studies, those receiving active treatment showed poorer bladder emptying than placebo recipients.

A clear increase in PVR was seen in both active groups by Week 2, with the 300 U group showing a mean increase to 176.0 mL, the 200 U group showing a mean increase of 94.1 mL and the placebo group showing almost no change (+3.3 mL). This difference was highly significant (Table 36). Compared to the changes in MCC reported as an efficacy benefit, most of the increased capacity of the bladder was volume that could not be voluntarily voided. For the pooled 300 U group in the pivotal studies, the MCC increased by 163.1 mL and for the pooled 300 U group in the safety analysis, the PVR in fact increased by a larger amount, 176.0 mL. As noted by the sponsor, their analyses did not include any attempt to relate these two volumes to each other, reporting the MCC in the efficacy section and the PVR in the safety section. The failure of the sponsor even to acknowledge this becomes an issue as members of the Advisory Committee on Prescription Medicines (ACPM) will observe.

As further noted by the clinical evaluator, there is a clear relationship between post void residual volume and the risk of urinary tract infection. Approximately a third of Botox recipients (44.2% of the 300 U group and 29.3% of the 200 U group) had at least 200 mL of residual urine in their bladders after a voluntary void, compared to only 3.4% of placebo recipients. For those not using clean intermittent catheterisation at baseline, the rates of urinary tract infection were 42.6% in the 300 U group, 40.4% in the 200 U group versus 11.9% in the placebo group. As noted by the clinical evaluator, commencing clean intermittent catheterisation posed an increased risk of urinary tract infection over and above that seen with the baseline use of clean intermittent catheterisation.

When the changes in PVR are viewed across multiple treatment cycles, no new issues emerge. However, as the clinical evaluator points out, there was no placebo controlled data beyond the first treatment cycle. Importantly, the clinical evaluator warns that, outside the controlled, regimented setting of a clinical trial, i.e. in routine clinical practice, it remains possible that patients may receive ACPM treatments at regular intervals such as every three months. This may in turn lead to a cumulative deleterious effect on bladder emptying with the consequence of higher rates of UTIs. The clinical evaluator has cautioned that the PI should warn about this possibility and the Delegate strongly endorses this recommendation.

Serious adverse events were relatively rare and their rates did not differ significantly between treatment groups. Even for urinary tract infections as serious AEs, the active treatment groups did not show an excess compared with placebo.

For those AEs flagged as potential systemic effects, urinary retention was the most common. However, the Delegate would agree with the clinical evaluator that this is more accurately regarded as a local effect. Muscular weakness was the next most common AE in this category, being more common in Botox recipients (5.5% and 3.8% in the 300 U and 200 U groups, respectively) than in placebo recipients (1.8%). It was more marked in the MS subgroup, having been reported in 10.3%, 7.6% and 3.8% of the MS patients in the 300 U, 200 U and placebo groups, respectively, during treatment cycle 1. However, given the evidence of a dose response, the Delegate would agree with the clinical evaluator that this finding cannot be dismissed as being totally due to confounding by the underlying disease. The sponsor is requested to acknowledge this dose response in the PI and craft a more balanced, accurate way of reporting this issue. Constipation was also more common in the active treatment groups, although once again this is probably more likely to be a local or regional effect.

A small number of AEs appeared to be related to the ID injection procedure itself and these included autonomic hyper reflexia, haematuria and bladder pain.

The Kaplan-Meier plots for time to first MS relapse suggested that Botox increased the risk of such a relapse but statistical modelling did not show a significant effect. Annualised relapse rates were 0.29, 0.23 and 0.20 in the 300 U, 200 U and placebo groups, respectively. Thus, as noted by the clinical evaluator, in the absence of better data, there does appear to be a slightly increased risk of a MS relapse.

Review of the shift tables for haematology and biochemistry monitoring did not reveal any concerning trends.

Most people in the major studies (total n=608, Botox treated n=514, Botox treated in pivotal studies n=477) were monitored for the development of antitoxin antibodies. With the exception of three patients in whom cross reacting antibodies were detected prior to treatment, no patient developed antitoxin antibodies. From these three, there was no clear pattern as to any possible pharmacodynamic effect of the antibodies.

Six deaths occurred in the pooled safety population including those in Study 082 (patients with respiratory compromise) and in Study 077 (patients with idiopathic overactive bladder). The deaths were distributed as follows: one in the 300 U group, two in the 200 U group, two in the < 200 U group, and one in the placebo group. Most of the deaths occurred well after treatment and the mechanism of death in each case was not consistent with the known pharmacology of Botox.

In the small Study 082 (n=34) in patients with respiratory compromise, there were overall no significant changes in pulmonary function and no difference between groups (300 U n=12, 200 U n=12 and placebo n=10). Study 077, that in patients with idiopathic overactive bladder, was not integrated into the safety analysis but the results from this study were consistent with those seen in the larger pooled safety population. In particular, there was a dose dependent increase in the overall rate of AEs with urinary retention and UTIs more common at higher doses, their rates greatly exceeding those in the placebo group.

First Round Risk-Benefit Balance

The clinical evaluation report contains an excellent summary of the risk-benefit balance of this product for the intended indication. As noted by the clinical evaluator, the efficacy benefits of ID Botox consist of a reduction in incontinence episodes and an improvement in bladder pressures. For patients using catheterisation, there is a clear increase in the holding capacity of the bladder as reflected by the maximum cystometric capacity, although this benefit is considerably offset in non catheterised patients by an increase in the post void residual volume. As also noted by the clinical evaluator, the risk of urinary tract infections was increased by Botox in the pivotal studies, particularly in patients who commenced catheterisation or in those who had elevated post void residual volumes and failed to commence catheterisation.

Second Round Evaluation of Clinical Data Submitted in Response to Questions

In a second-round evaluation, the sponsor responded to a number of questions. The second round evaluation was conducted in two stages because the sponsor's initial responses to the first two questions did not include the additional requested analyses. Finally, the sponsor submitted reanalyses which fully addressed the original concerns.

In answer to the first question, as to how much continence gains due to Botox were offset by continence losses during Botox induced UTIs, because bladder diaries were not used during those UTIs, the sponsor presented two reanalyses, the first a subgroup analysis based on the presence or absence of a UTI adverse event using the primary (but still censored) efficacy variable and a similar subgroup analysis using the secondary I-QoL variable. Critically, as noted by the evaluator, the UTIs which were censored, the

symptomatic ones, were the very ones most likely to have been associated with increased incontinence. Disappointingly, at this stage the sponsor had not acknowledged at all the original concern of the evaluator. Despite the submitted reanalyses, it was still unclear what effect diary censorship had had on the treatment effect for the primary efficacy variable. As noted by the clinical evaluator, concerns about censored data *cannot* be addressed by any subgroup analysis which uses the suspect data.

The sponsor was requested to perform sensitivity analyses to estimate the impact of the bias of the censoring of symptomatic UTIs. Finally, the sponsor complied with the request and the results of the sensitivity analysis were reassuring. Even using the most pessimistic imputation method, one which assumed that patients had a doubling of baseline incontinence during diary days which were incomplete because of UTIs, the treatment effect was statistically significant in both groups ($p < 0.001$). In fact the results were very similar to those observed in the initial primary analysis with standard LOCF imputation which indicates maintenance of a clinically useful effect.

The sponsor's response to the second question followed a similarly protracted course as the response to the first. As noted by the clinical evaluator, for patients not using a catheter, the PVR is very important. The residual volume not only influences the risk of UTIs, it offsets the gains in holding capacity. For example if the MCC increases by 150 mL and the PVR also increases by 150 mL, the amount of urine which can be stored between voids is essentially unchanged. In the original dossier, the sponsor neglected any robust discussion of the changes in MCC in relation to those in PVR, with the former discussed in the context of efficacy and latter discussed in the context of safety. The only addressing of the issue originally was via the comparison of the group mean for MCC with that for PVR, a comparison which was inadequate. As noted by the evaluator, what is crucial is how these two volumes, MCC and PVR, relate to each other in individual patients. Thus the sponsor was requested to compare the change in MCC to that in PVR on a per patient basis. The Delegate shares the clinical evaluator's incredulity at the sponsor's response which attempted to argue that the requested analysis was impossible. As pointedly noted by the evaluator, it is true that the PVR would ideally be measured on the same day and with similar technology as for the MCC, to allow a more direct comparison. However, a PVR measured by ultrasound, in the same general time period as the urodynamic studies, has direct bearing on what bladder emptying would have been, had it actually been measured on the day of the urodynamic studies. The Delegate will not give a blow by blow description of the interchanges between evaluator and sponsor. However, the Delegate would urge ACPM members to read very carefully the clinical evaluation report. It is both telling and compelling.

Eventually the sponsor responded by conducting a separate 'modified MCC' analysis, namely that of MCC-PVR in the subset of patients who were not performing clean intermittent catheterisation both at baseline and at Week 6 post treatment. The results of this analysis are presented in the clinical evaluation report alongside the results of the original analysis of MCC in the overall ITT population. One can see very clearly from this table that the original analysis comparing group means overall does not tell the whole story. For the subgroup of 90 patients in the 200 U dose group not performing clean intermittent catheterisation at baseline, the mean increase in the 'modified MCC', that is, MCC-PVR was only 29.1 mL from a baseline of 175.6 mL. It was not statistically different from the mean increase in storage capacity seen in the placebo patients not performing clean intermittent catheterisation at baseline (-13.0 mL, that is, actually a decrease of 13 mL).

As concluded by the evaluator, what this analysis shows is that the gains in MCC do not reflect available bladder storage capacity. Patients need to be advised that, although Botox

is likely to help their incontinence frequency, they cannot expect to store much more urine in their bladders between voids unless they use a catheter to achieve emptying. The unimpressive gains in functional storage capacity for non catheterised patients should be mentioned in the PI, in place of the current discussion that, by omission, falsely implies that the increased MCC is available in spontaneously voiding patients. The Delegate cannot strongly enough endorse the latter recommendation of the evaluator.

Risk Management Plan

The OPR has provided the following recommendations in the context that the submitted RMP is supportive to the application:

- The implementation of RMP version 4.0 (14 October 2010), and any subsequent updated versions, be implemented as a condition of registration;
- The next version of the RMP reflects the clinical comments regarding the relationship between risk of urinary tract infection and impaired bladder emptying and increased need for catheterisation. If the sponsor agrees with the recommendation, this will be followed up on submission of the next updated version of the RMP;
- The pharmacovigilance and risk minimisation plans are implemented as outlined in the RMP; and
- If the sponsor decides to market the 200 U vial of Botox in Australia, then the Dear Healthcare Professional Letter will be provided to the TGA (OPR).

With regard to the recommendation of the clinical evaluator that the RMP reflect the relationship between the risk of urinary tract infection and impaired bladder emptying and increased need for catheterisation, the Delegate regards this as a critically important issue with important ramifications for the safe use of this product. The Delegate is therefore intending to impose the appropriate amending of the RMP in this regard as a specific condition of registration and one which is to be implemented to the satisfaction of the OPR.

As noted by the clinical evaluator, the sponsor has clarified some aspects of the RMP, as discussed in detail in the clinical evaluation report. However, there were some residual issues identified by the evaluator and all of these are in turn endorsed by the Delegate as issues which still require satisfactory resolution since they are, without exception, issues which go to the heart of the safe and effective use of this product. These issues are:

- The sponsor's proposal to use a sales representative to audit the adequacy of physician education, rather than a more robust and objective monitoring program – the design and implementation of such a robust and objective monitoring program, one which has to be agreed to by the OPR, will be made a specific condition of registration,
- The need to ensure that CMI handouts actually reach patients – for example, the sponsor should include, as part of its physician education program, clear and specific advice that the CMI is to be passed on to patients and the sponsor must do all it can to facilitate this handing out of the CMI. As further recommended by the evaluator, compliance with this advice should be monitored as part of the robust and objective monitoring program mentioned under the previous dot point.
- The need to educate physicians when the 200 U vial is marketed in Australia – the issuing of a Dear Healthcare Professional Letter that must be cleared by the TGA will be made a specific condition of registration.

Risk-Benefit Analysis

Delegate Considerations

In the setting of the second line treatment of NDO (that is, after an adequate trial of anticholinergic agents has either been shown to be not effective or not to be tolerated), ID Botox at a dose of 200 U in divided injections significantly reduced the frequency of urinary incontinence, compared to placebo.

Botox improved most urodynamic parameters associated with detrusor overactivity, including MCC and MDP but it also increased PVRs.

Botox improved incontinence related quality of life.

Botox increased the risk of urinary retention and urinary tract infection and resulted in some patients having to initiate catheterisation.

Botox carries a low but poorly defined risk of causing weakness at sites distant from the bladder.

Results were broadly consistent across aetiological subgroups and efficacy was demonstrated in patients with MS or SCI, in males and females and in patients using or not using anticholinergic agents at baseline.

The efficacy and safety of repeat doses remains poorly characterised, because placebo controlled data is unavailable but the existing uncontrolled evidence is broadly reassuring.

Botox did not have acceptable efficacy in a study of its use in patients with idiopathic overactive bladder.

The sponsor's response to the question about the diary censoring during UTIs was reassuring. This methodological issue was demonstrated to produce no major bias and a significant efficacy benefit was observed even with pessimistic imputation assumptions. The sponsor has also shown that, even in a subgroup of subjects with UTIs, patients felt that incontinence related QoL was improved overall by Botox.

The sponsor's response to the question asking the sponsor to compare changes in MCC with changes in the PVR, patient by patient, confirmed the clinical evaluator's suspicions that the available storage capacity in the bladder of non catheterised Botox recipients was only moderately increased because, at the same time that Botox increased the maximum cystometric capacity, it also increased the post void residual volume. That is to say, analysis of the parameter MCC-PVR demonstrated that the functional storage capacity of the bladder between voids was not significantly increased by treatment in those patients relying on spontaneous voiding for bladder emptying. The mean increase in storage volume reflected in this 'modified MCC' was only 29.1 mL in the subgroup of 90 patients in the 200 U dose group not performing clean intermittent catheterisation at baseline, compared to a decrease of 13.0 mL in the corresponding placebo subgroup. By contrast, in the group of catheterised Botox recipients, increased storage was achieved. However, having said all of this, it is important to note that even in non catheterised patients, gains in continence are of more importance than gains in volume and outweigh the risks which do include the risks of increased urinary tract infections.

