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CADTH COMMON DRUG REVIEW

Clinical Review Report

abobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada, Inc.)

Indication: For the symptomatic treatment of focal spasticity affecting the upper limbs in adults.

Service Line:	CADTH Common Drug Review
Version:	1.0
Publication Date:	November 2017
Report Length:	123 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

aboBoNTA	abobotulinumtoxinA (Dysport Therapeutic)
AQoL	Assessment of Quality of Life
AROM	active range of motion
AE	adverse event
BoNT	botulinum neurotoxin
BoNTA	botulinum neurotoxin A
CBS	Caregiver Burden Scale
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
DAS	Disability Assessment Scale
DB	double-blind
DIC	Deviance Information Criterion
EQ-5D	European Quality of Life - 5 Dimensions
FE	fixed effect
GAS	Goal Attainment Scale
incoBoNTA	incobotulinumtoxinA (Xeomin)
ITC	indirect treatment comparison
ITT	intention-to-treat population
LSM	least squares mean
MAS	Modified Ashworth Scale
MCID	minimal clinically important difference
MCMC	Markov chain Monte Carlo methods
MD	mean difference
MFS	Modified Frenchay Scale
MS	multiple sclerosis
MS Society	Multiple Sclerosis Society of Canada
OR	odds ratio
onaBoNTA	onabotulinumtoxinA (Botox)
PGA	Physician Global Assessment
PL	placebo
PM	product monograph
PTMG	primary targeted muscle group
PTT	principal target of treatment

RE	random-effect
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SD	standard deviation
TS	Tardieu Scale
VAS	Visual Analogue Scale
WD	withdrawal
WDAE	withdrawal due to adverse event

Drug	AbobotulinumtoxinA (Dysport Therapeutic).
Indication	For the symptomatic treatment of focal spasticity affecting the upper limbs in adults.
Listing Request	For the symptomatic treatment of focal spasticity including the upper limbs in adults.
Manufacturer	Ipsen Biopharmaceuticals Canada, Inc.

Executive Summary

Introduction

Spasticity is a disabling condition characterized by involuntary muscle overactivity that commonly follows damage to the central nervous system.[1] This chronic, disabling condition needs lifelong surveillance and management with physical, pharmacological therapy, and psychological support. Upper limb spasticity (ULS) can cause significant disability. It is a common feature of many conditions affecting the brain and spinal cord, including stroke, brain injury, or multiple sclerosis, and can cause significant disability.[2] For example, the overall prevalence of spasticity post-stroke is estimated at 38%,[3] and varies from 19%[3] to 43%,[4] depending on the timing of assessment. It has been estimated that there are more than 12 million patients with spasticity worldwide.[5] In the US, approximately 80% of patients with cerebral palsy have spasticity, and approximately 80% of patients with multiple sclerosis (MS) have spasticity.[5] Other causes of spasticity include, for example, spinal cord injury, amyotrophic lateral sclerosis, and encephalitis.[5]

Usually, treatment is only required if the spasticity causes disruptive or painful symptoms or limits function; the clinical pattern of clenched fist is most likely to affect function and result in complications such as palmar skin breakdown, infection, and soft tissue contracture development. The management of ULS includes non-pharmacologic treatment, such as physiotherapy and splinting, and pharmacologic treatment, such as oral medication (e.g., muscle relaxants) and botulinum toxin A intramuscular injections[2,6]. Multiple therapies are often used concomitantly. Treatment goals in the management of ULS include relief from pain and muscle spasms, functional improvement in both active and passive dimensions, avoiding progression of impairment, and improving aesthetic and postural appearance. There may be little opportunity to restore active function, but improving the ease of caring for the affected limb, for example, in washing and dressing, can nevertheless make a significant impact on caregiver burden, and can potentially have significant cost benefits in reducing the time taken, or the number of people required, to perform care tasks.[7] Botulinum neurotoxin A (BoNTA) injections are recommended as safe and effective treatment for the reduction of muscle spasticity and improvement of passive function in patients with ULS.[7-13]Botulinum toxin injections are currently the first-line pharmacological option for treatment of focal ULS. In Canada, there are currently three BoNTA products approved for the treatment of ULS in adults: abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic), onabotulinumtoxinA (onaBoNTA, Botox), and incobotulinumtoxinA (incoBoNTA, Xeomin).[14]

Patients with ULS should be assessed to determine the severity and impact of their spasticity, and should first be managed with simple measures to reduce spasticity (for example, proper positioning, passive and active stretching, and splinting). Patients with persistent or progressive ULS for whom a therapeutic goal can be identified (for example, improving ease of care, reducing pain) should be offered intramuscular botulinum toxin. Goal attainment should be assessed four to six weeks after the injections, when the therapeutic effect is at its peak, and further treatment planned according to response.

AboBoNTA has a Health Canada–approved indication for the treatment of ULS and cervical dystonia (spasmodic torticollis) in adults.[15] The CADTH Common Drug Review (CDR) previously reviewed aboBoNTA for the treatment of cervical dystonia. In July 2017 the CADTH Canadian Drug Expert Committee recommended that aboBoNTA be reimbursed for reducing the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults, with or without botulinum toxin treatment experience, in a manner similar to the public plan listings for other BoNTA products and with a reduction in price.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of aboBoNTA for the treatment of ULS in adults.

Results and Interpretation

Included Studies

One double-blind randomized controlled trial (RCT) met the inclusion criteria of this review, which was the pivotal placebo-controlled trial (Study 145).[16] The objective of the pivotal trial[16] was to assess the efficacy and safety of aboBoNTA (500 units (U) or 1,000 U) versus placebo in the treatment of patients with ULS who were with or without the experience of botulinum neurotoxin (BoNT) treatment previously.[16,17] Patients were randomized to either aboBoNTA (500 U or 1,000 U, single IM injection into clinically indicated muscles) or placebo in a ratio of 1:1:1, and stratified between botulinum neurotoxin-naive and non-naive patients. Eighty-one patients were randomized to aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo, respectively (total N = 243).

Overall, the main baseline patient characteristics were generally balanced among the three treatment groups in Study 145. Patients were on average 53 years old in each group, ranging from 18 years to 78 years. The majority of patients in each group were male (greater than or equal to 62%) and Caucasian (greater than or equal to 84%). The cause of spasticity was stroke in 90.3% of patients and traumatic brain injury in 9.7% of patients. The mean duration of time since stroke was 5.1 years and the mean duration of time since traumatic brain injury was 10.3 years. Approximately half the patients (45.4%) were naive to treatment with any form of botulinum neurotoxin for the affected upper limb, and there were more botulinum neurotoxin-experienced patients in the US centres (71%) than in the non-US centres (49%). The muscle group chosen (by the physician) as the primary targeted muscle group (PTMG) was predominantly the extrinsic finger flexors (55.9%), followed by the elbow flexors (28.2%), and wrist flexors (16.0%). The choice of the principal target treatment (PTT) for the Disability Assessment Scale (DAS) at baseline was most often limb position (45.4%), dressing (26.5%), hygiene (21.4%), and, less often, pain (6.3%).[16] The baseline Modified Ashworth Scale (MAS) score and DAS score (mean) was 3.9 and 2.6, respectively, in all three treatment groups. Patients who were botulinum neurotoxin nonresponders previously and patients with major limitation in the passive range of motion (ROM) at the affected PTMG were excluded.

The primary outcome was the MAS score for the PTMG at week 4. The first secondary outcome was Physician Global Assessment (PGA) at week 4. The second secondary outcome was DAS for the PTT at week 4. Tertiary outcomes included responders to MAS or DAS, MAS or PGA, assessed at week 12 (and up to week 24), Tardieu Scale (TS), active range of motion (AROM), Modified Frenchay Scale (MFS) , ease of applying a splint, decreased need for restraints, health-related quality of life (Short Form (36) Health Survey [SF-36] and European Quality of Life – 5 Dimensions [EQ-5D]), and time to re-treatment.[17,18] The primary analysis used four-step hierarchical testing to control for multiple statistical testing in the order of: aboBoNTA 1,000 U versus placebo for MAS, aboBoNTA 1,000 U versus placebo for PGA, aboBoNTA 500 U versus placebo for MAS and aboBoNTA 500 U versus placebo for PGA.

One of the main limitations of the study was that clinically relevant outcomes such as passive and active function outcomes (TS, AROM, MFS, ease of applying a splint) and health-related quality of life outcomes (SF-36, EQ-5D) were analyzed as tertiary outcomes for exploratory purposes only and were not controlled for multiple statistical testing (i.e., increased risk of type I error). In addition, no Canadian sites were included in the study, and no patients experiencing spasticity due to causes other than stroke or traumatic brain injury (for example, MS or cerebral palsy) were included. The clinical expert consulted for this review indicated that patients included in the trial appeared to have spasticity that was more severe and of longer duration than would normally be seen in clinical practice.