Indication

The clinical evaluator has recommended revision of the wording of the Indications to tighten the target population and the Delegate strongly endorses this recommendation. The Delegate intends to request the advice of the ACPM on the adequacy, firstly of the sponsor's proposed indication and secondly of the clinical evaluator's amended indication.

Thus in line with the recommendation of the clinical evaluator, the Delegate requests the indication be amended to the following:

“treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as MS or SCI) and not controlled adequately by anticholinergic agents; this does not include idiopathic detrusor overactivity, for which there is insufficient evidence of efficacy.”

Summary

The Delegate concurs with the clinical evaluator that Botox for neurogenic detrusor overactivity has a favourable risk-benefit balance provided that the target population is sufficiently well defined to be consistent with the evidence from the clinical trial populations studied and provided that the sponsor makes appropriate amendments to the proposed PI in line with those recommended by the clinical evaluator in both the first and second rounds of the evaluation. The major risks attached to the use of Botox for the proposed indication are those of impaired bladder emptying and an increased risk of urinary tract infection. These and all other risks associated with the treatment must be fully, adequately and transparently acknowledged and explained in the PI.

Recommendation

I propose to **approve** this submission by Allergan Australia Pty Ltd to register Botox (containing botulinum toxin type A purified neurotoxin complex 100 U, AUST R 67311) based on the safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above.

The Delegate intends to impose the following specific conditions of registration:

- The implementation of RMP version 4.0 (14 October 2010), and any subsequent updated versions as agreed with the OPR;
- The amendment of the RMP so as to reflect the relationship between the risk of urinary tract infection and impaired bladder emptying and increased need for catheterisation, this amendment to be agreed to by the OPR;
- The design and implementation of a robust and objective program to monitor the continuing adequacy of physician education in relation to the use of Botox for the indication of NDO, this program to be agreed to by the OPR;
- At the time of marketing a 200 U vial of Botox, the sponsor is to issue an appropriate Dear Healthcare Professional Letter that must be cleared by the TGA;
- The provision to the TGA, as evaluable data within the context of a category 1 submission, of the final study report of Study 581;
- The provision to the TGA, as evaluable data within the context of a category 1 submission, of the final study report of the extension Study 094;
- The provision to the TGA, as evaluable data within the context of a category 1 submission, of the final study report of the post marketing study, requested by the MHRA and to be conducted within the UK, of the utilisation patterns and safety data for Botox used in the treatment of chronic migraine.

The sponsor should address the following issues in the pre ACPM response:

- An update to the registration status (with dates) for this submission of Botox in the USA, Europe/UK, Switzerland, Canada and New Zealand including any withdrawals, rejections or deferrals.

- The sponsor is requested to identify precisely all currently ongoing studies in relation to the indication of NDO as well as all studies for the same indication which were still ongoing at the time of submission of this application to the TGA. For example, the clinical evaluation report has identified Studies 581 and 094 as 'ongoing' studies, while the RMP evaluator identifies Studies 094 and 082 as 'ongoing' studies.

Response from Sponsor

Allergan Australia Pty Ltd refers to the pre ACPM report and concurs with the recommendation of the Delegate to approve the extension of indication for Botox (Botulinum Toxin Type A). However, Allergan respectfully disagrees with the Delegate's proposed wording for the indication and this will be discussed in further detail below.

Allergan would also like to take this opportunity to respond to some of the comments made by the Delegate. The following areas will be discussed in detail:

1. Wording of Indication
2. Other changes to the proposed PI
3. Additional issues raised by the Delegate

1. Wording of Indication

In line with the recommendation of the clinical evaluator, the Delegate requests the indication be amended to the following:

"treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as MS or SCI) and not controlled adequately by anticholinergic agents; this does not include idiopathic detrusor overactivity, for which there is insufficient evidence of efficacy"

Allergan agrees with modifying the indication by adding more explicit language. In addition, Allergan proposes to add clarity regarding the reference to anticholinergics to ensure it is clear that inadequately managed relates to both inadequate response or intolerable side effects; this wording is also aligned with the wording approved in other regions.

However, Allergan has some concerns over the wording of the precaution regarding IOAB. The Delegate's proposed wording could be interpreted as meaning that data had been submitted in support of this indication and found to be insufficient. However, Allergan would like to clarify that the IOAB Phase 2 study data was not submitted to the TGA to support the IOAB indication since Phase 3 clinical trials specifically related to support the IOAB indication are ongoing. It was submitted only because this indication involves injection into the same target muscle and was therefore provided for information only. Allergan plans to submit to the TGA a category 1 application for extension of indication to include treatment of patients with IOAB in 2012.

As such, a statement that implies inadequacy of data is not appropriate in the indication section as an application for the use of Botox in IOAB patients has not been submitted. Therefore Allergan would propose the following wording be placed in the Precautions section of the PI:

"The safety and effectiveness of Botox has not been established for patients with idiopathic overactive bladder."

Allergan believes that the indication section is not the most appropriate place to highlight a precaution related to use in IOAB as the indication section should describe only the patient populations in which the product has been approved to be used.

Therefore, Allergan's proposed wording for the indication is as follows:

"treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological condition (such as MS or SCI) in adults who have an inadequate response to or are intolerant of anticholinergic medication"

Conclusion

In conclusion Allergan agrees with the Delegate's decision to approve the extension of indication for Botox. However, Allergan proposes modified wording for the indication as follows:

"treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological condition (such as MS or SCI) in adults who have an inadequate response to or are intolerant of anticholinergic medication"

Advisory Committee Considerations

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have a positive benefit-risk profile for the indication;

Treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from defined neurological illness (such as MS or SCI) and not controlled adequately by anticholinergic agents.

This does not include idiopathic detrusor overactivity, for which there is insufficient evidence of efficacy.

In making this recommendation, the ACPM supported the proposal by the Delegate that the RMP should be strengthened to ensure development, implementation and monitoring of the effectiveness of an appropriate education program for both health professionals and consumers.

The ACPM supported the amendments proposed by the Delegate to the PI and CMI and advised inclusion of the following;

- a statement in the 'Precautions and Clinical Trials' sections to ensure the information accurately reflects the clinical trial populations and that the precautions are highlighted.
- amendments of the 'Contraindications' section to ensure emphasis of the patient group that is at higher risk of requiring catheterisation following this treatment.
- statements in the appropriate section of the 'CMI' to assist patients in self care activities to prevent urinary tract infections, for example post coital bladder emptying for female patients.

Specific conditions of registration which may be considered include requiring the sponsor to implement the revisions to the RMP, with particular regard to the sponsor's obligations to enable access to the CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Botox (botulinum toxin Type A) purified neurotoxin complex for the additional **new indication**:

Botox is approved for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder.

The full indications are now:

Botox (botulinum toxin Type A) purified neurotoxin complex is indicated for the following **therapeutic** indications:

- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as multiple sclerosis or spinal cord injury) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder;
- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine);
- treatment of strabismus in children and adults;
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VII nerve disorders (specifically hemifacial spasm) in patients twelve years and older;
- treatment of cervical dystonia (spasmodic torticollis);
- treatment of focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years of age and older;
- treatment of severe primary hyperhidrosis of the axillae;
- treatment of focal spasticity in adults; and
- treatment of spasmodic dysphonia.

Botox (botulinum toxin Type A) purified neurotoxin complex is indicated for the following **cosmetic** indications:

- temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

Special conditions of registration applying to these therapeutic goods:

1. Details of the distribution of the drug including quantities and forms of products distributed and related batch numbers should be supplied on request while the drug remains on the ARTG.
2. That the sponsor take all necessary steps to implement the RMP version 4.0 (14 October 2010), and any subsequent updated versions as agreed with the OPR.
3. That there is to be an amendment of the RMP so as to reflect the relationship between the risk of urinary tract infection and impaired bladder emptying and increased need for catheterisation, this amendment to be agreed to by the OPR. With respect to this condition of registration, the sponsor is required, within 30 calendar days of the date

on the approval letter signed by the Delegate, to enter into discussions with the OPR as to how the amendment to the RMP may be best achieved.

4. That the sponsor is to take all necessary steps to design and implement a robust and objective program to monitor the continuing adequacy of prescriber education in relation to the use of Botox for the indication of neurogenic detrusor overactivity, this program to be agreed to by the OPR and to be reflected, if necessary, by appropriate amendments to the RMP. With respect to this condition of registration, the sponsor is required, within 30 calendar days of the date on the approval letter signed by the Delegate, to enter into discussions with the OPR as to how any such amendments to the RMP may be best achieved.
5. That the sponsor is to take all necessary steps to ensure the development, implementation and monitoring of the effectiveness of an appropriate education program for consumers in relation to the use of Botox for the indication of neurogenic detrusor overactivity, this program to be agreed to by the OPR and to be reflected, if necessary, by appropriate amendments to the RMP. With respect to this condition of registration, the sponsor is required, within 30 calendar days of the date on the approval letter signed by the Delegate, to enter into discussions with the OPR as to how any such amendments to the RMP may be best achieved.
6. That, at the time of marketing a 200 U vial of Botox in Australia, the sponsor is to issue an appropriate Dear Healthcare Professional Letter which must be approved by the TGA.
7. That the sponsor is to provide to the TGA, as evaluable data within the context of a category 1 submission, the final study report of Study 518 (191622-518), the dose ranging study which was ongoing at the time of submission, the study report to be provided as soon as it is available.
8. That the sponsor is to provide to the TGA, as evaluable data within the context of a category 1 submission, the final study report of the extension Study 094 (191622-094) which was ongoing at the time of submission, the study report to be provided as soon as it is available.
9. That the sponsor is to provide to the TGA, as evaluable data within the context of a category 1 submission, the final study report of the safety Study 082 in patients with neurogenic detrusor overactivity who also have neurologically based respiratory impairment (Study 082), the study report to be provided as soon as it is available.
10. The sponsor is to provide to the TGA, as evaluable data within the context of a category 1 submission, the final study report of the post marketing study, requested by the MHRA and to be conducted within the UK, of the utilisation patterns and safety data for Botox used in the treatment of chronic migraine, the study report to be provided as soon as it is available.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #

NAME OF THE MEDICINE

BOTOX® purified neurotoxin complex injection (100 U or 200 U)
(botulinum toxin, type A)

DESCRIPTION

Composition

Active ingredient:

Each vial of BOTOX® contains either 100 units (U) or 200 units (U) of botulinum toxin, type A, as a haemagglutinin complex.

Excipients:

Human albumin: 0.5 mg for 100 U or 1.0 mg for 200 U

Sodium chloride: 0.9 mg for 100 U or 1.8 mg for 200 U

BOTOX® (botulinum toxin type A) Neurotoxin complex is produced from the fermentation of *Clostridium botulinum* type A (Hall strain) and is purified from the culture solution as an approximately 900 kD molecular weight complex consisting of the neurotoxin and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing human serum albumin and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice, performed in a mouse potency assay. This assay method is specific to Allergan's product, BOTOX®. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD₅₀ assays, units of biological activity of BOTOX® cannot be compared to or converted into units of any other botulinum toxin activity.

PHARMACOLOGY

Pharmacodynamics

Therapeutic class: neuromuscular blocking agent.

Clostridium botulinum type A neurotoxin blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals by cleaving SNAP-25, a protein integral to the docking and release of acetylcholine from vesicles located within the nerve terminals.

After injection, there is an initial high-affinity binding of toxin to specific cell surface receptors on cholinergic nerve terminals. Bound toxin is then internalised by endocytosis, and the catalytic light chain is translocated across the vesicular membrane into the cytosol where it cleaves SNAP-25. Progressive inhibition of acetylcholine release follows and clinical signs usually manifest within 2-3 days.

Recovery after intramuscular injection takes place normally within 12 weeks. Preclinical studies have demonstrated that, new sprouts from the original preterminal axons allow for a temporary reconnection of the neuron with the endplates. These sprouts are only partially effective and subsequently regress while the original nerve terminal at the primary neuromuscular junction becomes functional again. The relevance of these preclinical observations to the clinical condition remains to be established.

Neurogenic Detrusor Overactivity

Due to its pharmacological mechanism of action, it is expected that BOTOX[®] affects the efferent pathways of detrusor activity mainly via inhibition of acetylcholine release.

Chronic Migraine

Limited nonclinical data suggest that BOTOX[®] may reduce sensitisation processes, but the actual mechanism of action for headache prophylaxis is not known.

Blepharospasm

The relaxing effect on muscles injected with BOTOX[®] is useful in reducing the excessive, abnormal contractions associated with blepharospasm. Following peri-ocular injection of BOTOX[®], distant muscles show electrophysiological changes but no clinical weakness or other clinical change for a period of several weeks or months, parallel to the duration of local clinical paralysis.

Typically, patients with blepharospasm show improvement lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus

When used for the treatment of strabismus, it is postulated that the administration of BOTOX[®] affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist.

Focal Spasticity in adults and children two years and older

BOTOX[®] treatment reduces both the objective signs and subjective symptoms of spasticity. Improvements include reduction in muscle tone, increase in range of motion, reduction in pain and a reduction of spasticity-related functional disability.

Cervical Dystonia (spasmodic torticollis)

When injected into neck muscles, BOTOX[®] reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements may include reduced pain/discomfort, reduced head rotation, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and functional disability improvement. Based on the results of early publications in naïve patients, 40 to 58% of patients with cervical dystonia respond with a significant improvement in their symptoms after initial treatment with BOTOX[®]. Among patients who have previously benefited from BOTOX[®] injection for cervical dystonia, approximately 91% can expect improvement for any given treatment period based on patient withdrawal data in a recent trial.

Primary Hyperhidrosis of the Axillae

The proposed mechanism of action of BOTOX[®] in hyperhidrosis is the inhibition of cholinergically driven excessive sweating, by locally blocking the autonomic sympathetic cholinergic nerve fibres innervating sweat glands. This is achieved by injecting the toxin in the vicinity of the sweat glands, which are located within the dermis of the skin. Injections for this indication must therefore be given intradermally. Hyperhidrosis is typically treated by multiple intradermal injections given in a grid-like pattern over the affected area. The objective of treatment is to reduce sweating to a physiologically normal level which patients find tolerable. Anhidrosis is not the target.