Efficacy

Modified Ashworth Scale

In Study 145, at week 4, the difference in mean change from baseline in the MAS for the PTMG between aboBoNTA and placebo was statistically significant for the aboBoNTA 1,000 U group (–1.1, 95% CI, –1.4 to –0.8, $P < 0.0001$) and for the aboBoNTA 500 U group (–0.9, 95% CI, –1.2 to –0.6, $P < 0.0001$) (Table 1). At week 12, the between-treatment group difference in change from baseline in the MAS score for both aboBoNTA groups versus placebo (which was a tertiary, exploratory outcome) was numerically lower than what was observed at week 4 (Table 1). The subgroup analysis for the MAS assessed for individual muscle group also showed an improvement in both aboBoNTA groups compared with placebo.

Disability Assessment Scale

The DAS score for the PTT at week 4 was the second secondary outcome in Study 145. The DAS score for PTT at week 4 and week 12 are presented in Table 1. At week 4, DAS for PTT, there was no statistically significant treatment group difference for change from baseline for aboBoNTA compared with placebo (–0.1, 95% CI, –0.4 to 0.1, $P = 0.26$ and –0.2, 95% CI, –0.4 to 0.0, $P = 0.08$ for the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively). As tertiary outcomes, DAS score at week 12 was similar to that at week 4 (see Table 1).

Physician Global Assessment

At week 4, compared with placebo, the treatment group difference (aboBoNTA minus placebo) of the PGA score was 0.6 (95% CI, 0.3 to 1.0) and 1.1 (95% CI, 0.8 to 1.4) in the aboBoNTA 500 U and the aboBoNTA 1,000 U group, respectively. The results of the PGA demonstrated that aboBoNTA (500 U and 1,000 U) was statistically significantly more effective than placebo ($P = 0.0003$ and $P < 0.0001$, respectively). At week 12, the between-

treatment group difference in change from baseline in the PGA score for aboBoNTA versus placebo (which was a tertiary, exploratory outcome) was numerically lower than that observed at week 4 (Table 1).

Outcomes including the TS, AROM, MFS, ease of applying a splint, and health-related quality of life (SF-36, EQ-5D) were analyzed as tertiary outcomes for exploratory purposes only. Other outcomes, including the decreased needs for restraints that were identified as being important to patient groups in the patient group input, were not assessed in the trial.

Harms

In Study 145, the incidence of treatment-emergent adverse events was 43% in both aboBoNTA groups (500 U and 1,000 U) and 26% in the placebo group. According to the clinical expert consulted for this review, the overall incidence of treatment-emergent adverse event (TEAE) reported in the trial was lower than that usually observed in clinical practice . The most common TEAE was nasopharyngitis (8.6%, 1.2%, and 1.2% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively). Other TEAEs included sinusitis and urinary tract infections, which all occurred in less than 4% of patients. Serious adverse events were rarely reported (4% in each group). The number of patients who withdrew due adverse events were 1 (1.2%), 1 (1.2%) and 3 (3.7%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. Two deaths occurred during the study: one patient died in the aboBoNTA 500 U group and one patient died in the placebo group. Notable harms including muscle weakness and injection site pain occurred in less than 5% of patients and no patients were reported to have experienced dysphagia. Two patients (one in each aboBoNTA group) were found to be positive for anti-aboBoNTA antibody, for binding antibodies, and also for neutralizing antibodies. The data to assess the clinical impact of developing antibodies are limited. However, the clinical expert consulted for this review indicated that no meaningful impact of the antibody on the clinical effect of aboBoNTA in the treatment of ULS is expected and in clinical practice there is no readily available laboratory test for anti-aboBoNTA antibodies. No new safety signals were reported in the extension and non-pivotal studies.

Indirect Treatment Comparison

In the absence of direct evidence comparing aboBoNTA to other active treatments, the manufacturer submitted an indirect treatment comparison (ITC). Result of this analysis suggest that the three botulinum toxins (aboBoNTA, onaBoNTA, and incoBoNTA) may have similar treatment effects in patients with post-stroke spasticity. These results, however, are limited by the limited number of studies for some outcomes, the high amount of heterogeneity between studies, and the large number of assumptions required to facilitate the pooling of data for analysis.

Potential Place in Therapy[1]

Spasticity is a velocity dependent increase in muscle tone that is commonly seen in neurological disorders affecting the brain and spinal cord, including but not limited to stroke, traumatic brain injury, cerebral palsy, spinal cord injury, and MS. ULS can affect patients in various ways, including interfering with active function of the hand and performance of activities of daily living, preventing proper limb positioning, and causing painful muscle spasms. Spasticity is typically a chronic, lifelong condition, and can lead to

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

long-term complications such as skin breakdown and infection, and permanent soft tissue contracture.

The approach to spasticity management typically begins with non-pharmacological interventions, namely stretching, splinting, proper positioning, physiotherapy and/or occupational therapy, etc. If these are insufficient to control a patient's spasticity, then pharmacological options would be considered next. The choice of medication to use depends on the severity of spasticity and the number of limbs or muscle groups affected. For more generalized (i.e., whole body) or regional (e.g., hemibody) spasticity, oral antispasticity medications such as baclofen, dantrolene, or tizanidine can be utilized. For more focal spasticity (i.e., affecting a small number of muscle groups or one limb only), botulinum toxin injections would be considered as the first-line pharmacological option, as they have the advantage of bypassing systemic side effects typically experienced with the oral agents and allowing the clinician to target the specific muscle groups that are most affected by spasticity. Botulinum toxin injections and oral antispasticity medications can also be combined in cases where suboptimal treatment response is achieved with one or the other alone. Clinical judgment, provider experience, and patient factors (including patient preference, comorbidities and previous treatment exposures) are also factors which inform the decision whether to prescribe oral or injectable medications, or a combination of the two.

Prior to Health Canada's approval of aboBoNTA, there were two formulations of botulinum toxin available in Canada; onaBoNTA (Botox) and incoBoNTA (Xeomin). Botox and Xeomin are generally equivalent in efficacy and safety profile, and if a patient fails treatment with one botulinum toxin, they may be switched to the other in the hopes of achieving a superior treatment effect. A patient who fails both Botox and Xeomin treatment would be deemed a nonresponder to botulinum toxin, and would be limited to managing spasticity with oral medications and non-pharmacological interventions alone.

AboBoNTA (Dysport) is a third formulation of botulinum toxin that has been shown to have similar efficacy and safety results when compared with Botox and Xeomin in the treatment of ULS. Dysport offers patients a third injectable pharmacological option for spasticity, and could be used either as an equivalent first-line alternative to Botox and Xeomin, or as a second- or third-line injection option for patients who do not respond to the others. Any patient who is currently a candidate for Botox or Xeomin treatment would also be a candidate for Dysport, and any patient with ULS, regardless of their underlying neurological diagnosis, could benefit from Dysport. Dysport thus has the potential to significantly improve the function and quality of life for a wide spectrum of patients with diseases of the central nervous system. While not expected to provide superior therapeutic benefit compared with Botox and Xeomin, the availability of Dysport provides patients with an additional choice of botulinum toxin formulation to try for management of their focal ULS.

Conclusions

The CDR systematic review included one double-blind, placebo-controlled study (Study 145; N = 243). Based on the primary outcome (MAS score for the PTMG at week 4), aboBoNTA (1,000 U or 500 U) was statistically and clinically significantly more effective than placebo in reducing muscle tone in patients with ULS. According to the first secondary outcome (PGA score at week 4), a statistically significant global clinical benefit of aboBoNTA (1,000 U or 500 U) compared with placebo was also achieved. There was no statistically significant difference achieved between aboBoNTA (1,000 U or 500 U) and placebo for the second secondary outcome (DAS). Due to limitations in the design of the

study (tertiary outcomes analyzed for exploratory purpose only or not controlled by multiplicity for type I error), the clinical effect of the aboBoNTA compared with placebo was inconclusive for the following outcomes: passive and active function outcomes (TS, AROM, MFS, ease of applying a splint), and health-related quality of life (SF-36, EQ-5D). Outcomes reported as being important to patient groups from patient group input such as Goal Attainment Scale (GAS), caregiver burden, and decreased needs for restraints, were not measured in the pivotal study. Overall adverse events were low despite a numerically higher incidence of TEAEs in the aboBoNTA groups than in the placebo group. The open-label uncontrolled extension phase of the trial showed a similar efficacy and safety profile for aboBoNTA (1,000 U and 500 U) as reported in the double-blind phase. A network meta-analysis submitted by manufacturer suggested that the three botulinum toxins (aboBoNTA, onaBoNTA, and incoBoNTA) may have similar treatment effects in patients with post-stroke spasticity, however the statistical analyses are limited by the large number of assumptions required in order to estimate the relative efficacy between toxins.

Table 1: Summary of Key Results

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
MAS score	**(N = 80)**	**(N = 79)**	**(N = 79)**
Baseline			
n	80	79	79
Mean (SD)	3.9 (0.5)	3.9 (0.4)	3.9 (0.4)
Week 4			
n	80	79	79
Mean (SD)	2.7 (1.0)	2.6 (1.2)	3.7 (0.7)
CFB to week 4			
LSM of CFB (95% CI)[a]	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	**–0.9 (–1.2 to –0.6)**	**–1.1 (–1.4 to –0.8)**	NA
P value	< 0.0001	< 0.0001	NA
Week 12[b]			
n	76	76	75
LSM of CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
PGA	**aboBoNTA 500 U (N = 80)**	**aboBoNTA 1,000 U (N = 79)**	**Placebo (N = 79)**
Week 4			
n	80	78	78
LS M (95% CI)[c]	[redacted]	[redacted]	[redacted]
LS M diff (95% CI) (aboBoNTA – placebo)	**0.6 (0.3 to 1.0)**	**1.1 (0.8 to 1.4)**	**NA**
P value	**0.0003**	**< 0.0001**	**NA**
Week 12[b]			
n	76	75	75
LSM (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	
DAS	**aboBoNTA 500 U N = 81**	**aboBoNTA 1,000 U N = 81**	**Placebo N = 81**
Baseline			
Mean (SD)	2.6 (0.5)	2.5 (0.5)	2.6 (0.5)
Week 4			
Mean (SD)	1.9 (0.8)	1.8 (0.7)	2.1 (0.8)
CFB to week 4			
LSM of CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	**–0.1 (–0.4 to 0.1)**	**–0.2 (–0.4 to 0.0)**	NA
P value	**0.2560**	**0.0772**	NA

DAS	aboBoNTA 500 U N = 81	aboBoNTA 1,000 U N = 81	Placebo N = 81
Week 12[b]			
n	76	76	75
LSM of CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM Diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Adverse Events	**aboBoNTA500 U N = 81**	**aboBoNTA1000 U N = 81**	**Placebo N = 81**
# of patients with ≥ 1 TEAE n (%)	[redacted]	[redacted]	[redacted]
Withdrawals at week 12, n (%)	[redacted]	[redacted]	[redacted]
# of patients with ≥ 1 SAE n (%)	[redacted]	[redacted]	[redacted]
WDAE	[redacted]	[redacted]	[redacted]
Notable TEAE n (%)	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]
Injection reaction[d]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]

= number; aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; NR = not reported; PTMG = primary targeted muscle group; SAE = serious adverse events; SD = standard deviation; TEAE = treatment-emergent adverse events; U = units; WDAE = withdrawals due to adverse events.

Note: Results for the TS, AROM, and MFS are presented in Appendix 4.

a LSM for MAS were adjusted with baseline MAS score in the PTMG, BoNTA treatment status at baseline, and the study sites, all as fixed effects.

b Data at week 12 was an exploratory outcome.

c LSM for PGA were adjusted with BoNTA treatment status at baseline and the study sites, all as fixed effects.

d Injection site reaction includes injection site erythema, injection site bruising, and injection site pain.

Source: Study 145 CSR,[16] Gracies 2015.[17]

Introduction

Disease Prevalence and Incidence

Spasticity is a disabling condition characterized by involuntary muscle overactivity that commonly follows damage to the central nervous system.[1] This chronic, disabling condition needs lifelong surveillance and management with physical therapy, pharmacological therapy, and psychological support. Upper limb spasticity (ULS) is a common feature of many conditions affecting the brain and spinal cord, including stroke, brain injury, or multiple sclerosis (MS) and can cause significant disability.[2] For example, overall prevalence of spasticity post-stroke is estimated at 38%,[3] and varies from 19%[3] to 43%[4] depending on the timing of assessment. It is estimated that more than 12 million patients worldwide are affected by spasticity.[5] In the US, about 80% of patients with cerebral palsy and 80% of patients with multiple sclerosis (MS) have spasticity.[5] Other causes for spasticity include spinal cord injury, amyotrophic lateral sclerosis, encephalitis, and etc.[5]

Standards of Therapy

Usually, treatment is only required if the spasticity causes disruptive or painful symptoms or limits function. The clinical pattern of clenched fist is the most likely to affect function and result in complications such as palmar skin breakdown, infection, and soft tissue contracture development. The management of ULS includes non-pharmacologic treatment, such as physiotherapy and splinting, and pharmacologic treatment, including oral medication (such as muscle relaxants) and BoNTA intramuscular injections.[2,6] Multiple therapies are often used concomitantly. Treatment goals in the management of ULS include relief from pain and muscle spasms, functional improvement in both active and passive dimensions, avoiding progression of impairment, and improving aesthetic and postural appearance. There may be little opportunity to restore active function, but improving the ease of caring for the affected limb, for example, in washing and dressing, can nevertheless have a significant impact on caregiver burden, and can potentially have significant cost benefits in terms of reducing the time taken, or the number of people required, to perform care tasks.[7] BoNTA injections are recommended as safe and effective treatment for the reduction of muscle spasticity and improvement of passive function in patients with ULS.[7-13] Botulinum toxin injections are currently the first-line pharmacological option for treatment of focal ULS. In Canada, there are currently three BoNTA products approved for the treatment of ULS in adults: abobotulimumtoxinA (aboBoNTA, Dysport Therapeutic),[15] onabotulimumtoxinA (onaBoNTA, Botox),[19] and incobotulinumtoxinA (incoBoNTA, Xeomin).[20]

Patients with ULS should be assessed to determine the severity and impact of their spasticity, and should first be managed with simple measures to reduce spasticity e.g., proper positioning, passive and active stretching, and splinting. Patients with persistent or progressive ULS for whom a therapeutic goal (e.g., improving ease of care, reducing pain) can be identified should be offered intramuscular botulinum toxin. Goal attainment should be assessed four to six weeks after the injections, when the therapeutic effect is at its peak, and further treatment planned according to response. AboBoNTA was approved by Health Canada for the treatment of ULS in adults.[15]

Drug

AboBoNTA is a botulinum neurotoxin A (BoNTA) that blocks neuromuscular transmission by preventing cellular acetylcholine release (chemodenervation) and remains the mainstay for the treatment of patients with ULS.[14] In the American Academy of Neurology guidelines, aboBoNTA is recommended with Level A evidence for the treatment of ULS patients.[11] AboBoNTA received a Health Canada Notice of Compliance on June 15, 2016.[15] AboBoNTA is produced as a 150 kDa single polypeptide chain composed of 1,296 amino acid residues (1,295 after cleavage of the N-terminal methionine). On a genetic level, the toxin gene occurs in a cluster of genes which also encode for the non-toxic non-hemagglutinin protein (NTNH), a regulator protein, and the hemagglutinin (HA) proteins. These proteins and their derivatives, except for the regulator protein, form the components of the neurotoxin type A complex.[15]AboBoNTA is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps.[15] Due to differences in specific details such as vehicle, dilution scheme, and laboratory protocols for various mouse LD50 assays, units of biological activity of aboBoNTA are not interchangeable with units of any other BoNTA (i.e., onaBoNTA or incoBoNTA).[15]

The recommended dosing of aboBoNTA (Dysport Therapeutic) in initial and sequential treatment sessions should be tailored to the individual based on the size, number, and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with aboBoNTA.[15] the Recommended Dose section of the Health Canada–approved product monograph (PM) refers to the dosing used in the pivotal trial and provides a range for individual muscles. In the pivotal trial,[16] the initial doses of 500 U or 1,000 U were divided among selected muscles at a given treatment session. No more than 1 mL should generally be administered at any single injection site.[15]

The key characteristics of the three BoNTA formulations are summarized in Table 2.

Table 2: Key Characteristics of Three Botulinum Neurotoxin A Formulations

	aboBoNTA (Ipsen)[15]	incoBoNTA (Merz)[20]	onaBoNTA (Allergan)[19]
Molecular weight (kD)	500 to 700	~150	900
Complexing proteins	Hemagglutinin/non-hemagglutinin	Hemagglutinin/non-hemagglutinin	None
***Clostridium botulinum* strain**	Hall Strain	Hall A	Hall A
Recommended re-treatment interval	≥ 12 wks (3 mos)	≥ 12 wks	≥ 12 wks
Mechanism of action	BoNTA inhibits release of the neurotransmitter acetylcholine from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor-mediated endocytosis, and blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves. Recovery of transmission occurs gradually as the neuromuscular junction recovers and as new nerve endings are formed.		
Indication[a]	For the symptomatic treatment of focal ULS in adults.	For the treatment of ULS associated with stroke in adults.	In the management of focal spasticity, including the treatment of ULS associated with stroke in adults.
Route of administration	IM injection only		
Recommended dose	• Recommended dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number, and location of muscles involved, etc.[b] • Re-treatment interval, if needed, ≥ 12 wks (3 mos).	• Initial dosing should begin at the lowest recommended dose and cautiously titrated within recommended dose range for optimal patient outcome. Total dosing should not exceed 400 U per treatment session.[c] • Re-treatment interval, if needed, ≥ 12 wks.	• Recommended dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number, and location of muscles involved, etc.[d] • Re-treatment interval, if needed, ≥ 12 to 16 wks.
Serious side effects / safety issues	Rare SAEs reported were sepsis, muscle spasms, Behcet's syndrome, cardiovascular disorder, death; partial seizures, syncope, ligament sprain, and cerebrovascular accident. Caution should be used when BoNTA is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle.		

aboBoNTA = AbobotulinumtoxinA; BoNTA = botulinum neurotoxin A; IM = intramuscular; inco BoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA; pts = patients; SAE = serious adverse event; U = units; ULS = upper limb spasticity; wks = weeks.