When injected intradermally, BOTOX[®] produces temporary chemical denervation of the sweat gland resulting in local reduction of sweating.

Spasmodic Dysphonia

Spasmodic dysphonia is a focal laryngeal dystonia with task specific spasms of the vocal cords seriously interfering with communication. Approximately 90% of the patients have adductor spasmodic dysphonia with spasms of the adductor muscles including thyroarytenoid, lateral cricoarytenoid and interarytenoid muscles. About 10% of patients have abductor spasmodic dysphonia with spasms of the abductors of the vocal cords, in particular the posterior cricoarytenoid muscles. Many studies have shown that at least 90% of patients with adductor spasmodic dysphonia obtain a satisfactory or better result with BOTOX[®] injections. Treatment of abductor spasmodic dysphonia is more technically difficult and results are less satisfactory, but with a tailored approach most patients still obtain satisfactory improvement with BOTOX[®] injections.

Glabellar Lines

Glabellar lines are secondary to relative overactivity (or hyperfunctioning) of the muscles associated with frowning. When injected into the corrugator and/or procerus muscles, BOTOX[®] weakens the overactive underlying muscle contraction, decreasing the severity of the glabellar lines and improving appearance. In controlled clinical trials, onset of action was rapid (effect of BOTOX[®] was apparent at the first assessment timepoint of 7 days) and lasted at least 4 months for many subjects.

Crow's Feet

Crow's feet are well established, deep, radiating, horizontal and oblique furrows at the temporal aspect of each eye and are the direct result of the contraction of the lateral fibers of the orbicularis oculi muscles. In controlled clinical trials, injections of BOTOX[®] into the lateral orbital area resulted in rapid onset of action (effect of BOTOX[®] was apparent at the first assessment timepoint of 7 days) and reduced the severity of wrinkling in this area for up to 17 weeks.

Forehead Lines

Horizontal forehead lines are associated with chronic functional activity of the frontalis muscle. At two weeks post-injection, 84-95% of BOTOX[®]-treated patients were considered by investigators as treatment responders; 75-80% of patients felt they had improvement (16 or 24 U at four sites in the frontalis muscle). Higher doses of BOTOX[®] resulted in greater efficacy and longer duration of effect. Injections of BOTOX[®] reduced the severity of horizontal forehead lines for up to 24 weeks as determined by a trained observer.

Pharmacokinetics

Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the nature of this product.

Distribution in rats was studied following injection of ^{125}I -botulinum neurotoxin A complex into the gastrocnemius muscle. Radioactivity associated with the toxin complex was mostly retained at the injection site, declining with a half-life of approximately 10 hours. Radioactivity detected in other locations (plasma, muscle, thyroid, skin) was mainly associated with probable breakdown products, indicating minimal systemic exposure to toxin. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. The toxin is probably metabolised by proteases and the molecular components cycled through normal metabolic pathways.

CLINICAL TRIALS – Therapeutic Indications

Neurogenic Detrusor Overactivity

Two double-blind, placebo-controlled, randomised, multi-centre phase 3 clinical studies were conducted in patients with urinary incontinence due to neurogenic detrusor overactivity who were either spontaneously voiding or using catheterization (indwelling catheters were not allowed). A total of 691 spinal cord injury (lesion at T1 or below) or multiple sclerosis patients (EDSS at 6.5 or below), not adequately managed with at least one anticholinergic agent, were enrolled. These patients were randomised to receive either 200 U of BOTOX[®] (n=227), 300 U of BOTOX[®] (n=223), or placebo (n=241). Both pivotal trials (191622-515 and 191622-516) were superiority studies compared to placebo. The primary endpoint was the number of episodes of urinary incontinence as recorded by patient bladder diary. Analysis of covariance was used to assess differences in efficacy between BOTOX[®] and placebo, with baseline value as a covariate, and treatment arm, etiology (MS or SCI), concurrent use/non-use of anticholinergics, and investigator site as factors. Baseline demographics of the pooled pivotal trial population are shown in the table below:

Baseline Demographics per Etiology in Phase 3 Studies

	MS	SCI
N (%)	381 (55.1%)	310 (44.9%)
Age, median years (range)	50.0 (22-77)	41.5 (18-77)
Male gender, N (%)	70 (18.4%)	221 (71.3%)
Using CIC, N (%)	112 (29.4%)	263 (84.8%)
Spontaneously Voiding, N (%)	265 (69.6%)	42 (13.5%)

In both phase 3 studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed favouring BOTOX[®] (200 U and 300 U) at the primary efficacy time point at week 6, including the percentage of dry patients. Significant improvements in some urodynamic parameters were observed, including decreases in peak detrusor pressure during the first involuntary detrusor contraction. Increases in maximum cystometric capacity were observed, but in patients who were spontaneously voiding these were offset by almost equivalent increases in post-void residual volume (please see last row of the table below).

Significant improvements in patient reported incontinence specific health-related quality of life scores as measured by the Incontinence Quality of Life questionnaire (I-QOL) (including avoidance limiting behaviour, psychosocial impact and social embarrassment) were also observed. No additional benefit of BOTOX[®] 300 U over 200 U was demonstrated.

Results from the pivotal studies are presents below:

Primary and Secondary Efficacy Variables at Baseline and Change from Baseline in Phase 3 Studies

	Study 1 (191622-515)			Study 2 (191622-516)		
	BOTOX[®] 200 U (N=135)	Placebo (N=149)	p-values	BOTOX[®] 200 U (N=92)	Placebo (N=92)	p-values
Weekly Frequency of Urinary Incontinence*						
Mean Baseline	32.3	28.3		32.5	36.7	
Mean Change at Week 2	-16.9	-8.6	p=0.008	-18.8	-9.7	p<0.001
Mean Change at Week 6^a	-21.0	-8.8	p<0.001	-21.8	-13.2	p=0.002
Mean Change at Week 12	-20.8	-8.3	p<0.001	-20.5	-12.2	p=0.002
Maximum Cystometric Capacity (mL)						
Mean Baseline	252.3	256.0		247.3	249.4	
Mean Change at Week 6^b	+151.2	+15.5	p<0.001	+157.0	+6.5	p<0.001
Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH₂O)						
Mean Baseline	51.3	50.9		51.7	41.5	
Mean Change at Week 6^b	-35.1	-2.4	p<0.001	-28.5	+6.4	p<0.001
Incontinence Quality of Life Total Score^{c,d}						
Mean Baseline	33.95	35.06		37.46	35.72	
Mean Change at Week 6^b	+26.90	+10.81	p<0.001	+24.43	+11.71	p<0.001
Mean Change at Week 12	+31.42	+9.05	p<0.001	+25.08	+8.56	p<0.001
Maximum Cystometric Capacity minus Post Void Residual^e						
N	50	46		40	37	
Mean Baseline	195.1	170.1		151.2	160.0	
Mean Change at Week 6	+35.8	-36.9	-	+20.8	+16.8	-

p-values are based on an LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.

* Percentage of dry patients (without incontinence) throughout week 6 was 36.3% (200 U BOTOX[®] group) and 10.1% (placebo) in Study 1, and 38.0% (200 U BOTOX[®] group) and 7.6% (placebo) in Study 2

^a Primary endpoint

^b Secondary endpoints

^c I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

^d In the phase 3 studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

^e Maximum cystometric capacity (MCC) and post void residual (PVR) may not have been measured on the same day, but they were measured within the same visit window. Only patients who had MCC and PVR data at both baseline and Week 6 visits and not using CIC at baseline were analysed.

The median duration of response in the two phase 3 studies, based on patient request for re-treatment, was 256-295 days (36-42 weeks) for the 200 U dose group compared to 92 days (13 weeks) with placebo.

Placebo recipients crossed over to active therapy for subsequent treatment cycles so there are no placebo-controlled data beyond the first treatment cycle. For all efficacy endpoints, patients receiving a second treatment experienced a broadly similar response. Data beyond two intradetrusor treatments are limited.

Chronic Migraine

BOTOX[®] was evaluated in two multi-national, multi-centre 56-week studies that included a 24-week, 2 injection cycle, double-blind phase comparing BOTOX[®] to placebo (saline), followed by a 32-week, 3 injection cycle, open-label phase. A total of 1,384 chronic migraine adults who had either never received or were not using any concurrent headache prophylaxis during a 28-day baseline, had ≥ 15 headache days, with 50% being migraine/probable migraine, and ≥ 4 headache episodes were studied in two phase 3 clinical trials. These patients had a mean duration of chronic migraine for 19.2 ± 12.56 years, and during the 28-day baseline 906 (65.5%) patients were and 478 (34.5%) patients were not overusing acute headache pain medications. These patients were randomised to placebo (saline) or to 155 U - 195 U BOTOX[®] injections every 12 weeks; maximum 5 injection cycles. During the trial, patients were allowed to use acute headache treatments. BOTOX[®] treatment demonstrated statistically significant ($p < 0.001$) and clinically meaningful improvements from baseline compared to placebo (saline) for 50% reduction in headache days, mean frequency of moderate/severe headache days and total cumulative hours of headache on headache days (see Tables 1, 2, 3 and 4). Results of the Headache Impact Test (HIT-6) and Migraine-Specific Quality of Life (MSQ) questionnaires indicated BOTOX[®] had a sustained duration of action and improved functioning, vitality, psychological distress and overall quality of life (refer to Tables 1, 2, 3 and 4).

Table 1: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX [®] (N=688)	Placebo (saline) (N=696)	p- value
Mean change from baseline in frequency of headache days ^a	-8.4	-6.6	<0.001
Mean change from baseline in frequency of migraine/probable migraine days ^a	-8.2	-6.2	<0.001
Mean change from baseline in number of moderate/severe headache days ^a	-7.7	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days ^a	-119.73	-80.49	<0.001
Mean change from baseline in frequency of headache episodes ^a	-5.2	-4.9	0.009
Decrease from baseline in 50% or more headache days ^a	47.1%	35.1%	<0.001
Proportion of patients with severe HIT-6 category scores ^b	67.6%	78.2%	<0.001
Total HIT-6 scores ^b	-4.8	-2.4	<0.001
Mean change from baseline in MSQ scores ^b			
Role function- Restrictive	-17.0	-8.6	<0.001
Role function- Preventative	-13.1	-6.4	<0.001
Role function- Emotional Function	-17.9	-9.5	<0.001

^a Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

^b Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 2: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in Medication Overuse Subgroup

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX [®] (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days ^a	-8.2	-6.2	<0.001
Mean change from baseline in frequency of migraine/probable migraine days ^a	-8.1	-6.0	<0.001
Mean change from baseline in number of moderate/severe headache days ^a	-7.7	-5.7	<0.001
Mean change from baseline in total cumulative hours of headache on headache days ^a	-111.91	-73.26	<0.001
Mean change from baseline in frequency of headache episodes ^a	-5.6	-4.9	0.028
Proportion of patients with severe HIT-6 ^b category scores	71.0%	81.9%	<0.001
Total HIT-6 scores ^b	-4.7	-2.2	<0.001
Mean change from baseline in MSQ scores ^b			
Role function- Restrictive	-16.9	-7.6	<0.001
Role function- Preventative	-13.9	-5.8	<0.001
Role function- Emotional Function	-18.3	-8.7	<0.001

^a Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

^b Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 3: Week 24 (Primary Timepoint) Key Efficacy Variables for Pooled Phase 3 Studies in No Medication Overuse Subgroup

Efficacy per 28 days	Pooled Studies 191622-079 & 191622-080		
	BOTOX [®] (N=445)	Placebo (saline) (N=459)	p- value
Mean change from baseline in frequency of headache days ^a	-8.8	-7.3	0.013
Mean change from baseline in frequency of migraine/probable migraine days ^a	-8.4	-6.6	0.004
Mean change from baseline in number of moderate/severe headache days ^a	-7.7	-6.1	0.005
Mean change from baseline in total cumulative hours of headache on headache days ^a	-128.75	-99.73	0.023
Mean change from baseline in frequency of headache episodes ^a	-5.1	-4.5	0.146
Proportion of patients with severe HIT-6 ^b category scores	61.3%	70.9%	0.027
Total HIT-6 scores ^b	-5.1	-2.7	<0.001
Mean change from baseline in MSQ scores ^b			
Role function- Restrictive	-17.2	-10.6	0.001
Role function- Preventative	-11.7	-7.7	0.032
Role function- Emotional Function	-17.4	-11.0	0.017

^a Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

^b Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Table 4: Week 24 (Primary Timepoint) Key Efficacy Variables for Phase 3 Studies

Efficacy per 28 days	Study 191622-079			Study 191622-080		
	BOTOX [®] (N=341)	Placebo (saline) (N=338)	p- value	BOTOX [®] (N=347)	Placebo (saline) (N=358)	p- value
Mean change from baseline in frequency of headache days ^a	-7.8	-6.4	0.006	-9.0	-6.7	<0.001
Mean change from baseline in frequency of migraine/probable migraine days ^a	-7.6	-6.1	0.002	-8.7	-6.3	<0.001
Mean change from baseline in number of moderate/severe headache days ^a	-7.2	-5.8	0.004	-8.3	-5.8	<0.001
Mean change from baseline in total cumulative hours of headache on headache days ^a	-106.70	-70.40	0.003	-132.41	-90.01	<0.001
Mean change from baseline in frequency of headache episodes ^a	-5.2	-5.3	0.344	-5.3	-4.6	0.003
Proportion of patients with severe HIT-6 category scores ^b	68.9%	79.9%	0.001	66.3%	76.5%	0.003
Total HIT-6 scores ^b	-4.7	-2.4	<0.001	-4.9	-2.4	<0.001
Mean change from baseline in MSQ scores ^b						
Role function- Restrictive	-16.8	-8.8	<0.001	-17.2	-8.4	<0.001
Role function- Preventative	-12.6	-7.6	0.005	-13.5	-5.4	<0.001
Role function- Emotional	-16.9	-10.0	0.001	-19.0	-9.1	<0.001
Function						

^a Evaluated over a 28 day pre-randomisation baseline period and a 28 day period leading up to Week 24

^b Administered once at baseline and once at Week 24, and designed to collect data based on patient's one month recall

Blepharospasm

In one study, botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six of the patients had previously undergone drug treatment utilising benztropine mesylate, clonazepam and/or baclofen without adequate clinical results. Three of these patients then underwent muscle stripping surgery still without an adequate outcome. One patient of the 27 was previously untreated. Upon using botulinum toxin, 25 of the 27 patients reported improvement within 48 hours. One of the other patients was later controlled with a higher dosage. The remaining patient reported only mild improvement but remained functionally impaired.