[a] Health Canada indication.[15]

[b] Recommended initial and sequential dose should be tailored to the individual based on the size, number, and location of muscles involved, severity of spasticity, the presence of local muscle weakness, etc. Repeat aboBoNTA should be ≥ 12 weeks after the previous injection.[15]

[c] The effect of each injection varies, generally it lasts for about 3 months. The interval between each treatment session was recommended to be ≥ 12 weeks.[20]

[d] The 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, etc. Re-injections should be ≥ 12 weeks.[19]

Source:

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of aboBoNTA (Dysport Therapeutic) for the symptomatic treatment of focal spasticity affecting the upper limbs in adults.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult (> 18 yrs.) patients with ULS Subgroups: Botulinum toxin experienced versus Botulinum toxin naive patients Baseline severity Primary target muscle group (e.g., extrinsic finger flexors vs. wrist flexors, vs. elbow flexors) Clinical conditions causing ULS (e.g., post-stroke vs. TBI, etc.)
Intervention	aboBoNTA (Dysport Therapeutic) as per HC-approved monograph Initial dose: Individual tailored dosage (in the pivotal trial, initial 500 U or 1,000 U), IM, as a divided dose among affected muscles[a] Re-treatment dose if needed: individual tailored dosage, IM, as a divided dose among affected muscles. Re-treatment should not occur in intervals of ≤ 12 weeks.[b]
Comparators	incoBoNTA (Xeomin) onaBoNTA (Botox)
Outcomes	**Key efficacy outcomes:** **Functional / disability outcomes**[c] (e.g.,) MAS TSS AROM DAS MFS Ease of applying a splint GAS Decreased need for restraints **PGA**[d] **Symptom reduction** (e.g., pain)[c] **Health-related quality of life measured by validated scales (e.g., SF-36; EQ-5D)**[c] **Other efficacy outcomes:** Caregiver burden (measured by validated scales)[c] Duration of effect and re-treatment intervals

	Harms outcomes: AEs, SAEs, WDAEs, Mortality, add notable harms/harms of special interest (antibodies, injection site reaction, muscle weakness, dysphagia).
Study Design	Published and unpublished phase III RCTs

aboBoNTA = abobotulinumtoxinA; AE = adverse event; AROM = active range of motion; DAS = Disability Assessment Scale; DB = double-blind; EQ-5D = European Quality of Life - 5 Dimensions; GAS = Goal Attainment Scale; HC = Health Canada; IM = intramuscular; incoBoNTA = incobotulinumtoxinA; MAS = Modified Ashworth Scale; MFS = Modified Frenchay Scale; onaBoNTA = onabotulinumtoxinA; PGA = Physician Global Assessment; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) ; TBI = traumatic brain injury; TSS = Tardieu Scale score; vs. = versus; WDAE = withdrawal due to adverse event; yrs = years.

a Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number, and location of muscles involved; severity of spasticity; the presence of local muscle weakness; the patient's response to previous treatment; and/or adverse event history with aboBoNTA. A table for aboBoNTA dosing by muscle for ULS is found in the PM. In the pivotal trial, doses of 500 U or 1,000 U were divided among selected muscles, at a given treatment session (see PM). No more than 1 mL should generally be administered at any single injection site (see PM).[15]

b In the extension study: dosage were 500 U, 1,000 U or 1,500 U).[21,22]

c Identified as an important outcome in the patient input submission to CDR.

d PGA was analyzed as co-primary outcome as requested by Health Canada.[23]

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

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

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 15, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on September 20, 2017. Regular search updates were performed on databases that do not provide alert services.

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

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4. The excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of 523 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

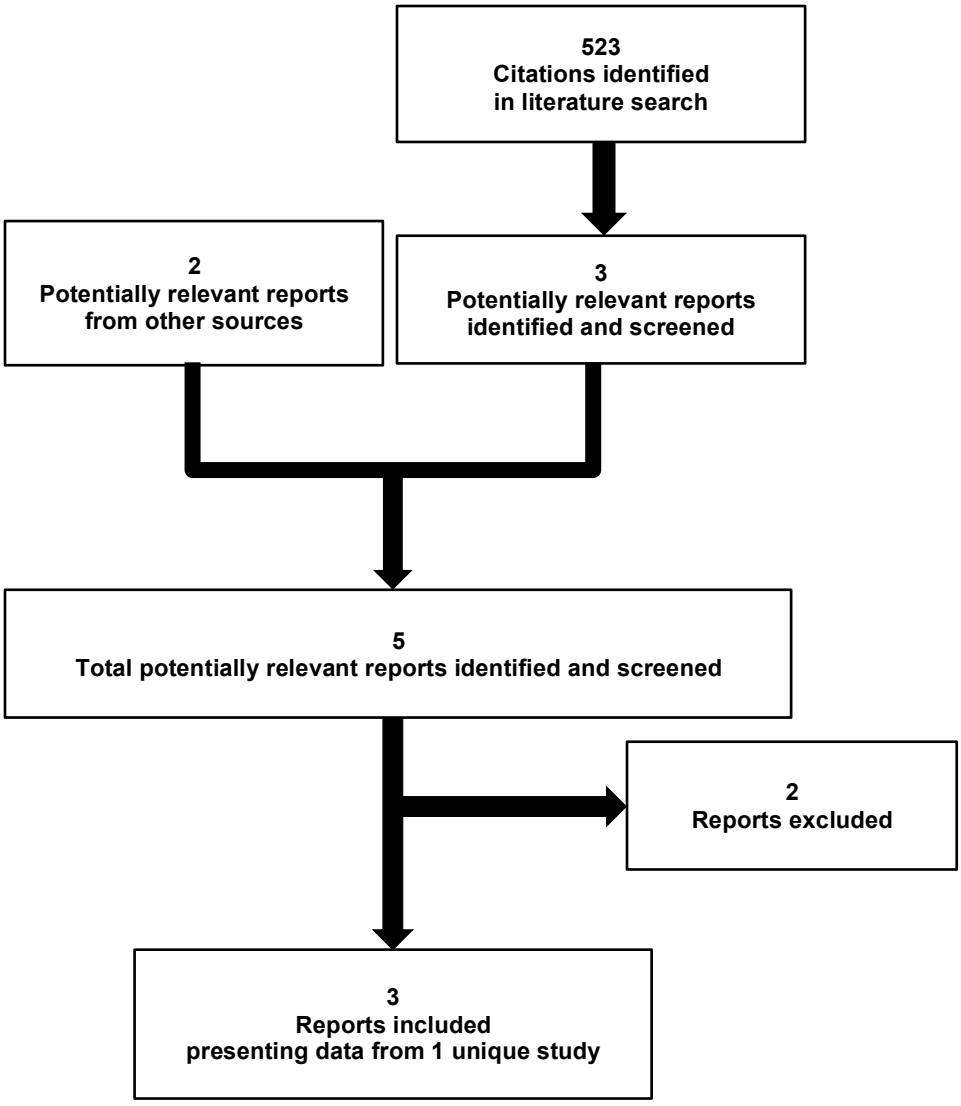


Table 4: Details of Included Studies

		Study 145 [16-18]
Designs & Populations	**Study Design**	DB RCT
	Locations	34 centres in nine countries: US, France, Belgium, Czech Republic, Hungary, Italy, Poland, Russia, and Slovakia.
	Randomized (N)	243
	Inclusion Criteria	• Pts with hemiparesis and aged 18 yrs to 80 yrs • Pts with stroke episode or brain trauma, or a non-evolutive lesion diagnosed prior to the stroke. • ≥ 6 mos post-stroke or traumatic brain injury. • MAS score ≥ 2 in the PTMG for BoNT-naive patients, or MAS score ≥ 3 in the PTMG for BoNT-experienced pts at least 4 months after the last BoNT injection. • DAS score ≥ 2 on the PTT. • Spasticity angle ≥ 10° in the PTMG. • MFS overall score 1 to 8

	Exclusion Criteria	• Major limitation in the passive ROM as defined by:
		  ○ Maximum passive elbow extension < 150° (0° corresponding to the minimal stretch of the elbow flexors, which corresponds to a fully flexed elbow position).
		  ○ Maximum passive wrist extension < 70° (0° corresponding to the minimal stretch of the wrist flexors, which corresponds to a fully flexed wrist position).
		  ○ Maximum passive finger extension < 70° (0° corresponding to the minimal stretch of the extrinsic finger flexors, which corresponds to a formed fist with the second phalanx parallel to the metacarpal).
		• Physiotherapy initiated < four wks before entry or expected to be initiated during the study.
		• Previous treatment with BoNT of any type within four mos prior to study entry for any condition.
		• Previous primary or secondary non-response to any BoNT for the targeted condition.
		• Any medical condition which may have compromised compliance with the study.

Drugs	**Intervention**	aboBoNTA (500 U or 1,000 U)
	Comparator(s)	Placebo
Duration	**Phase**	
	Run-in	None
	Double-blind	At least 12 wks
	Follow-up	Discretionary follow-up for up to 24 wks
	Open-label phase	Up to 15 mos (5 cycles, for each patient)
Outcomes	**Primary End Point**	MAS score change from baseline to wk 4 in the PTMG
	Other End Points	**Secondary outcomes:** • PGA of treatment response at wk 4. • DAS score at wk 4 **Tertiary outcomes (up to wk 24):** • MAS, PGA and DAS measured at wks 12 to 24), DAS scores within each domain of disability at wk 4, up to wk 24 • MFS at wk 4, 12, up to wk 24 • TS in the PTMG • AROM against the PTMG • Ease of applying a splint • Quality of Life Scales **AEs**

Notes	Publications	Gracies, 2015[17]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); AE = adverse event; AROM = active range of motion; BoNT = botulinum neurotoxin; BoNTA = botulinum neurotoxin A; CI = confidence interval; DAS = Disability Assessment Scale; DB = double-blind; EQ-5D = European Quality of Life - 5 Dimensions; HC = Health Canada; MAS = Modified Ashworth Scale; MFS = Modified Frenchay Scale; mos = months; PGA = Physician Global Assessment; PTMG = primary targeted muscle group; pts = patients; PTT = principal target treatment; RCT = randomized controlled trial; TS = Tardieu Scale; U = units; wk = week; yrs = years.

Note: One additional report is included: HC report.[24]

Note: BoNT-naive pt was defined as a pt who had never received any BoNT in the affected upper limb. The PTMG was selected by the investigator at baseline, from among the following muscle groups: extrinsic finger flexors (flexor digitorum profundus and flexor digitorum superficialis) , wrist flexors (flexor carpi radialis and flexor carpi ulnaris), or elbow flexors (brachialis and, in addition, potentially brachioradialis). The PTMG was identified as the muscle group with the most severe MAS score. In case of similar MAS scores, the choice of PTMG was made by the investigator based on his/her clinical judgment.

Source: Study 145 CSR,[16] Gracies, 2015.[17]

Included Studies

Description of Studies

One double-blind randomized controlled trial (RCT) met the inclusion criteria; the pivotal placebo-controlled trial (Study 145).[16]

Study 145 was a phase III, multi-centre, prospective, double-blind, randomized, placebo-controlled, single treatment cycle study.[16] The objective of the pivotal trial[16] was to assess the efficacy and safety of aboBoNTA (500 U or 1,000 U) versus placebo in the treatment of patients with ULS who were with or without the experience of BoNTA treatment previously. Patients were randomized to either aboBoNTA (500 U or 1,000 U, single IM injection into clinically indicated muscles) or placebo, in a ratio of 1:1:1, and stratified between BoNTA-naive and BoNTA-experienced patients. The study's randomization manager was a statistician independent from the study, who prepared and kept the master randomization list for this study. Allocation concealment was sufficiently described. The randomization list was then dispatched to the sites. In Study 145, 81 patients were randomized to aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo respectively (total N=243).

Populations

Inclusion and exclusion criteria

The main inclusion criteria for Study 145 were patients (age 18 to 80 years old) with a post-stroke or post-traumatic brain injury hemiparesis for at least 6 months. Patients were required to have a Modified Ashworth Scale (MAS) score greater than or equal to 2 in the primary target muscle group (PTMG) for those who had no previous botulinum toxin injection in the paretic limb, or greater than or equal to 3 for patients with previous injections of botulinum toxin in the paretic limb. A Disability Assessment Scale (DAS) score of greater than or equal to 2 was required on the principal target of treatment (PTT, one of four functional domains: dressing, hygiene, limb position, or pain); spasticity angle was greater than or equal to 10° in the PTMG; and mean Modified Frenchay Scale (MFS) score was 1 to 8 (out of a total possible score of 10). The main exclusion criteria included: major limitations in the passive range of motion in the affected limb, physiotherapy initiated less than 4 weeks before the trial, or treatment with botulinum toxin initiated less than 4 months before the trial, as well as any medical conditions increasing the risk of BoNTA-related adverse events or affecting the outcome measurement.

Baseline characteristics

Overall, the main baseline patient characteristics were generally balanced among the three treatment groups in the pivotal placebo-controlled RCT (Table 5). Patients were on average 53 years old in each group, ranging from 18 years to 78 years (Table 5). The majority of patients were male (greater than or equal to 62%) and Caucasian (greater than or equal to 84%) in each group. The cause of spasticity was stroke in 90.3% of patients and traumatic brain injury in 9.7% of patients. The mean duration of time since stroke was 5.1 years and the mean duration since traumatic brain injury was 10.3 years. Approximately half of the patients (45.4%) were naive to treatment with any form of BoNT for the affected upper limb. There were more BoNT-experienced patients in the US centres (71%) than in the non-US centres (49%). The muscle group chosen as the PTMG was predominantly the extrinsic finger flexors (55.9%), followed by the elbow flexors (28.2%) and wrist flexors (16.0%). The choice of the PTT for the DAS at baseline was most often limb position (45.4%), dressing (26.5%) and hygiene (21.4%), and less often, pain (6.3%).[16] The baseline MAS score and mean DAS score were 3.9 and 2.6, for all three treatment groups (See Table 5).

Table 5: Summary of Baseline Characteristics

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N =7 9)
Age, yrs			
Mean (SD)	52.8 [redacted]	52.8 [redacted]	52.7 [redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	52 [redacted]	52 [redacted]	49 [redacted]
Female	28 [redacted]	27 [redacted]	30 [redacted]
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black/African American	[redacted]	[redacted]	[redacted]
Caucasian/White	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Weight, kg			
n	80	78	77
Mean (SD)	82.4 (17.5)	82.0 (18.7)	78.5 (19.6)
Median (range)	[redacted]	[redacted]	[redacted]
Affected arm, n (%)			
Left	37 [redacted]	50 [redacted]	34 [redacted]
Right	43 [redacted]	29 [redacted]	45 [redacted]
Cause of spasticity, n (%)			
Stroke	72 [redacted]	73 [redacted]	70 [redacted]
Traumatic brain injury	8 [redacted]	6 [redacted]	9 [redacted]
Time since stroke, yrs	n = 72	n = 73	n = 70
Mean (SD)	5.4 (4.1)	5.0 (4.4)	4.9 (4.65)
Median (range)	[redacted](0.7 to 16.8)	[redacted](0.7 to 21.1)	[redacted](0.6 to 20.9)
Time since traumatic brain injury, yrs	[redacted]	[redacted]	[redacted]
Mean (SD)	12.1 (6.2)	10.8 (11.5)	8.4 (8.2)
Median (range)	[redacted] (5 to 22)	[redacted](2 to 34)	[redacted](1 to 26)
BoNT tx naive, n (%)			
Total	35 [redacted]	36 [redacted]	37 [redacted]
Non-US centres	[redacted]	[redacted]	[redacted]
US centres	[redacted]	[redacted]	[redacted]
BoNT tx experienced, n (%)			
Total	[redacted]	[redacted]	[redacted]
Non-US centres	[redacted]	[redacted]	[redacted]
US centres	[redacted]	[redacted]	[redacted]
Neutralizing anti-botx-a antibody status, n (%)			
Positive	[redacted]	[redacted]	[redacted]
Primary target muscle group, n (%)			
Elbow flexors	25 [redacted]	19 [redacted]	23 [redacted]
Wrist flexors	11 [redacted]	12 [redacted]	15 [redacted]

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N =7 9)
Extrinsic finger flexors	**44** [redacted]	**48** [redacted]	**41** [redacted]
Principal Target of Treatment of DAS, n (%)			
Hygiene	22 [redacted]	17 [redacted]	12 [redacted]
Dressing	21 [redacted]	21 [redacted]	21 [redacted]
Limb position	**32** [redacted]	**38** [redacted]	**38** [redacted]
Pain	5 [redacted]	2 [redacted]	8 [redacted]
Missing	0 [redacted]	1 [redacted]	0 [redacted]
Prior physiotherapy, n (%)	[redacted]	[redacted]	[redacted]
Physiotherapy concomitantly during the trial, n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; BoNTA = botulinum toxin A; DAS = Disability Assessment Scale; M = mean; pts = Patients; N = total number of patients in treatment groupgroup; n = number of patients in subgroup; NR = not reported; SD = standard deviation; tx = treatment; U = units; ULS =upper limb spasticity; yrs =years.