In another study, twelve patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. All patients receiving botulinum toxin (n=8) were improved compared with no improvements in the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61% and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.

In a separate study, blepharospasm patients received an average dose per eye of 33 U of BOTOX[®] injected at 3 to 15 sites. The most frequently reported treatment-related adverse events were ptosis (20.8%), superficial punctate keratitis and eye dryness (6.3% each).

Strabismus

Six hundred and seventy-seven adult patients with strabismus treated with one or more injections of BOTOX[®] were evaluated in a large retrospective case review. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection (1). Large strabismus angles tended to return to pre-injection position and required re-injection more frequently than smaller angles. Thirty-five percent of adults with horizontal strabismus were corrected by one injection to within 10 prism diopters of orthoposition.

Focal spasticity in children 2 years and older

Upper limb spasticity

Two randomised, evaluator-blinded studies compared BOTOX[®] plus standard care with standard care alone in a total of 72 children with hemiplegic cerebral palsy and upper limb spasticity. In these studies the muscles in the arm and hand that were injected included the biceps brachii, brachialis, brachioradialis, flexor carpi ulnaris and radialis, pronator teres, pronator quadratus, flexor digitorum profundus and sublimis, flexor pollicis longus and brevis, thumb adductor, short flexor of the thumb and interossei.

In the 6-month study (n = 42; 2 to 8 years) spasticity as measured by the Modified Ashworth Scale (MAS) was significantly reduced in children treated with BOTOX[®] (1-2 U/kg/muscle, maximum dose 240 units, mean 137 units) at months 1 and 3, but returned to baseline values at month 6. Quality of upper limb movement as measured by the Quality of Upper Extremity Skills Test (QUEST) improved significantly from baseline in both groups but to a greater extent in BOTOX[®]-treated children at months 1 (61% vs. 19%, p=0.004) and 3 (71% vs 33%, p=0.03), but not at month 6 (p=1.0). Children treated with BOTOX[®] had a significantly greater improvement in function as measured by Goal Attainment Scaling (GAS). Children treated with BOTOX[®] improved more quickly than those treated with standard care alone. No treatment-related adverse effects were reported.

In the three month study (n = 30, 5-15 years) upper limb function was measured using the Melbourne Assessment of Unilateral Upper Limb Function. Children in the BOTOX[®] group (0.5 to 2.0 U/kg/muscle) had a 14% improvement in function compared with no change in children in the control group at month 3 (p = 0.002). In this study, there was no difference between treatment groups on the GAS. Three treatment-related adverse effects were reported, 2 localised weakness and one increased frequency of micturition.

Lower limb spasticity – Equinus

A three-month, double-blind, placebo-controlled parallel study was conducted in cerebral palsy children, aged 2 to 16 years with equinus ankle position. Seventy-two were administered 4U/kg body weight of BOTOX[®] into the medial and lateral heads of the gastrocnemius at baseline (2 U/kg/muscle), for hemiplegic patients and 1 U/kg/muscle for diplegic patients) and again at 4 weeks. The cumulative dose of BOTOX[®] over 4 weeks was 2-4 U/kg/muscle and overall 8 U/kg body weight up to a maximum of 200 units during a 30 day period. BOTOX[®] was significantly more effective than placebo (as assessed by improvement of 3 or more grades on the composite score of Rating Scale (PRS) of dynamic gait (gait pattern, ankle position, hindfoot position during foot strike, knee position during gait, degree of crouch and speed of gait). Improvement was reported by 53%, 50%, 60% and 54% of BOTOX[®] patients versus 25%, 27%, 25% and 32% of placebo patients at weeks 2, 4, 8 and 12, respectively. Of the individual assessments included on the PRS, a significantly greater number of BOTOX[®] patients versus placebo patients had improvements in gait pattern (weeks 2, 8 and 12) and ankle position (weeks 2, 6 and 12).

In the 39 month long-term, open-label follow-up of these patients, the medial and lateral gastrocnemius muscles were injected at a dose of 2 U/kg/muscle with a maximum total dose of 200 U of BOTOX[®] into the medial and lateral heads of the gastrocnemius, and then as needed thereafter. Of the 207 patients evaluated; 115 patients were followed for 12 months, 100 for 18 months, 45 for 2 years and 6 for up to 3 years. The percent of patients who showed an improvement based on the PRS ranged from 41% to 67% over the 3-year period. Of the individual assessments which were included in the PRS, significant improvements were seen at every visit over the 3-year period.

Lower limb spasticity – hip adductor

Published studies showed that BOTOX[®] is effective in reducing pain and spasticity and improving function. A double-blind placebo-controlled study⁸ (n=16) in children aged 2 to 10 years found that 4U/kg body weight to each adductor muscle group (total dose 8 units/kg total body weight) administered 5 -10 days before scheduled isolated adductor surgery significantly reduced mean pain scores (74% reduction, p=0.003), analgesic requirements (50% reduction, p=0.005) and length of hospital stay (33% reduction, p=0.003) compared with placebo.

A second study⁹ (n = 43, mean age 8.2 ± 2.5 years) compared the efficacy of BOTOX[®] (300 U injected into the adductor and medial hamstring muscles) with a pressure splint against hip adductor muscle spasticity. Both groups improved during the study period, however, at the 3 month visit, BOTOX[®] was significantly more effective than pressure splints for spasticity and motor performance as measured by the MAS (p=0.002) and knee distance (p=0.02).

Adverse events were not reported in these studies.

Focal spasticity in adults

Three double-blind placebo-controlled studies involving 256 post-stroke patients with upper limb spasticity showed clinically and statistically significant improvements in wrist, elbow and finger flexor muscle tone. The Ashworth scale was used to measure clinically significant changes in muscle tone which was assessed from a score of zero (no increase in muscle tone) to 4 (limb rigid in flexion or extension).

In one study, 126 patients were treated with 200 U to 240 U of BOTOX® into the wrist, finger and thumb flexor muscles. A clinically and statistically significantly greater reduction in muscle tone was observed in BOTOX®-treated patients compared to placebo as measured on the Ashworth scale ($p < 0.001$) at 1, 4, 6, 8, and 12 weeks post-treatment. The Physician Global Assessment also showed statistically significant improvements at all post-treatment visits for these patients ($p < 0.001$). Furthermore, patients treated with BOTOX® had significant improvement for a pre-determined, targeted disability item associated with upper limb spasticity at 4, 6, 8 and 12 weeks post-treatment ($p \leq 0.05$).

In two studies, patients treated with a total dose of either 300 U or 360 U of BOTOX® had significantly greater reduction in wrist and elbow flexor tone compared to placebo. Additionally, the Physician Global Assessment also showed significant benefit from BOTOX® at doses of 75, 180 and 360 U.

In a double-blind, placebo-controlled study of 85 patients with moderate to severe lower limb spasticity, injections of up to 300 U of BOTOX® into the soleus, posterior tibialis and either gastrocnemius or flexor digitorum longus muscles resulted in a reduction of spasm frequency, a reduction in pain, an improvement in spasticity as rated by the physician and increase in range of motion of the ankle as measured by goniometry. All of these changes were clinically and statistically significant. In addition, treatment with BOTOX® in patients with severe spasticity (Ashworth score of 3) resulted in a clinically and statistically significant reduction in muscle tone. In an open-label follow-up to this study, a second injection of BOTOX® clinically and statistically significantly reduced muscle tone in both moderate and severe patients at 4, 8 and 12 weeks post 2nd injection.

Cervical Dystonia (spasmodic torticollis)

In a multicentre study, 170 cervical dystonia patients who had responded to an open-label run-in period (out of 214 patients) were randomised to receive BOTOX® (n=88) or placebo (n=82) in a double-blind, parallel-group evaluation for 10 weeks. Physicians determined the muscles and doses injected for each patient and used a mean total body BOTOX® dose of 236 U (Range: 95 to 360 U). BOTOX® was significantly better compared with placebo by measures of improvement in the Cervical Dystonia Severity Scale (head position rating), physician global assessment, patient global assessment, frequency and intensity of pain, and functional disability by week 6, with sustained benefit for up to 10 weeks. Improvement, as measured by physician global assessment, was 50.6% for the BOTOX® group and 31.1% for the placebo group, a difference of 19.5% ($p = 0.009$), which was essentially the same as the pre-defined value of 20% set for a clinically meaningful difference.

In a separate multicentre study, a total of 135 patients were treated. Patients received a single 100-300 U injection of one formulation followed by the other, 8-16 weeks later. Physicians determined the muscles and doses to be injected for each patient and used a mean total body BOTOX® dose of approximately 155 U for all treatment periods. Maximum clinical improvement was observed at 6 weeks, with over 80% of patients achieving a treatment success by week 6. In relation to time-to-retreatment, at week 6 (42 days) post-injection, 67% of the BOTOX® group had not yet worsened since baseline compared to 45% of the placebo group. At week 10 (70 days) post-injection, 60% of the BOTOX® group remained improved compared to 30% in the placebo group. These differences were statistically significant ($p = 0.0002$).

Primary Hyperhidrosis of the Axillae

In a double-blind, parallel-group, multicentre study, 320 patients with bilateral axillary primary hyperhidrosis were randomised to receive BOTOX[®] (n=242) or placebo (n=78). Subjects were eligible for enrolment in the study if their baseline spontaneous axillary, as measured by gravimetric assessment over 5 minutes at room temperature and at rest, was \geq 50 mg. Baseline axillary sweat production was similar in the two treatment groups (216 mg in the BOTOX[®] group and 236 mg in the placebo group). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric assessment.

The incidence of responders among BOTOX[®]-treated patients was significantly higher ($p < 0.001$) than placebo-treated patients at all post-treatment time points for up to 16 weeks. The incidence of responders among BOTOX[®]-treated patients ranged from 95% at week 1 to 82% at week 16 compared to 32% at week 1 to 21% at week 16 for placebo-treated patients. The mean percentage reduction in the BOTOX[®]-treated group ranged from 83% at week 1 to 69% at week 16 compared to 22% at week 1 to 4% at week 16 in the placebo-treated group. The corresponding mean amounts of sweat production at these timepoints were 29 mg and 54 mg in the BOTOX[®]-treated patients compared to 166 mg and 190 mg in the placebo-treated patients.

Subject's global assessment of treatment satisfaction was significantly higher ($p < 0.001$) in BOTOX[®]-treated than placebo-treated patients at all post-treatment timepoints.

Spasmodic Dysphonia

In the largest series reported 639 patients with adductor spasmodic dysphonia and 108 patients with abductor spasmodic dysphonia were injected with a mean dose of 3.1 ± 3.1 units and 2.16 ± 1.07 units of BOTOX[®] respectively. The patients recorded the responses in a diary, including their percentage of normal function, on a global visual analogue scale where 100% was a normal voice and 0% was inability to phonate. For adductor spasmodic dysphonia the mean onset of effect was 2.4 ± 4.3 days with a mean peak effect of 9 ± 12.7 days. The mean duration of benefit was 15.1 ± 12.3 weeks, the percent of normal function rose from $52.4\% \pm 22\%$ to $89.71\% \pm 13\%$. For abductor spasmodic dysphonia mean onset of effect was 4.1 ± 5.5 days with a mean peak effect of 10 ± 12.5 days. The mean duration of benefit was 10.5 ± 12.2 weeks. The percentage of normal function rose from $54.8\% \pm 21.9\%$ to $66.7\% \pm 23.4\%$ respectively.

In another large series of 169 patients (adductor spasmodic dysphonia 88.8%, abductor spasmodic dysphonia 1.8% and mixed spasmodic dysphonia 4.1%) the median treatment outcome score was excellent in 63.9% of patients, very good in 18%, satisfactory in 14.5% and unsatisfactory in 3.5%, as judged by a subjective self-rating scale which patients recorded in a diary. Speech rate increased after BOTOX[®] therapy by approximately 12 syllables per minute. Nasendoscopy, before and after treatment in many patients, confirmed the weakening of the vocal cords and abolition of the spasms.

CLINICAL TRIALS – Cosmetic Indications

Glabellar Lines

In two multicentre, double-blind, placebo-controlled, parallel-group studies of identical design, patients with moderate to severe glabellar lines evaluated at maximum frown were randomised to receive BOTOX[®] (n=405) or placebo (n=132). In these studies, the severity of

glabellar lines was significantly reduced for up to 120 days in the BOTOX[®] group compared to the placebo group as measured by investigator rating of glabellar line severity at maximum frown and at rest, and by subjects global assessment of change in appearance of glabellar lines. Thirty days after injection, 80% of BOTOX[®]-treated patients were considered by investigators as treatment responders (glabellar line severity score of mild or none), and 89% of patients felt they had moderate or better improvement, compared to 3.0% and 6.8% of placebo-treated patients respectively.

A third, open-label study was also conducted to support the continued efficacy of repeat BOTOX[®] injections. At the completion of the double-blind studies, patients were able to enter this open-label phase with repeat treatments given at 120 day intervals. Therapeutic effect was maintained over the three injection cycles assessed with results showing increased efficacy following multiple injection sessions.

Crow's Feet

Two multicentre, double-blind, placebo-controlled, parallel-group studies were performed to examine the safety and efficacy of BOTOX[®] for the treatment of crow's feet. In one study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile were randomised to receive BOTOX[®] (n=130) [age range 27 to 64 years (mean = 47 years)], injected bilaterally at three sites per side, for a dose of 3 U, 6 U, 12 U or 18 U per side or placebo (n=32). Treatment with BOTOX[®] showed a dose-related response up to 12 U; although the response was similar in the two highest dose groups, 12 U and 18 U. The duration of response was dose-related, with significant mean reductions from baseline in crow's feet severity to day 180 for the 12 U ($p \leq 0.032$) and 18 U ($p \leq 0.003$) groups, day 150 for the 6 U group ($p \leq 0.017$) and day 120 for the 3 U group ($p \leq 0.006$). No significant changes were seen within the placebo group at any post-treatment timepoint. Maximum responder rates were observed at day 30 for all treatment groups. The safety profile in the active treatment groups was similar to placebo.