Note: Percentages were based on the number of patients in a given group.

Note: n for physiotherapy was calculated by CADTH.

Source: Study 145 CSR,[16] Gracies 2015.[17]

Interventions

In the pivotal RCT, patients were randomized to receive aboBoNTA 500 U, 1,000 U, or placebo. AboBoNTA was administered by intramuscular injection into clinically indicated upper limb muscles in a single dosing session. The number of injection sites and the dose at each site were determined by the investigator. The investigator selected the PTMG, as the muscle group with the most severe MAS score, from the wrist flexors, the extrinsic finger flexors, or the elbow flexors. The volumes or dose range of either aboBoNTA or placebo injected in the PTMG are presented in Table 6 and Table 7. In order to maintain blinding, each treatment pack was prepared using a double dummy technique. The contents of each pack were identical in appearance and the procedure for reconstitution was identical in each group.

Patients were allowed to maintain the following concomitant medications: pain medication, anticholinergic drugs , dantrolene, tizanidine, gaba-ergic drugs (including oral baclofen), opioid, or other antispasticity agents, like benzodiazepines. If physiotherapy was initiated prior to study entry, the therapy regimen was allowed to be continued at the same frequency and intensity up to the week 4 visit, and whenever possible until the end of study. The percentages of patients receiving muscle relaxants concomitantly during the study in each group were similar (See Table 18: in Appendix 4)

No physiotherapy was to be initiated less than four weeks prior to study entry or during the first four weeks of the study. Effort was made to keep concomitant medication dose and dose regimen or frequency of physiotherapy constant throughout the course of the study.

The number of patients who received physiotherapy concomitantly with the study treatment were similar among the three study groups (47.5%, 48.1% and 44.3%, in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively). (See Table 5.)

Table 6: Injection Volume per Primary Targeted Muscle Group

Primary Targeted Muscle Group	Volume Injected (mL)
Extrinsic finger flexors	[redacted]
Flexor digitorum profundus	[redacted]
Flexor digitorum superficialis	[redacted]
Wrist flexors	[redacted]
Flexor carpi ulnaris	[redacted]
Flexor carpi radialis	[redacted]
Elbow flexors	[redacted]
Brachialis (mandatory)	[redacted]
Brachioradialis	[redacted]

mL = millilitres; PTMG =primary targeted muscle group.

Source: Study 145 CSR.[16]

Table 7: Dose Range per Muscle

Muscle Group	Volume (mL)	aboBoNTA 500 U	aboBoNTA 1,000 U
Elbow muscles			
Brachioradialis	[redacted]	[redacted]	[redacted]
Brachialis	[redacted]	[redacted]	[redacted]
Biceps brachii	[redacted]	[redacted]	[redacted]
Pronator teres	[redacted]	[redacted]	[redacted]
Wrist muscles			
Flexor carpi radialis	[redacted]	[redacted]	[redacted]
Flexor carpi ulnaris	[redacted]	[redacted]	[redacted]
Finger muscles			
Flexor digitorum profundus	[redacted]	[redacted]	[redacted]
Flexor digitorum superficialis	[redacted]	[redacted]	[redacted]
Flexor pollicis longus	[redacted]	[redacted]	[redacted]
Adductor pollicis	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; mL = millilitres; U = units.

Source: Study 145 CSR.[16]

Outcomes

Efficacy

In Study 145, the primary outcome was the change from baseline in MAS score at week 4 for the PTMG. The first secondary outcome was Physician Global Assessment (PGA) at week 4. The second secondary outcome was the change from baseline in the DAS at week 4. The second secondary outcome was the change from baseline in the DAS at week 4. Tertiary outcomes included responders to MAS or DAS, MAS or PGA, assessed at week 12 (and up to week 24), TS score, active range of motion (AROM), MFS, ease of applying a splint, decreased need for restraints, quality of life (SF-36, EQ-5D), and time to re-treatment.[17] Please refer to Appendix 5 for more information on the validity of the outcome measures described in this section.

MAS Score

The MAS is a commonly used outcome in the assessment of spasticity.[25] It provides a semi-quantitative measure of the resistance to passive movement.[26] The original Ashworth Scale (AS) for rating spasticity involves an assessor manually moving the affected limb passively to stretch the muscle. Bohannon and Smith found that many patients demonstrated levels of spasticity toward the lower end of the scale; therefore they modified the original AS by adding an extra category (1+) to indicate resistance through less than half of the test movement. The MAS was adopted as a common scale in the clinical trial. The score ranges from 0 to 4 points and the degree of spasticity is rated as follows:

- 0 = no increase in muscle tone
- 1 = slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part(s) is moved in flexion or extension
- 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement
- 2 = more marked increase in muscle tone though most of the range of movement, but the affected part(s) is easily moved
- 3 = considerable increase in muscle tone, passive movement is difficult
- 4 = affected part(s) rigid in flexion or extension.[27]

The MAS is a validated and reliable instrument to assess response to treatment for patients with spasticity.[26,28-30] In general, a one-point difference in the MAS score is considered to be clinically significant.[31] However, the MAS has been commonly used in the clinical trials for ULS and was accepted as the primary outcome by Health Canada.[23] In Study 145, assessment of the MAS was independently undertaken by a different assessor to the one who assessed the PGA.

Patients were also assessed as MAS responders at each visit (tertiary outcome), defined as patients with at least one grade reduction from baseline on the MAS in the PTMG.

PGA

The PGA of treatment response at week 4 was analyzed as the first secondary outcome in Study 145. The PGA was conducted by the investigator who scored responses to the question: “How would you rate the response to treatment in the subject’s upper limb since the last injection?” Responses were scored on a 9-point scale that ranged from –4 (markedly worse) to +4 (markedly improved). Assessment of the PGA was undertaken independently by a different investigator than the investigator who assessed the MAS.[16,27] Higher scores indicate better results. The psychometric properties (i.e., reliability, validity, and responsiveness to change) of the PGA have not been assessed in ULS trials. A minimal clinically important difference (MCID) for this outcome has not been established.[14]

DAS Score

The change from baseline of DAS for the PTT at week 4 was analyzed as the secondary outcome in Study 145. One of the four DAS domains (hygiene, dressing, limb position, and pain) was selected as the principal targeted treatment (PTT) by patients and investigator together as the baseline. DAS is a questionnaire that measures changes in four disability domains: hygiene, dressing, limb position, and pain. This scale was specifically developed for the objective measurement of disability in patients with upper limb post-stroke spasticity

(its use is not limited to patients with post-stroke spasticity) and to assess the response to BoNTA treatment. The investigator or rater interviews the patient to determine the extent of functional impairment in each domain which is individually rated on a scale of 0 to 3, where 0 = no disability and 3 = severe disability. Higher scores indicate poorer functioning.[27] Decrease in the DAS score is considered clinically relevant and contributes to improving the daily activities of the patients.[25,32] No studies have examined the construct/criterion/content validity of the DAS.[33]

Patients were also assessed as DAS responders at each visit (tertiary outcome), defined as patients with at least one grade reduction from baseline on the DAS for the PTT.

Tardieu Scale

The Tardieu Scale (TS) measuring the change from the baseline at week 4 (up to week 24) of spasticity angle and spasticity grade for individual muscle groups was analyzed as a tertiary outcome in Study 145. The TS was developed by Tardieu et al. in 1954 to measure spasticity that takes into account resistance to passive movement at both slow and fast speed. Several modifications have been made to the original scale since then. Held and Pierrot-Deseilligny modified the scale by comprising quantitative joint angle measurements taken at three speeds of passive movements: very slow (V1), a passive fall of the limb under gravity (V2), and as fast as possible (V3).[34] The modified TS determines the passive range of movement (PROM) at different movement velocities, with the relative difference between a slow and a fast velocity passive stretch determining the dynamic component of the muscle contracture. With the modified TS, two resulting joint angles are measured by goniometer which include the R1 angle which is the “angle of catch” after a fast velocity stretch and the R2 angle defined as the passive joint range of movement following a slow velocity stretch. The R2 minus R1 value indicates the level of dynamic component of spasticity in the muscle. A larger difference between R1 and R2 means large dynamic component, whereas a small difference between R1 and R2 means static contracture in the muscle.[35,36] Two components included in the TS are spasticity angle, which measures the angle of muscle reaction (angle of arrest at slow speed V1 minus angle of catch at fast speed V3) and spasticity grade, which measures the quality of muscle reaction (scored between 0 to 5 where 0 = no resistance to passive range of movement and 5 = joint is immobile – higher score indicates severe spasticity grade). The validity and reliability of the TS are inconsistently reported in the literature.[34,37] An MCID has not been established for TS in patients with ULS.[14]

Modified Frenchay Scale

The change from baseline of the MFS at week 4 (up to week 24) was analyzed as a tertiary outcome in Study 145. The MFS was developed to measure upper limb active function. The original scale consisted of seven pass or fail tasks and was a simple and easy-to-conduct test rated by clinicians; however, the binary pass/fail assessment limited the sensitivity of the test at both ends of the range. The MFS is an expanded version of the Frenchay Scale and consists of 10 tasks (six bimanual and four unimanual with the affected hand). These 10 tasks consist of asking the patient to reach, grasp, carry, and release different objects of different sizes which patients are likely to use in their daily life (such as a bottle, a glass, or a comb). These tasks can only be accomplished by mobilizing the whole affected arm, with or without the contralateral non-affected arm, and involve the finger, wrist, elbow, and shoulder muscles. Each of these tasks is rated on a 10-point visual analogue scale (VAS). Higher scores indicates better function (“0” = no movement; “10” = normal).[27] One key advantage of this test is that videos of patients performing the tasks

can be recorded and centrally rated, leading to a relatively objective and homogeneous assessment of upper limb active function.[27] The intra- and inter-rater reliability were assessed in 10 adult patients with chronic hemiparesis in a cross-sectional study.[14] No MCID for the MFS was identified in the literature. In Study 145, the patients was asked to perform the 10 tasks, which were videotaped. Videos were sent to an external company in charge of distributing the videos for reading and scoring by two independent readers.

Active Range of Motion

The change from baseline in active range of motion (AROM) for individual muscle groups at week 4 (up to week 24) was analyzed as tertiary outcome in Study 145. The AROM in the individual muscle groups was assessed by asking the patient to move the elbow, wrist, or finger flexors. Goniometry (to measure joint angle) was used for the elbow and wrist flexors but not for the extrinsic finger flexors. This was a supportive measure of treatment response.[16]

The Ease of Applying a Splint

The change from baseline in ease of applying a splint at week 4 (up to week 24) was analyzed as tertiary outcome in Study 145. Improving the ease of applying a splint by the patient is associated with improving the ease of caring for the affected limb, e.g., in washing and dressing. Furthermore, it can alleviate caregiver burden and thus may have significant cost benefits by reducing the time taken, or the number of people required, to perform care tasks.[7] In Study 145, the ease of applying a splint was evaluated on a 6-point scale. Higher score indicates more difficulty in applying a splint (0 = no splint needed; 1 = splint needed and applied with no difficulty; 2 = splint needed and applied with mild difficulty; 3 = splint needed and applied with moderate difficulty; 4 = splint needed and applied with severe difficulty; and 5 = splint needed, but unable to apply).[27] Ease of applying a splint has not been validated and an MCID is not available to assess the clinical importance of between-group differences.[14]

Health-Related Quality of Life Scales

Short Form (36) Health Survey (SF-36)

The SF-36 was assessed at the end of the study (any time after week 12) and was analyzed as a tertiary outcome in Study 145. SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. The SF-36 consists of eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm. The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, which are t scores (mean of 50 and standard deviation of 10) that have been standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm. An increase in score indicates improvement in health status on any scale. In general use of the SF-36, a change of 2 points in the SF-36 PCS and 3 points in the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient.[37] An MCID for SF-36 was not identified for patients with ULS.[38]

European Quality of Life Scale (EQ-5D-5L)

The EQ-5D is a generic quality of life instrument developed by the EuroQol Group. It may be applied to a wide range of health conditions and treatments.[39] As a generic measure of health-related quality of life that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient's perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[40] The EQ-5D - 5 level version (EQ-5D-5L) was introduced in 2005 based on an earlier version (EQ-5D-3L). It consists of an EQ-5D descriptive system and the EQ VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels. A level 1 response represents "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension.

The EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a 5-digit descriptor, such as 11121, 21143, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ VAS.

EQ-5D-5L has been validated in a diverse patient population in six countries.[39] However, no studies specifically validating EQ-5D in patients with ULS were identified. The MCID estimates in the Canadian population have a summarized mean (SD) of 0.056 (0.011).[41]

Harms

Adverse events (i.e., treatment-emergent adverse events (TEAE), serious adverse events (SAE), withdrawals due to adverse events (WDAE), and notable adverse events (i.e., adverse events especially interested in this review) were reported in the pivotal RCT.

Statistical Analysis

Multiple statistical testing

The primary statistical analysis used hierarchical testing (four steps) according to the sequence below:

1. aboBoNTA 1,000 U versus placebo for MAS at 4 weeks (primary efficacy outcome);
2. aboBoNTA 1,000 U versus placebo for PGA at 4 weeks (secondary efficacy outcome);
3. aboBoNTA 500 U versus placebo for MAS (primary efficacy outcome); and
4. aboBoNTA 500 U versus placebo for PGA (secondary efficacy outcome).

Establishing the superiority of aboBoNTA 1,000 U compared with placebo was the first step in the statistical testing hierarchy, and was tested at a significance level of 0.05. If the *P value* associated with that testing was less than 0.05, then it was considered significant; otherwise, the procedure was stopped. The superiority of any aboBoNTA dose to placebo was demonstrated if that dose was superior to placebo for both the primary efficacy end point and the first secondary efficacy end point. For the purposes of the statistical analysis, treatment response using the PGA at week 4 was considered the first secondary outcome,

and the DAS was considered the second secondary outcome by the manufacturer. The DAS as the second secondary outcome was not controlled for multiple statistical testing. All tertiary efficacy outcomes were analyzed for exploratory purposes only, to compare each aboBoNTA dose to placebo at a 0.05 type I error rate.

In Study 145, the primary efficacy outcomes were the changes from baseline in MAS score at week 4. Secondary outcomes included PGA and DAS measured at week 4. The tertiary outcomes included the MAS, PGA, and DAS assessed at week 12 (and up to week 24), MFS, TS, AROM, ease of applying a splint, and quality of life scales (SF-36 and EQ-5D).

Power calculation

The primary outcome (MAS) and first secondary outcome (PGA) were taken into account for the sample size calculation. Separate sample size calculations were conducted for both the planned primary and first secondary end points (MAS and PGA respectively). Allowing 3% dropouts, a total of 228 patients (76 in each group) were required to detect a statistically significant treatment effect based on the MAS. With 79 patients in each treatment group, there was a greater than 85% power to detect a statistically significant difference (2-sided significance level, $P = 0.05$) based on mean changes from baseline to week 4 in the MAS of 1.0 (SD: 0.8) and 0.6 (SD: 0.8) in the aboBoNTA and placebo groups, respectively. A total of 165 patients (55 in each group) were needed to detect a statistically significant treatment effect for the first secondary efficacy outcome (PGA). There was a 90% chance to detect a statistically significant difference (2-sided significance level, $P = 0.05$) for PGA using a between-group mean difference in the PGA score at week 4 of 0.7 (SD: 1.1). Using a sample size of 228 has meant that the estimated power for the PGA score comparison has risen to 97.0%. As a result, the power of the study to detect a significant effect of any aboBoNTA dose for both MAS and PGA at week 4 simultaneously (US targeted methodology) was estimated to be 82.5%.[27] The rationale for the above threshold was based on previous study by Kaji.[14,42]

Statistical model

The primary efficacy analysis consisted a single mixed-effect ANCOVA model, controlling for the baseline score in the primary targeted muscle group, the randomization stratification factor (BoNT treatment status at baseline), and the centre as fixed effects.[27] However, the mean PGA score assessed at week 12 was compared between treatment groups by using an ANOVA. All outcomes assessed after week 12 (i.e., week 16, 20, and 24) were treated as discretionary post hoc analyses for which no statistical analysis was performed. All tertiary efficacy outcomes were analyzed as exploratory analyses. For each aboBoNTA dose compared with placebo, the difference (aboBoNTA dose minus placebo) in least square means of the change from baseline (or between-group difference for PGA) with the 95 % CI and *P value* was provided.[27] In addition, a sensitivity analysis was conducted in order to investigate homogeneity of treatment response across centres: The ANCOVA model was re-run, adding the treatment by centre interaction term, fitted as fixed effect. This interaction was regarded as statistically significant if its *P* value was significant at level less than 0.1.