The second study examined the safety and efficacy of treatment of crow's feet with 1 of 3 dosages of BOTOX[®] (n=148) or placebo (n=49) [age range 27 to 65 years (mean = 47 years)], and the effect on the severity of forehead lines and glabellar lines. In this study, patients with bilaterally symmetrical, moderate or severe crow's feet at maximum smile; forehead line severity of mild, moderate or severe at maximum eyebrow elevation and glabellar line severity of mild, moderate or severe at maximum frown were treated with BOTOX[®], injected bilaterally at three sites per side, for a dose of 6 U, 12 U or 18 U per side or placebo. Although significant improvements in crow's feet were seen with all BOTOX[®] doses when compared to placebo, the treatment of crow's feet did not affect the severity of either horizontal forehead lines or glabellar lines. Thus it appears that the treatment of crow's feet at doses of 18 U, 12 U and 6 U does not affect adjacent areas and as such dose modification is not considered necessary. No safety concerns were seen at any dose of BOTOX[®] treatment.

The safety and efficacy of BOTOX[®] for the treatment of crow's feet has been described in published clinical studies. In one study, 60 patients were treated with 6 U, 12 U or 18 U of BOTOX[®] in the orbicularis oculi muscle on one side of the face and placebo contralaterally. At 16 weeks after injection, patients were treated with 12 U or 18 U of BOTOX[®] bilaterally. BOTOX[®] was associated with significantly higher success rates than placebo at all dose levels, as determined by both trained observers and patients. At 4 weeks post-injection, 89-95% of patients on the BOTOX[®]-treated side were considered by investigators as treatment

responders and 60-80% of patients felt they had treatment success, compared to approximately 5-15% and 15-45%, respectively on the placebo treated side. No clear dose response relationship was observed. Benefits of the second injection lasted longer than the first, with success rates for the second injection reaching 100% for the 12 U and 18 U groups at week 4. BOTOX[®] was well tolerated. No serious or severe adverse events were reported.

Forehead Lines

The safety and efficacy of BOTOX[®] for the treatment of horizontal forehead lines has been described in published clinical studies. In one study, BOTOX[®] was administered to 59 patients with horizontal forehead lines scoring 2 (moderate) or 3 (severe) on the facial wrinkle scale (FWS). Patients were randomly assigned to receive 8 U, 16 U and 24 U of BOTOX[®] injected into the frontalis muscle with additional brow depressor injections. Approximately 90% of subjects responded to treatment as rated by investigators and up to 75-80% by self-assessment at week four. There was a reduction in horizontal rhytide severity in all three BOTOX[®] treatment groups at both contraction and repose. There was a significant dose-response trend ($p \leq 0.019$) for sustained duration of improvement: 53% in the 24 U group versus 15% in the 8 U group at 16 weeks ($p \leq 0.023$ for difference between groups), by trained observer. There was a significant dose-response trend ($p \leq 0.011$) for rate of relapse to baseline: 35% in the 24 U group versus 75% in the 8 U group at 16 weeks ($p \leq 0.038$ for difference between groups), by trained observer. BOTOX[®] was well tolerated. No serious adverse events were reported.

INDICATIONS

BOTOX[®] (botulinum toxin type A) purified neurotoxin complex is indicated for the following therapeutic indications:

- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) and not controlled adequately by anticholinergic agents. This does not include idiopathic overactive bladder.
- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- treatment of strabismus in children and adults
- treatment of blepharospasm associated with dystonia, including benign blepharospasm and VIIth nerve disorders (specifically hemifacial spasm) in patients twelve years and over
- treatment of cervical dystonia (spasmodic torticollis)
- treatment of focal spasticity of the upper and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older
- treatment of severe primary hyperhidrosis of the axillae
- treatment of focal spasticity in adults
- treatment of spasmodic dysphonia.

BOTOX[®] (botulinum toxin type A) purified neurotoxin complex is indicated for the following cosmetic indications:

- temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.

CONTRAINDICATIONS

BOTOX[®] (botulinum toxin type A) purified neurotoxin complex is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation.

BOTOX[®] is contraindicated in patients with myasthenia gravis or Eaton Lambert Syndrome.

BOTOX[®] is contraindicated in the presence of infection at the proposed injection site(s).

Intradetrusor injection of BOTOX[®] is contraindicated in patients who have acute urinary tract infection, and in patients with acute urinary retention who are not routinely catheterising.

Due to the risk of urinary retention, intradetrusor injection of BOTOX[®] is also contraindicated in patients who are not willing and/or able to initiate catheterisation post-treatment, if required (See **Clinical Trials**).

PRECAUTIONS

General

Lack of interchangeability between botulinum toxin products

DUE TO THE LACK OF AN INTERNATIONAL UNIT, BOTOX[®] IS NOT THERAPEUTICALLY EQUIVALENT TO ANY OTHER BOTULINUM TOXIN TYPE A PREPARATIONS. THE POTENCIES OF BOTOX[®] AND OTHER BOTULINUM TOXIN TYPE A PREPARATIONS ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR BOTULINUM TOXIN TYPE A, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. THE EFFECT OF ADMINISTERING DIFFERENT BOTULINUM NEUROTOXIN SEROTYPES AT THE SAME TIME OR WITHIN SEVERAL MONTHS OF EACH OTHER IS UNKNOWN. EXCESSIVE NEUROMUSCULAR WEAKNESS MAY BE EXACERBATED BY ADMINISTRATION OF ANOTHER BOTULINUM TOXIN PRIOR TO THE RESOLUTION OF THE EFFECTS OF A PREVIOUSLY ADMINISTERED BOTULINUM TOXIN.

Spread of toxin effect

Postmarketing safety data from BOTOX[®] and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin, have been reported hours to weeks after injection, and may include muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing and respiratory depression. The risk of symptoms is probably greatest in children treated for spasticity, but these symptoms can also occur in patients who have underlying conditions and co-morbidities that would predispose them to these symptoms including adults treated for spasticity and other conditions, and are treated with high doses. Swallowing and breathing difficulties can be life threatening and there have been reports of death, although an exact relationship to BOTOX[®]

has not been established. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur.

Pre-existing neuromuscular disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should only receive BOTOX[®] with extreme caution. Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX[®]. Published medical literature has reported rare cases of administration of botulinum toxin to patients with known or unrecognised neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. When exposed to very high doses, patients with neurologic disorders, e.g. paediatric cerebral palsy or adult spasticity may also be at increased risk of clinically significant systemic effects.

Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX[®] either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX[®] inappropriately diluted with 5 mL of 1% lidocaine. The causal role of BOTOX[®], lidocaine, or both cannot be reliably determined.

The recommended dosages and frequencies of administration for BOTOX[®] should not be exceeded (see **Dosage and Administration**).

Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX[®] treatment by inactivating the biological activity of the toxin. The critical factors for neutralising antibody formation have not been well characterised. The potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections.

There have been rare reports of adverse events following administration of BOTOX[®] involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. The exact relationship of these events to BOTOX[®] has not been definitely established and will continue to be monitored by Allergan Australia Pty Ltd.

The safe and effective use of BOTOX[®] (botulinum toxin, type A) purified neurotoxin complex depends upon proper storage of the product, selection of the correct dose and proper reconstitution and administration techniques. Physicians administering BOTOX[®] should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Care should be taken when injecting near vulnerable anatomic structures and direct injection into these structures must be avoided.

Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX[®] injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX[®] near the thorax, and therefore extreme caution is required when injecting in this area. Caution is warranted when injecting in proximity to the lung, particularly the apices. An understanding of standard electromyographical techniques may be useful for the treatment of hemifacial spasm, cervical dystonia (spasmodic torticollis) and for the treatment of dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy patients.

Caution should be exercised when BOTOX[®] is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscles.

As with any injection, procedure-related injury could occur. An injection could result in localised infection and pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the BOTOX[®] injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.

This product contains human serum albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Neurogenic Detrusor Overactivity

The intradetrusor administration of BOTOX[®] is only to be conducted by a urologist/urogynaecologist who has been trained in this highly specialised technique or by a urologist/urogynaecologist under the direct supervision of a urologist/urogynaecologist who has been so trained.

Appropriate medical caution should be exercised when performing a cystoscopy. In these patients, autonomic dysreflexia associated with the procedure could occur, which may require prompt medical therapy.

The safety and effectiveness of BOTOX[®] has not been established for patients with idiopathic overactive bladder.

In patients who are not catheterising, BOTOX[®] may decrease their ability to fully empty the bladder due to the pharmacological mode of action on the detrusor contractions. Therefore, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks in these patients. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required. Patients who develop an increase in post-void residual urine and/ or patients who start to catheterise may have an increased risk of developing urinary tract infections. Patients who are not catheterising need to be made aware of this prior to treatment.

Patients who are not catheterising and who subsequently develop a clinically relevant increase in post-void residual urine, may need to start to catheterise to achieve desired efficacy (See **Clinical Trials**).

Safety and efficacy data beyond two intradetrusor treatments are limited.

Please refer to the Adverse Events General section for local weakness or weakness of adjacent muscles.

Blepharospasm

Reduced blinking following BOTOX[®] injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with cranial nerve VII disorders. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower medial lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

As a result of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles. Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin.

Strabismus

BOTOX[®] is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX[®] treatment in deviations over 50 prism dioptres, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required.

During the administration of BOTOX[®] for the treatment of strabismus, retrobulbar haemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to examine and decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Spasticity

BOTOX[®] is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens and is not intended as a replacement for these treatment modalities. BOTOX[®] treatment is not likely to be effective in improving range of motion at a joint affected by a known fixed contracture.

Identification of treatment goals and clinical examination to identify the specific muscles causing spasticity is necessary, and use of electromyography, muscle ultrasound or electrical stimulation may facilitate the accuracy of the BOTOX[®] injections.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin.

Caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Cervical Dystonia (spasmodic torticollis)

Dysphagia and Breathing Difficulties

Treatment with BOTOX[®] and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Primary Hyperhidrosis of the Axillae

Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, pheochromocytoma) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Spasmodic Dysphonia

The diagnosis of spasmodic dysphonia should also be established by a multidisciplinary approach including neurological, ENT and speech pathology assessment. Laryngoscopy (preferably by a nasendoscope) is mandatory during the diagnostic evaluation to exclude other structural disorders of the larynx causing any form of dysphonia and to observe the nature of the hyperadductive or hyperabductive movements.

In general, treatment of spasmodic dysphonia with BOTOX[®] injections should not be administered in pregnant or breastfeeding women. It should be avoided in patients who are due to have elective surgery requiring general anaesthetic as BOTOX[®] relaxes the vocal cords, potentially increasing the risk of peri-operative aspiration etc. It is recommended that this procedure be carried out by appropriately trained physicians in facilities prepared to manage reflex stridor should it occur in association with the procedure.

Upper Facial Rhytides (forehead lines, crow's feet and glabellar lines)

Reduced blinking from BOTOX[®] injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII disorders. Caution should be used when BOTOX[®] treatment is used in patients who have an inflammation at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

Chronic migraine

Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX[®] should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX[®]. The use of BOTOX[®] for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

The safety and effectiveness of BOTOX[®] have not been established for the prophylaxis of headaches in adults with episodic migraine (14 headache days or fewer per month) or tension type headache.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX[®] injection. BOTOX[®] is not structurally related to any known carcinogens.

Genotoxicity

BOTOX[®] was inactive in *in vitro* tests for gene mutation and in *in vitro* and *in vivo* tests for clastogenicity.

Effects on Fertility

Intramuscular BOTOX[®] doses of 4 U/kg (males) and 8 U/kg (females) did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in Pregnancy: Pregnancy Category B3.

There are no adequate data regarding the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX[®] should not be used during pregnancy unless the benefits clearly outweigh the potential risks. If the use of BOTOX[®] is determined to be warranted during pregnancy, or if the patient becomes pregnant whilst being treated with BOTOX[®], the patient should be apprised of the potential risks.

There was no evidence of teratogenicity in animal studies. Intramuscular administration of BOTOX[®] to mice and rats during the period of organogenesis reduced dam weight gain and fetal ossification (4 U/kg); higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification. Intramuscular administration to rabbits twice during the period of organogenesis resulted in abortions (2 U/kg) and maternal deaths (4 and 6 U/kg), while daily intramuscular administration during organogenesis resulted in reduced fetal weights (0.25 and 0.5 U/kg) and increased resorptions (0.5 U/kg); the no-effect dose was 0.125 U/kg, although all doses were maternotoxic. Intramuscular treatment of rats with a maternotoxic dose of BOTOX[®] (16 U/kg) twice during gestation and once during lactation resulted in increased post-implantation loss and reduced pup weights, but post-weaning pup development was unaffected. The significance of the adverse findings in animals for clinical risk is uncertain.

Use in Lactation

There is no information on whether BOTOX[®] is excreted in human milk. The use of BOTOX[®] during lactation is not recommended.

Paediatric Use

The safety and effectiveness of BOTOX[®] in the treatment of urinary incontinence due to neurogenic detrusor overactivity have not been established in patients below the age of 18 years.

Safety and effectiveness in paediatric patients below the age of 18 years have not been established for the indication of chronic migraine.

Safety and effectiveness in children below the age of 12 years have not been established for the indications of blepharospasm, hemifacial spasm, cervical dystonia, hyperhidrosis, spasmodic dysphonia or upper facial lines (forehead, crow's feet and glabellar lines). The safety and effectiveness of BOTOX[®] in the treatment of focal spasticity has not been investigated in children under two years of age.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BOTOX[®] has not been established in these cases and will continue to be monitored by Allergan Australia Pty Ltd. Some of these patients had risk factors including significant neuromuscular debility, dysphagia, aspiration pneumonia, seizures and cardiovascular disease. Post-marketing reports of possible distant effects from the site of injection have been very rarely reported in paediatric patients with co-morbidities, predominately with cerebral palsy who received >8 U/kg. Extreme caution should be

exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

New onset or recurrent seizures have also been reported, typically in children who are predisposed to experiencing these events. The exact relationship of these events to the BOTOX[®] injection has not been established.

Use in the Elderly

The reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Effects on the ability to drive and use machines

Asthenia, muscle weakness, dizziness and visual disturbance have been reported after treatment of BOTOX[®] and could make driving or using machines dangerous.

Interactions with other Medicines

The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or any other drugs that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants). Caution should be exercised when BOTOX[®] is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmycin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs which interfere with neuromuscular transmission.

No specific tests have been carried out to establish the possibility of clinical interaction with medicinal products. No drug interactions of clinical significance have been reported.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Information for Patients

Patients should be informed that the BOTOX[®] Consumer Medicines Information leaflet is available and must be provided to them by prescribers.

If BOTOX[®] is used during pregnancy, or if the patient becomes pregnant while being treated with BOTOX[®], the patient should be apprised of the potential risks, including abortion seen in animal studies.

Patients with cervical dystonia (spasmodic torticollis) should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration and/or dyspnoea. In rare cases, tube feeding, aspiration pneumonia and death have been reported. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Patients or caregivers should be advised to seek immediate medical consultation if swallowing, speech or respiratory disorders arise.

After bladder injections for urinary incontinence, patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required. Patients not already catheterising prior to BOTOX[®] bladder injections, should be advised to attend a clinic visit approximately 2 weeks after the procedure for measurement of their post-void residual volume.

Patients who are not catheterising and who subsequently develop a clinically relevant increase in post-void residual urine, may need to start to catheterise to achieve desired efficacy (See **Clinical Trials**).

Effects on Laboratory Tests

There were no significant differences in routine laboratory variables between the placebo and BOTOX[®] groups in patients receiving doses up to 360 U, for the treatment of cervical dystonia.

ADVERSE EFFECTS

General

In general, adverse events occur within the first few days following injection of BOTOX[®] and while generally transient may have duration of several months or, in rare cases, longer. As is expected for any injection procedure, localised pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Local weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles and/or muscles remote from the site of injection has been reported.

Neurogenic Detrusor Overactivity

Table 1 presents the most frequently reported adverse reactions in double-blind studies within 12 weeks of injection for neurogenic detrusor overactivity.

Table 1: Adverse Reactions Reported by $\geq 1\%$ of BOTOX[®] -treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX[®] 200 Unit (N=262)	Placebo (N=272)
Infections and infestations Urinary tract infection	24.4%	17.3%
Renal and urinary disorders Urinary retention	17.2%	2.9%
General disorders and administration site conditions Fatigue	3.8%	1.1%
Psychiatric disorders Insomnia	1.5%	0%

The following rates with BOTOX[®] 200 Units were reported during the complete treatment cycle (median duration of 44 weeks of exposure): urinary tract infections (49.2%), urinary retention (17.2%), fatigue (6.1%), and insomnia (3.1%).

In these neurogenic patients, the following additional adverse reactions were reported during the complete treatment cycle: constipation (4.2%), muscular weakness (3.8%), fall (3.1%), gait disturbance (2.7%), muscle spasm (2.3%), and bladder diverticulum (1.1%). Procedure-related events in the 200 Unit BOTOX[®] group included: haematuria (3.8%), dysuria (2.3%), and autonomic dysreflexia (1.5%). No change was observed in the overall safety profile with repeat dosing.

In the multiple sclerosis (MS) patients enrolled in the pooled pivotal studies, the annualised MS exacerbation rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX[®] and 0.20 for placebo. The annualised MS exacerbation rates reported in the individual studies, showed differing trends between the two pivotal studies: 0.14 for BOTOX[®] and 0.22 for placebo for study 191622-515, and 0.36 for BOTOX[®] and 0.19 for placebo for study 191622-516.

Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 38.9% following treatment with BOTOX[®] 200 U versus 17.3% on placebo.

In the pivotal studies of neurogenic detrusor overactivity, in the subgroup not using catheterisation at baseline, only 10.1 % of placebo recipients had commenced catheterisation at Week 12, compared to 25.5% of the 200 U group. Urinary tract infections were increased in patients who developed elevated residual volumes, even if they did not commence catheterisation.

The following table presents a summary of UTI rates by pre- and post-treatment CIC status and post-void residual urine volume during the first 12 weeks.

Summary of UTI Rates by Pre- and Post-treatment CIC Status and post-void Residual Urine Volume During the First 12 Weeks

CIC Status		200U BOTOX [®]	Placebo
Pre-treatment	Post-treatment		
Using CIC	Using CIC ^a	22.0% (29/132)	20.7% (29/140)
Not Using CIC	Using CIC	40.4% (19/47)	11.9% (5/42)
	Not Using CIC	21.3% (13/61)	16.4% (10/61)
	Not Using CIC and PVR urine ≥ 200 mL	32.0% (8/25)	0.0% (0/5)
	Not Using CIC and PVR urine < 200 mL	13.9% (5/36)	17.9% (10/56)

CIC = clean intermittent catheterisation; PVR = post-void residual

^a Patients who were using CIC pre-treatment continued to use it post-treatment

Chronic Migraine

Safety data were compiled from two Chronic Migraine double-blind, placebo-controlled studies involving 687 patients treated with BOTOX[®]. The following adverse reactions were reported.

Adverse Reactions Reported by ≥1% of BOTOX[®] treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions	BOTOX [®] N=687	Placebo N=692
Nervous system disorders		
Headache	32 (4.7%)	22 (3.2%)
Migraine	26 (3.8%)	18 (2.6%)
Facial paresis	15 (2.2%)	0 (0.0%)
Eye disorders		
Eyelid ptosis	25 (3.6%)	2 (0.3%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (8.7%)	19 (2.7%)
Musculoskeletal stiffness	25 (3.6%)	6 (0.9%)
Muscular weakness	24 (3.5%)	2 (0.3%)
Myalgia	21 (3.1%)	6 (0.9%)
Musculoskeletal pain	18 (2.6%)	10 (1.4%)
Muscle spasms	13 (1.9%)	6 (0.9%)
Muscle tightness	9 (1.3%)	3 (0.4%)
General disorders and administration site conditions		
Injection site pain	23 (3.3%)	14 (2.0%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (1.0%)	2 (0.3%)
Rash	7 (1.0%)	6 (0.9%)

Migraine, including worsening migraine, was reported in 3.8% of BOTOX[®] and 2.6% of placebo (saline) patients, typically occurring within the first month after treatment. These reactions did not consistently reoccur with subsequent treatment cycles, and the overall incidence decreased with repeated treatments.

Other adverse reactions reported more frequently in the BOTOX[®] group compared to the placebo group at a frequency less than 1% include: dysphagia, pain in jaw, and pain of skin.

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX[®] vs. 1.2% for placebo (saline).

Blepharospasm

In clinical studies of 1684 patients who received 4258 treatments (involving multiple injections) for blepharospasm, the incidence rates of adverse reactions per treated eye are listed below:

Ptosis	11.0%
Irritation/tearing (includes dry eye, lagophthalmos and photophobia)	10.0%
Ectropion, keratitis, diplopia and entropion were reported rarely	<1.0%

Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

Diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection were reported infrequently in clinical studies.

In two cases of VIIth nerve disorder (one case of an aphakic eye) reduced blinking from BOTOX[®] injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect and corneal ulceration. Perforation requiring corneal grafting occurred in one case, an aphakic eye. Avoidance of injection into the lower lid area to avoid ectropion may reduce this hazard. Vigorous treatment of any corneal epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses or closure of the eye by patching or other means.

Two patients previously incapacitated by blepharospasm experienced cardiac collapse attributed to over-exertion within three weeks following BOTOX[®] therapy. Sedentary patients should be cautioned to resume activity slowly and carefully following the administration of BOTOX[®].

Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin (See **Precautions**).

Strabismus

In a clinical investigation of botulinum toxin use in strabismus over a 9-year period, the incidence rates (% injections) of adverse events from 8,300 injections are reported (1). The total number of patients who received the injections is not reported.

Effects on adjacent muscles: the incidence of partial ptosis and vertical deviation were 16% and 17% respectively. Complete ptosis was rare. In one series, slight residual ptosis (0.16%) and induced vertical deviation of greater than two prism dioptres (2%) persisted for 6 months or longer.

Retrobulbar haemorrhage (0.2%) occurred without visual loss. Decompression of the orbit after five minutes was performed to restore retinal circulation in one case.

Scleral perforation (0.11%): these tended to occur in myopic eyes and at a prior surgical site. A vitreous haemorrhage occurred in one patient which reduced vision for several months before clearing. In another patient, a reduction in vision from 20/25 to 20/30 was reported.

Pupillary dilation (0.06%): at least two of these were consistent with ciliary ganglion damage (Adie's pupil).

Past pointing and spatial disorientation may result from inducing paralysis in one or more extraocular muscles. Covering the affected eye may alleviate these symptoms.

Diplopia is common after treatment in patients with good vision in both eyes. Diplopia in adults can be managed by patching. In one case, diplopia appeared to be permanent due to loss of suppression.

No systemic paralytic effect has been seen or suspected in any patient treated with the small doses used for strabismus.

Variation in incidence rates of the most frequently observed effects, ptosis and vertical deviation per patient, have also been reported in other retrospective observational studies. There is no obvious explanation for the substantial variation. In the literature, 3 different studies (2-4) evaluating BOTOX[®] for the treatment of strabismus (n=266) indicated percent incidence of ptosis occurred in a range of 30% to 37% of injections or 37% of patients. Vertical deviation was reported in 42% of injections or from 10% to 34% of patients.

Other studies have shown side effects such as sub-conjunctival and conjunctival haemorrhages to be fairly common. There have also been infrequent reports of headache, cycloplegia, ocular vertigo and corneal irritation. In one study, 5/45 (11.1%) patients were shown to exhibit an increase in intra-ocular pressure which was reversible.

VIIth Nerve Disorders (hemifacial spasm)

Adverse effects reported after injection of BOTOX[®] have included blurring of vision, facial droop, dizziness and tiredness, in addition to those listed above.

Focal spasticity in children two years and older

The safety of BOTOX[®] used for the treatment of focal spasticity was evaluated, from clinical studies for the treatment of dynamic equinus foot deformity, upper limb spasticity and lower limb spasticity. As is expected for any intramuscular injection procedure, localised pain, discomfort, bruising and oedema was associated with the injection in these patients. All treatment-related adverse events were mild to moderate in severity and were self-limiting.

In children treated for upper limb spasticity, the most frequently reported treatment related adverse events included local and general weakness, trigger finger, clumsiness, hypokinesia, falling and increased frequency of micturition, joint dislocation and muscle spasms. The percent of patients who experienced these events at least once during the study are summarised below:

	BOTOX [®] (n=74)
Muscular weakness, local	5.4%
Muscular weakness, general	2.7%
Trigger finger	2.7%
Clumsiness	1.4%

Falling	1.4%
Hypokinesia	1.4%
Increased frequency of micturition	1.4%
Joint dislocation	1.4%
Muscle spasms	1.4%

Other adverse events reported commonly or very commonly in these studies were convulsions, nasopharyngitis, pneumonia, vomiting and contusion.

In children treated for dynamic equinus foot deformity due to spasticity in juvenile cerebral palsy, the adverse events most frequently reported treatment-related included falling, leg pain, leg (local) weakness and general weakness. The percent of patients who experienced these events at least once during the study are summarised below:

BOTOX[®] (n=215)

Falling	9.3%
Leg Pain	2.3%
Weakness, local	2.3%
Weakness, general	2.3%

Falling may be attributable to a change in ankle position and gait pattern and/or local weakness. Local weakness represents the expected pharmacological action of botulinum toxin.

Other treatment-related adverse reactions reported in 1% of patients were: leg cramps, fever, knee pain, ankle pain, pain at the injection site post-treatment and lethargy. Urinary incontinence has also been reported.

In children treated for spasticity of the hip adductor muscles, there were no adverse events reported in the studies evaluated.

Focal Spasticity in Adults

The safety of BOTOX[®] was evaluated in 339 unique patients who received treatment for upper limb spasticity associated with stroke in double-blind and open-label studies. In general, the majority of adverse events reported were mild to moderate in severity and were typically self-limiting.

The following events were reported as treatment related in 1 - 4% of patients and are listed in decreasing order of incidence: arm pain and hypertonia.

Fever and flu syndrome were also reported in approximately 1% of patients. The following events were reported as treatment related in less than 1% of patients and are listed in decreasing order of incidence: hyperesthesia, arthralgia, asthenia, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension and pruritus.

The safety of BOTOX[®] was evaluated in 82 patients who received a single treatment for lower limb spasticity associated with stroke in either a double-blind or an open-label study. The following treatment related adverse events were reported: accidental injury (1.2%), incoordination (1.2%) and paresthesia (1.2%). Adverse events reported were mild to moderate in severity.

Of the 56 patients who received BOTOX[®] in the double-blind phase of the study, 44 went on to receive a second injection in the open-label study. Additional treatment related adverse reactions reported were: hypertonia (4.5%), asthenia (2.3%), headache (2.3%) and hyperkinesia (2.3%).

Cervical Dystonia (spasmodic torticollis)

The following adverse events were reported following BOTOX[®] treatment for cervical dystonia. Patients received an average dose of 155 U (range 100 – 300 U).

ADVERSE EVENT	BOTOX [®] (n = 131)
Body as a whole:	
- neck pain	5.3%
- asthenia	3.1%
- headache	1.5%
- pain at injection site	1.5%
Digestive system	
- dysphagia	12.2%
Muscular system	
- muscle weakness	0.8%

Dysphagia was the most commonly reported adverse event after treatment with BOTOX[®]. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX[®] resulting from the spread of the toxin outside the injected muscles. Dysphagia is usually reported as mild to moderate severity in most patients. However, in an occasional patient it may be associated with more severe problems. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia. (See **Precautions**).

Neck pain due to BOTOX[®] injection may be due to a change in resting tone for the contralateral muscles, or other muscles not previously affected by dystonia. In rare instances, neck pain has been severe. Dysphonia has also been reported in the literature for patients who have been treated for cervical dystonia. Rhinitis has also been reported.

Primary Hyperhidrosis of the Axillae

The safety of BOTOX[®] was evaluated in 287 patients who received at least 1 treatment exposure of primary hyperhidrosis of the axillae in double-blind and open-label studies. Adverse events reported as treatment related in greater than 1% of BOTOX[®]-treated patients are listed in decreasing order of incidence: perceived increase in non-axillary sweating (4.5%), injection site pain (1.7%), pain (1.4%) and vasodilation (hot flushes) (1.0%). Two of 207 subjects (1.0%) who received repeated injections of BOTOX[®] developed transient arm weakness. Body odour has also been reported.

Spasmodic Dysphonia

In the largest series reported of BOTOX[®] treatment for this disorder common adverse events after treatment with BOTOX[®] were breathy dysphonia (47.6% of all treatment sessions), dysphagia (14.9%) and aspiration (5.9%) for adductor spasmodic dysphonia and dysphagia (11.2%) and stridor (6.9%) for abductor dysphonia.

In another large trial of 169 patients with spasmodic dysphonia, the following adverse events were recorded in ≥ 1 of 1093 BOTOX[®] treatments. Paralytic dysphonia (breathy dysphonia) in 338/1093 (31%) treatments (mild 139, moderate 114, severe 73, very severe 12), technical failure in 90/1093 (8%) treatments, dysphagia in 38/1093 (3%) treatments (mild 17, moderate 15, severe 4, very severe 2), pain in 13/1093 (1%) treatments (mild 5, moderate 6, severe 2), gagging in 6/1093 (0.5%) treatments (mild 3, moderate 3), diplophonia in 3/1093 treatments, flu-like symptoms in 2/1093 treatments of moderate severity, and persistent cough in 2/1093 treatments.

Glabella Lines

Safety of BOTOX[®] for the treatment of glabellar lines was evaluated in two multicentre, double-blind, placebo-controlled, parallel-group studies (n=535; 405 in the BOTOX[®]-treated group and 130 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment related adverse events were headache (9.4% in the BOTOX[®] group and 12.3% in the placebo group) and blepharoptosis (3.2% in the BOTOX[®] group and 0% in the placebo group). Blepharoptosis is consistent with the pharmacologic action of BOTOX[®] and may be injection technique-related.

Adverse events reported as treatment related in 1-3% of BOTOX[®]-treated patients, listed in decreasing order of incidence were: injection site pain/burning/stinging (2.5%), face pain (2.2%), erythema (1.7%), local muscle weakness (1.7%), injection site oedema (1.5%), ecchymosis (1.0%), skin tightness (1.0%), paresthesia (1.0%) and nausea (1.0%).

Crow's Feet

The safety of BOTOX[®] for the treatment of crow's feet was evaluated in two multicentre, double-blind, placebo-controlled, parallel group studies (246 in the BOTOX[®]-treated groups (6 U to 18 U/side) and 80 in the placebo-treated group). Most adverse events reported were of mild to moderate severity and all were transient. The most frequently reported treatment-related adverse events were injection site haemorrhage i.e. bruising at the injection site (8.1% in the BOTOX[®] 6 U to 18 U/side groups and 10.0% in the placebo group) and headache (3.7% in the BOTOX[®] 6 U to 18 U/side groups and 2.5% in the placebo group). Flu syndrome was reported in 1.6% of BOTOX[®]-treated patients (6 U to 18 U/side) and in none of the placebo-treated patients. All other adverse events reported as treatment-related in the BOTOX[®] groups were reported in less than 1% of patients.

Other studies have reported the incidence of injection site bruising to be between 4-25% of BOTOX[®]-treated patients, with similar rates noted for placebo. Other adverse events related to BOTOX[®] treatment included temporary droop of the lateral portion of the lower eyelid (5%), which is consistent with the pharmacologic action of BOTOX[®] and may be injection technique-related.

Forehead Lines

In a clinical study where BOTOX[®] was administered to 59 patients with horizontal forehead lines (8 U to 24 U into frontalis), the following treatment related adverse events were reported: headache (22.0%), bruising (10.2%), eyebrow ptosis (10.2%), eyelid swelling (20.3%), aching/itching forehead (5.1%), nausea (3.4%), feeling of tension (1.7%), flu-like symptoms/cold (1.7%) and other (6.8%). All adverse events were mild or moderate in severity and no serious adverse events were reported.

Post-marketing Experience

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with BOTOX[®].

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including skin rash, urticaria, soft tissue oedema, and dyspnoea (See **PRECAUTIONS**).

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes following BOTOX[®] treatment. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported following BOTOX[®] treatment, typically in patients who are predisposed to experiencing these events.

Angle closure glaucoma has been reported very rarely following BOTOX[®] treatment for blepharospasm.

The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in the **PRECAUTIONS** and **ADVERSE EFFECTS** sections: denervation/muscle atrophy; respiratory depression and/or respiratory failure (non-Cosmetic indications); dyspnea; aspiration pneumonia (non-Cosmetic indications); dysarthria; dry mouth; strabismus; peripheral neuropathy, abdominal pain; diarrhoea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; rash; erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis; and alopecia including madarosis.

DOSAGE AND ADMINISTRATION

Route of Administration

Intramuscular injection. Reconstituted BOTOX[®] is injected with the purpose of reaching the motor endplate region of the muscle to be treated. May be subcutaneous for blepharospasm. Intradermal for primary hyperhidrosis of the axillae.

General

BOTOX[®] should only be given by physicians with the appropriate qualifications and experience in the treatment of patients and the use of required equipment.

The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative. Once opened and reconstituted, store in the refrigerator and use within twenty four hours. Discard any remaining solution. Do not freeze reconstituted BOTOX®.

In general, dosing of BOTOX® should be individualised for each patient and always start with the minimal effective dose. The dosing interval should typically not be more frequent than every three months.

If different vial sizes of BOTOX® are being used as part of one injection procedure, care should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 mL. The amount of diluent varies between BOTOX® 100 Allergan Units and BOTOX® 200 Allergan Units. Each syringe should be labelled accordingly.

Neurogenic Detrusor Overactivity

The intradetrusor administration of BOTOX® is only to be conducted by a urologist/urogynaecologist who has been trained in this highly specialised technique or by a urologist/urogynaecologist under the direct supervision of a urologist/urogynaecologist who has been so trained.

Patients should not have an acute urinary tract infection at the time of treatment. Prophylactic antibiotics should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment.

It is recommended that patients discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

An intravesical instillation of diluted local anaesthetic with or without sedation, or general anaesthesia, may be used prior to injection, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 U of BOTOX®.

Reconstitute a 200 Unit vial of BOTOX® with 6 mL of 0.9% non-preserved saline solution and mix the vial gently. Draw 2 mL from the vial into each of three 10 mL syringes. Complete the reconstitution by adding 8 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX®. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstitute two 100 Unit vials of BOTOX®, each with 6 mL of 0.9% non-preserved saline solution and mix the vials gently. Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe. Complete the reconstitution by adding 6 mL of 0.9% non-preserved saline solution into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL

(~67 Units in each), for a total of 200 Units of reconstituted BOTOX[®]. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX[®] (200 U/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 U) each (total volume of 30 mL) should be spaced approximately 1 cm apart. For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.

Clinical improvement generally occurs within 2 weeks. It is not recommended that patients be retreated pre-emptively, at fixed intervals. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 256-295 days (36-42 weeks) for BOTOX[®] 200 U), but no sooner than 3 months from the prior bladder injection.

Limited data is available beyond two treatments so the decision to perform a second treatment should be made only after considering the risks and benefits.

Chronic Migraine

The recommended dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 U) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the table below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.

The recommended re-treatment schedule is every 12 weeks.

Due to the difficulties in establishing a diagnosis of chronic migraine, patients being considered for prophylaxis of headaches with BOTOX[®] should be evaluated by a neurologist or pain management specialist prior to receiving treatment with BOTOX[®]. The use of BOTOX[®] for prophylaxis of headaches in adults with chronic migraine has been assessed for 3 cycles over 32 weeks. No long term safety or efficacy data for this indication are available. Patients who do not have an adequate response after 2 treatment cycles should not continue treatment. Patients should not receive more than 3 cycles of treatment prior to an assessment of the need for further treatment.

Recommended injection sites for chronic migraine:



BOTOX[®] Dosing By Muscle for Chronic Migraine

	Recommended Dose
Head/Neck Area	Total Number of Units (U) (number of IM injection sites ^a)
Frontalis ^b	20 U (4 sites)
Corrugator ^b	10 U (2 sites)
Procerus	5 U (1 site)
Occipitalis ^b	30 U (6 sites) up to 40 U (up to 8 sites)
Temporalis ^b	40 U (8 sites) up to 50 U (up to 10 sites)
Trapezius ^b	30 U (6 sites) up to 50 U (up to 10 sites)
Cervical Paraspinal Muscle Group ^b	20 U (4 sites)
Total Dose Range:	155 U to 195 U

^a 1 IM injection site = 0.1 mL = 5 U BOTOX[®]

^b Dose distributed bilaterally for minimum dose

Blepharospasm

An injection of BOTOX[®] (botulinum toxin type A) purified neurotoxin complex is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see **Dilution Table**) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to the injection needle, preferably a 1½", 27-30 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new, sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX[®].

For blepharospasm, diluted BOTOX[®] injection (see Dilution Table) is injected using a sterile, 27-30 gauge needle with or without electromyographic guidance. 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid is the initial recommended dose. Pre-tarsal injections are often appropriate and may vary based on the patient's presentation. In the upper lid, maximising the distance of the injection from the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the

complication of diplopia. Ecchymosis may occur easily in the soft eyelid tissues. This may be reduced by applying light pressure at the injection site immediately after the injection.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated as needed. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient – usually defined as an effect that does not last longer than two months. However there appears to be a minimal increase in benefit from injecting more than 5.0 U per site. Some tolerance may be found when BOTOX® is used in treating blepharospasm if treatments are given any more frequently than every three months. The effect is rarely permanent.

The cumulative dose of BOTOX® in a two month period should not exceed 200 U.

Strabismus

BOTOX® is intended for injection into extraocular muscles utilising the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX® injection, it is recommended that several drops of a local anaesthetic and an ocular decongestant be given several minutes prior to injection.

Note: The volume of BOTOX® injected for treatment of strabismus should be between 0.05 – 0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX® (see **Dilution Table** below) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over 6 months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilise the alignment.

- I. Initial doses in units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
 - A. For vertical muscles, and for horizontal strabismus of less than 20 prism dioptres: 1.25 – 2.5 U in any one muscle.
 - B. For horizontal strabismus of 20 prism dioptres to 50 prism dioptres: 2.5 – 5.0 U in any one muscle.
 - C. For persistent sixth nerve palsy of one month or longer duration: 1.25 – 2.5 U in the medial rectus muscle.
- II. Subsequent doses for residual or recurrent strabismus.
 - A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
 - B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
 - C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.

- D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- E. The maximum recommended dose as a single injection for any one muscle is 25 U.

VIIth Nerve Disorders (hemifacial spasm)

Patients with hemifacial spasm or VIIth nerve disorder should be treated as for unilateral blepharospasm. Further injections may be necessary into the corrugator, zygomaticus major, orbicularis oris and/or other facial muscles according to the extent of the spasm. Electromyographical control may be useful to identify small circumoral muscles.

The cumulative dose of BOTOX[®] in a two-month period should not exceed 200 U.

Treatment of focal spasticity of the upper limb and lower limbs, including dynamic equinus foot deformity, due to juvenile cerebral palsy in patients two years and older

The exact dosage and number of injection sites should be tailored to the child's needs based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials the dose per muscle ranged from 0.5-2.0 U/kg body weight in the upper limb and 2.0 -4.0 U/kg/body weight in the lower limb per treatment session. For the treatment of equinus foot deformity the total dose is up to 4 U/kg or 200 U (whichever is the lesser amount) divided into two sites in each medial and lateral head of the gastrocnemius muscle. In other muscles the dose per muscle ranged from 3.0-8.0 U/kg body weight and did not exceed 300U divided among selected muscles at any treatment session. Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes, but typically not more frequently than every three months. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX[®] and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX[®] in the treatment of focal spasticity in children aged 2 years and older. The maximum cumulative dose should generally not exceed 8.0 units/kg body weight and up to a maximum of 300 U divided among selected muscles at any treatment session or in a 3 month interval:

Muscles in upper limb	Dosage in U/kg/muscle
Biceps brachii	0.5 - 2.0 U
Brachialis	0.5 - 2.0 U
Brachioradialis	0.5 - 2.0 U
Flexor carpi ulnaris	0.5 - 2.0 U
Flexor carpi radialis	0.5 - 2.0 U
Pronator teres	0.5 - 2.0 U
Pronator quadratus	0.5 - 2.0 U
Flexor digitorum profundus	0.5 - 2.0 U
Flexor digitorum sublimis	0.5 - 2.0 U
Flexor pollicis longus	0.5- 2.0 U
Flexor pollicis brevis	0.5 - 2.0 U
Opponens pollicis	0.5 - 2.0 U
Adductor pollicis	0.5 - 2.0 U
Muscles in lower limb	Dosage in U/kg/muscle
Hip adductor group (adductor longus, adductor brevis, adductor magnus, medial hamstrings)	4.0 U
Gastrocnemius	2.0-4.0 U

Focal Spasticity in Adults

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session. Clinical improvement in muscle tone generally occurs within two weeks following treatment with the peak effect seen four to six weeks following treatment. In clinical studies, patients were reinjected at 12- to 16-week intervals. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX[®] and muscles to be injected.

The table below is intended to give dosing guidelines for injection of BOTOX[®] in the treatment of focal spasticity.

Muscle	Total Dosage; Number of Sites
Biceps brachii	100 – 200 U; up to 4 sites
Flexor digitorum profundus	15 - 50 U; 1-2 sites
Flexor digitorum sublimis	15 - 50 U; 1-2 sites
Flexor carpi radialis	15 - 60 U; 1-2 sites
Flexor carpi ulnaris	10 - 50 U; 1-2 sites
Adductor pollicis	20 U; 1-2 sites
Flexor pollicis longus	20 U; 1-2 sites
Posterior tibialis	70 – 100 U; 1-2 sites
Soleus	80 – 125 U; 1-2 sites
Flexor digitorum longus/brevis	50 – 100 U; 2-4 sites
Gastrocnemius medial/lateral	50 – 200 U; 2-4 sites

A 27 or 30 gauge needle should be used with an appropriate needle length to reach the targeted muscles. For focal spasticity, localisation techniques include electromyography, muscle ultrasound or electrical stimulation.

Multiple injection sites may allow BOTOX[®] to have more uniform contact with the innervation areas of the muscle and may be especially useful in larger muscles.

Cervical Dystonia (spasmodic torticollis)

Dosing must be tailored to the individual patient based on the patient's head and neck position, localisation of pain, muscle hypertrophy, patient's bodyweight, and patient response.

Multiple injection sites allow BOTOX[®] to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated. The treatment of cervical dystonia typically may include, but is not limited to, injection of BOTOX[®] into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s).

A 25, 27 or 30 gauge needle should be used for superficial muscles and a needle of appropriate length should be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

The table below is intended to give dosing guidelines for injection of BOTOX[®] in the treatment of cervical dystonia.

Dosage Guide

Classification of Cervical Dystonia	Muscle Groupings	Total Dosage; Number of Sites
Type I Head rotated toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Splenius capitis Trapezius	50-100 U; at least 2 sites 50 U; 1-2 sites 25-50 U; 1-2 sites 25-75 U; 1-3 sites 25-100 U; 1-8 sites
Type II Head rotation only	Sternocleidomastoid	25-100 U; at least 2 sites if >25 U given
Type III Head tilted toward side of shoulder elevation	Sternocleidomastoid Levator scapulae Scalene Trapezius	25-100 U; at posterior border; at least 2 sites if >25 U given 25-100 U; at least 2 sites 25-75 U; at least 2 sites 25-100 U; 1-8 sites
Type IV Bilateral posterior cervical muscle spasm with elevation of the face	Splenius capitis and cervicis	50-200 U; 2-8 sites, treat bilaterally

This information is provided as guidance for the initial injection. The extent of muscle hypertrophy and the muscle groups involved in the dystonic posture may change with time

necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualised for each patient.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection.

Treatment intervals of less than two months are not recommended. The duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on the patient's individual disease and response.

The table below shows the median dose of BOTOX[®] injected per muscle in a clinical study in which dose was determined by the practitioner based on the presentation of the individual cervical dystonia patient.

Muscle(s)	Range of Medians* (U)	Minimum-Maximum Dose, U/muscle**
Sternocleidomastoid	50	15-190
Trapezius	50-60	5-200
Levator scapulae	50	10-180
Splenius capitis/cervicis	90	10-240
Scalene	40	5-90

* Two medians were given: for those patients who received one injection cycle (n=121) and for those patients who received two injection cycles (n=90). When only one number is given, the medians were the same for both groups of patients.

** Limiting the dose injected into the sternocleidomastoid muscle to less than 100 U may decrease the occurrence of dysphagia (See **Precautions**).

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of BOTOX[®] ranged from 140 to 280 U. In more recent studies, the doses have ranged from 95 to 360 U (with an approximate mean of 240 U). As with any drug treatment, initial dosing should begin at the lowest effective dose.

In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia. The time-to-retreatment will vary between patients, however data from controlled clinical studies indicates that symptoms may start to re-emerge at approximately 8-10 weeks post-injection (see **Pharmacology – Clinical Trials**).

Repeat doses should be administered when the clinical effect of a previous injection diminishes, though usually not more frequently than every two months. “Booster” injections are not recommended.

Primary Hyperhidrosis of the Axillae

For the treatment of hyperhidrosis, 100 U of BOTOX[®] should be reconstituted with 4.0 mLs of sterile 0.9% sodium chloride for injection. For each axilla, 50 U of BOTOX[®] (2.0 mL) should be injected intradermally and evenly distributed in 10-15 sites approximately 1-2 cm apart within the hyperhidrotic area. For the treatment of hyperhidrosis, a 30 gauge needle should be used. The hyperhidrotic area may be defined using standard staining techniques (e.g Minor's iodine starch test). Each dose is injected to a depth of approx. 2 mm and at a 45

degree angle to the skin surface with the bevel side up to minimise leakage and ensure the injections remain intradermal. Repeat injections for axillary hyperhidrosis should be administered when the effects from the previous injection subside. However, repeat injections at intervals of less than four months are not recommended.

Spasmodic Dysphonia

Patients with spasmodic dysphonia should be treated by physicians skilled in the anatomy and physiology of the larynx, and have facility with nasal endoscopy and also electromyographically guided injections. The procedure should be carried out in a facility equipped to manage potential acute complications such as reflex stridor. The treatment program should be individualised for each patient at each treatment session. Peak effect is generally seen within 7 days following an injection.

BOTOX® (100 U/vial) should be reconstituted with 4.0 to 5.0 mL of 0.9% sterile non-preserved saline, giving a final concentration of 2.0–2.5 units per 0.1 mL. It is usual to commence with a standard dose of 1.0–2.5 units in 0.1 mL of BOTOX® to each thyroarytenoid muscle in adductor spasmodic dysphonia and subsequently vary the dose by altering the concentration according to patient requirements and response to therapy. An occasional patient will require 3 units per vocal cord and many patients over the years have reduced their dose, down to even 0.2 units per vocal cord. Bilateral injections are generally recommended but an occasional patient will benefit from unilateral injections, sometimes alternating between sides with each subsequent treatment.

In abductor spasmodic dysphonia 2-5 units of BOTOX® are usually injected unilaterally into one posterior cricoarytenoid muscle via a lateral retrocricoid, supracricoid or transcricoid approach.

The injection is usually performed in the supine position with a small pillow under the shoulders to improve laryngeal exposure. For adductor spasmodic dysphonia, the laryngeal surface landmarks are identified, including the thyroid and cricoid cartilage, and in particular the small gap of the cricothyroid membrane. Identification of the landmarks is a critical part of this procedure and sometimes this can be difficult in individuals with thick necks.

In adductor spasmodic dysphonia the EMG recording needle is advanced in the midline through the cricothyroid membrane, directing the needle rostrally, and approximately 30° laterally towards the intended thyroarytenoid muscle. For a bilateral procedure, the needle is redirected towards the corresponding contralateral muscle. Once within the muscle, EMG insertional activity is audible and placement can be confirmed by having the patient phonate an "e". Having confirmed needle placement, the desired amount of BOTOX® in 0.1 mL is injected.

In all cases of abductor spasmodic dysphonia, endoscopy should be performed prior to each treatment to assess the dynamic activity of each vocal cord and the size of the glottal airway. Typically, the posterior cricoarytenoid (PCA) muscle on the more active side is chosen for therapy. A retrocricoid approach should be used whereby the injection needle, containing 2-5 units of BOTOX® in 0.1 mL, is directed towards the PCA muscle in a curving fashion at the level of the cricoid cartilage to lie behind the larynx. The larynx may be rotated laterally on the appropriate side to improve access. To confirm needle placement, the patient sniffs sharply to activate the posterior cricoarytenoid muscle resulting in a characteristic EMG

interference pattern. BOTOX[®] is then injected. Only unilateral injections are recommended at each treatment session. The determination of which PCA muscle to treat at any injection session is determined by endoscopic review. Treatment sessions are performed only when the non-injected cord has sufficient motion to protect from stridor in the event that the injected cord would become immobile. An occasional patient with abductor spasmodic dysphonia will have increased activity of the cricothyroid muscle, which can also be evaluated by EMG, and may also benefit from supplemental injections into this muscle.

To date there has only been one report of a patient developing resistance to the injections, with the development of neutralising antibodies, probably because the doses used are very small compared to other indications.

Upper Facial Lines (Glabellar Lines, Crow's Feet and Forehead Lines)

As optimum dose levels and number of injection sites per muscle may vary among patients, individual dosing regimes should be drawn up. The recommended injection volume per injection site is 0.1 mL.

Glabellar Lines

BOTOX[®] should be reconstituted with 0.9% sterile non-preserved saline (100 U/2.5 mL) and injected using a sterile 30 gauge needle. A volume of 0.1 mL (4 U) is administered in each of 5 injection sites, 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 U.

In order to reduce the complication of ptosis, injection near the levator palpebrae superioris muscle should be avoided, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Improvement of severity of glabellar lines generally occurs within one week after treatment. The effect was demonstrated for up to 4 months.

Crow's Feet

BOTOX[®] should be injected bilaterally at 3 sites in the lateral aspect of the orbicularis oculi (i.e. total of 6 injections), where most lines are seen when a smile is forced. In general, 2-6 U is recommended per injection site at a 2-3 mm depth, for a total dose of 6-18 U per side.

Injections should be at least 1 cm outside the bony orbit, not medial to the vertical line through the lateral canthus and not close to the inferior margin of the zygoma.

Forehead Lines

BOTOX[®] should be injected intramuscularly at each of 4 injection sites in the frontalis muscle. In general, 2-6 U is recommended per injection site every 1-2 cm along either side of a deep forehead crease, for a total dose of 8-24 U.

Injections should be at least 2-3 cm above the eyebrow to reduce the risk of brow ptosis.

Dilution Technique

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. To reconstitute vacuum-dried BOTOX[®] injection, use sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe.

Since BOTOX[®] is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX[®] should be administered within 24 hours after reconstitution in the vial.

During this time period, reconstituted BOTOX[®] should be stored in a refrigerator (2°C to 8°C). Reconstituted BOTOX[®] should be clear, colourless to slightly yellow and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration and whenever the solution and the container permit.

Dilution Table for 100 U and 200 U vials:

Diluent Added (0.9% Sodium Chloride Injection)	100 U Vial	200 U Vial
	Resulting dose (U/0.1 mL)	Resulting dose (U/0.1 mL)
0.5 mL	20	40
1 mL	10	20
2 mL	5	10
4 mL	2.5	5
5 mL	2	4
8 mL	1.25	2.5
10 mL	1	2

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX[®] dose is also possible by administering a smaller or larger injection volume from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

For reconstitution technique for intradetrusor injections for neurogenic detrusor overactivity, please refer to Dosage and Administration section under heading Neurogenic Detrusor Overactivity.

Lack of Response

In the absence of the desired effect after the first treatment session, i.e. no significant clinical improvement from baseline by one month after injection, the following actions should be considered:

- Analysis of potential causes of lack of effect, e.g. inappropriate selection of muscles to be injected; insufficient dose; poor injection technique; muscles inaccessible to injection; underlying structural abnormalities; such as muscle contractures or bone disorders; relative weakness of antagonist muscles; change in pattern of muscle involvement; patient perception of benefit compared with initial results; inappropriate storage or reconstitution; and/or formation of toxin-neutralising antibodies.
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A.

For the second treatment session, in the absence of any undesirable effects after the first treatment session, the physician should consider the following:

- adjust the dose, taking into account the analysis of the earlier treatment failure;

- use of EMG guidance as appropriate; and
- maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections, taking into account dosage adjustments and targeting of injections, alternative treatment methods should be considered.

A neutralising antibody is defined as an antibody that inactivates the biological activity of the toxin. In general, the proportion of patients who lose their response to botulinum toxin therapy and have demonstrable levels of neutralising antibodies is less than 5%, though in a long-term juvenile cerebral palsy study, of 117 patients treated with BOTOX[®], antibodies were detected in 33/117 (28%) at either 27 or 39 months. Thirty-one of these 33 had been responders, 19/31 (6%) continued to respond, with 7/31 (2%) becoming non-responders, and no data available for 5/31.

In the pivotal studies, none of the 475 neurogenic detrusor overactivity patients with analysed specimens developed the presence of neutralising antibodies.

The critical factors for neutralising antibody production are the frequency and dose of injection. Tolerance may be observed in some patients treated more frequently than every three months. The potential for neutralising antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections (injection intervals should typically be no more frequent than three months). The dose should not exceed 360 U in any two month period for adult spasticity patients and patients with cervical dystonia. In treating paediatric patients, the maximum cumulative dose should generally not exceed 8 U/kg, up to a maximum of 300 U, in a 3 month interval. More than one ineffective treatment course should occur before classification of a patient as a non-responder, because there are patients who continue to respond to therapy despite the presence of neutralising antibodies.

OVERDOSAGE

Overdose of BOTOX[®] is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are likely not to be apparent immediately post-injection. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis. Local weakness is usually well tolerated and resolves spontaneously without intervention. However, dysphagia may result in loss of airway protection and aspiration pneumonia.

The entire contents of a vial is below the estimated dose (from primate studies) for toxicity in humans weighing 6 kg or greater.

Should symptoms (muscular weakness, ptosis, diplopia, blurred vision, facial weakness, swallowing and speech disorders, constipation, aspiration pneumonia, difficulty breathing or respiratory depression) occur post injection or oral ingestion, the person should be medically monitored for up to several weeks. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalisation. Advise patients or caregivers to seek immediate medical attention if any of these symptoms occur. Specific anti-toxin to botulinum toxin is only likely to be effective if given within thirty minutes of the botulinum toxin injection.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

BOTOX[®] (botulinum toxin type A) purified neurotoxin complex is a sterile, vacuum-dried preparation. It is supplied in a clear glass vial with a rubber stopper and tamper-proof aluminium seal, containing a white powder for reconstitution. BOTOX[®] is available in 100 U and 200 U of vacuum-dried *Clostridium botulinum* toxin type A. Refer to description for list of excipients.

Storage

Store the vacuum-dried product in the refrigerator between 2°C to 8°C.

Administer BOTOX[®] (botulinum toxin type A) purified neurotoxin complex within 24 hours after the vial is removed from the refrigerator and reconstituted. During these twenty four hours, reconstituted BOTOX[®] should be stored in a refrigerator (2°C to 8°C). When reconstituted BOTOX[®] is further diluted in a syringe for use in urinary incontinence, it should be used immediately. Reconstituted BOTOX[®] should be clear, colourless or slightly yellow and free of particulate matter.

The reconstituted product does not contain a preservative. It should be used for one patient only and any residue discarded.

Disposal

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste. Unused vials should be reconstituted with a small amount of water and then autoclaved. Any unused vials or equipment (such as syringes) should be autoclaved (120°C for 30 minutes), or the residual BOTOX[®] inactivated using dilute hypochlorite solution (0.5% or 1%) for five minutes and then disposed of as medical waste.

NAME AND ADDRESS OF THE SPONSOR

Allergan Australia Pty Ltd
810 Pacific Highway
Gordon NSW 2072
A.B.N. 85 000 612 831

BOTOX[®] 100 U - AUST R 67311
BOTOX[®] 200 U* - AUST R 172264
*- not marketed

POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on: 20 March 2012