Analysis populations

All efficacy outcomes were evaluated based on the modified intention-to-treat (ITT) population, which included all randomized patients who received at least one injection of study medication and had an MAS score in the PTMG assessed at baseline and at week 4. The per-protocol population comprised all patients in the modified ITT population who were not classified as major protocol violators between baseline and week 4. Safety outcomes were evaluated for all patients who received at least one dose of study medication.[16]

Patient disposition

In Study 145, a total of 281 patients were screened, of whom, 243 were randomized (81 in each group). The percentage of patients discontinuing at week 12 were 3.7%, 4.9%, and 8.6% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups respectively. (Table 8). The most common reason for not completing the study to week 12 was due to adverse events. The percentage of patients who withdrew due to adverse events at week 12 was 1.2%, 1.2%, and 3.7% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. Reasons for withdrawal from the study are also summarized in Table 8.

Table 8: Patient Disposition

	aboBoNTA 500 U (N = 81)	aboBoNTA 1,000 U (N = 81)	Placebo (N = 81)
Screened, N	281		
Randomized, N	[redacted]	[redacted]	[redacted]
Discontinued, N (%)	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]
Consent withdrawn	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Completed, N (%)	[redacted]	[redacted]	[redacted]
mITT, N	[redacted]	[redacted]	[redacted]
PP, N	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; mITT = modified intention-to-treat; N = total number of patients in treatment group; n = number of patients in subgroup; PP = per-protocol; U = units.

Source: From consort table in the manufacturer's submission to CDR,[14] CSR,[16] and additional data from manufacturer.[27]

Exposure to Study Treatments

Study 145 was designed for one single aboBoNTA intramuscular injection treatment. Either 500 U or 1,000 U doses were used.[16,22] The duration of the treatment exposure (mean number of weeks ± SD) was 15.87 ± 4.91, 15.28 ± 3.89 and 13.74 ± 2.54 in aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. The dose injected in individual PTMG is presented in Table 10.

Table 9: Summary of Duration of Follow-Up

		aboBoNTA 500 U (N = 78)	aboBoNTA 1,000 U (N = 77)	Placebo (N = 74)
Dose (U)		500	1,000	NA
# of treatment cycles		[redacted]	[redacted]	[redacted]
Duration of follow-up[a]				
Weeks	Mean ± SD	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Range	[redacted]	[redacted]	[redacted]

= number; aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; SD = standard deviation; U = units.

a Duration of follow-up indicated the time to re-treatment (or time to eligible re-treatment).

Source: Study CSRs.[16]

Table 10: Doses of aboBoNTA Administered to Each Muscle Group – Safety Population

Muscle Group	aboBoNTA 500 U (N = 81)	aboBoNTA 1,000 U (N = 81)
PTMG		
Elbow flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Extrinsic finger flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Wrist flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
All injected muscles		
Elbow flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Brachioradialis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Brachialis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Other elbow muscles	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Biceps brachii	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Pronator teres	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Wrist flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Flexor carpi radialis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Flexor carpi ulnaris	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Extrinsic finger flexors	[redacted]	[redacted]

Muscle Group	aboBoNTA 500 U (N = 81)	aboBoNTA 1,000 U (N = 81)
Mean (SD) [range]	[redacted]	[redacted]
Flexor digitorum profundus	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Flexor digitorum superficialis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Other finger flexors	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Flexor pollis longus	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Adductor pollicis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Shoulder muscles	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Triceps brachii	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Pectoralis major	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Subscapularis	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]
Latissimus dorsi	[redacted]	[redacted]
Mean (SD) [range]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; mITT = modified intention-to-treat; N = total number of patients in treatment group; n=number of patients in subgroup; PP = per-protocol; PTMG = primary targeted muscle group; SD = standard deviation; U = units.

Source: Study 145 CSRs.[16]

Critical Appraisal

Internal validity

The objectives of the study were well defined. Randomization was stratified by centre and patient's previous exposure to botulinum toxin treatment. Allocation concealment was sufficiently described. The randomization manager who was a statistician independent from the study, prepared and kept the master randomization list for this study. The randomization list was then dispatched to the sites. The sample size was determined based on the power (≥ 85%) to detect a difference of change from baseline (mean ± SD: 1.0 ± 0.8 and 0.6 ± 0.8, in the aboBoNTA and placebo groups, respectively) for MAS score at week 4 ($P < 0.05$), as well as based on the power (≥ 90%) to detect a between-group mean difference (mean ± SD: 0.7 ± 1.1) for the PGA score at week 4. The rationale for the above threshold was based on a previous clinical trial conducted in patients with lower limb spasticity.[14,42] ANCOVA analysis was performed for the primary outcome controlling for the baseline MAS score in the PTMG, the randomization stratification factor (BoNT treatment status at baseline) and the centre, all as fixed effects. Key patient baseline characteristics were balanced across treatment groups. The intervention (the range of dose and volume used for the PTMG as well as for each muscle) was reported in detail. The relevant

concomitant medications (for spasticity) and physiotherapy were well described and balanced in the aboBoNTA and placebo groups. The outcome measurement (especially the primary outcome and the secondary outcomes) were well described. The primary outcome and the secondary outcomes are commonly used in clinical trials for ULS and accepted by Health Canada.[23] The overall dropout was low. The study was conducted in multi-centres and multi-countries.

While overall the study was generally well-designed as mentioned above, some methodological limitations of the RCT need to be discussed in the interpretation of the results. Although the master randomization list was prepared independently and the allocation concealment was sufficient, how the randomization list was generated was not clearly described in the CSR.[16] While identical active and placebo vials were provided to maintain blinding for patients and investigators, there was a risk of unblinding in this trial as overall 55% patients (71% patients in the US study sites) were known to have previously responded to botulinum toxin, and were therefore likely to expect a reduction in symptoms after the injection. Placebo patients would not experience this reduction in symptoms and therefore patients might be able to identify treatment based on response – potentially impacting subjective outcomes and adverse effect reporting. Further, the criteria for re-treatment was not clearly defined, and the analysis set for the primary analysis was based on a modified ITT population, not a true ITT population. Except for the primary outcome (MAS at week 4) and the first secondary outcome (PGA at week 4), which were analyzed based on a 4-step statistical testing hierarchy to control type I error, the DAS and all tertiary outcomes (such as MAS, PGA assessed at week 12 , TS, AROM, MFS, SF-36, EQ-5D, outcomes assessed for individual PTMG, and analysis for individual DAS domain, etc.) were analyzed as for exploratory purpose only. Furthermore, there is no MCID established for PGA, and the clinical significance of the benefit of aboBoNTA compared with placebo in terms of PGA was not clear from the literature. However, based on input from the clinical expert consulted for this review, the between-group difference compared with placebo of 0.6 in the aboBoNTA 500 U group and 1.1 for the aboBoNTA 1,000 U group was considered clinically meaningful.

External validity

There were no Canadian sites enrolled in Study 145. According to the clinical expert consulted for this review, the population enrolled in the pivotal trial was generally representative of Canadian patients with ULS. The expert did note, however, that based on the baseline MAS score and MFS score, the patient population appeared to be more severe than the patients that would routinely be seen in Canadian clinical settings who are eligible for BoNT treatment. Furthermore, the duration of time since stroke (approximately 5 years) or brain injury (approximately 12 years) was longer than would typically be seen in Canadian practice. According to the experience of the clinical expert, patients with ULS would be treated with BoNT within one or two years post-stroke or post-traumatic brain injury. Only patients with ULS as a result of stroke or traumatic brain injury were included in the pivotal trial. No patients with ULS from other causes such as MS, cerebral palsy, spinal cord injury, or amyotrophic lateral sclerosis were included in Study 145, and it is therefore unclear if the reported efficacy and safety of aboBoNTA could be generalized to patients who have ULS due to other causes. However, the clinical expert consulted for this review indicated that the underlying cause of the ULS would not impact the treatment strategy applied. Finally, one of the exclusion criteria in the pivotal trial was to exclude the patients who had previously experienced a poor response to botulinum toxin. It is unclear if the findings reported in the pivotal study can be generalized to patients who had a poor

response to botulinum neurotoxin treatment previously, however, the clinical expert indicated that it is likely that if patients experienced a poor response or no response to onaBoNTA or incoBoNTA previously, that they would be eligible to switch to aboBoNTA.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See Appendix 4 for more detailed efficacy data.

Modified Ashworth Scale

In Study 145, the MAS scores at baseline (mean ± SD) were 3.9 ± 0.4, 3.9 ± 0.5, and 3.9 ± 0.4 in the aboBoNTA 1,000 U, aboBoNTA 500 U, and placebo groups, respectively. At week 4, the between-group mean difference in change from baseline was statistically significant (–1.1, 95% CI, –1.4 to –0.8, $P < 0.0001$) in the aboBoNTA 1,000 U group compared with the placebo group. Likewise, the between-group mean difference in change from baseline for the aboBoNTA 500 U group compared with placebo was statistically significant (–0.9, 95% CI, –1.2 to –0.6, $P < 0.0001$). MAS scores assessed at week 12 were analyzed as a tertiary outcome for exploratory purposes only. The improvement in MAS score observed for both aboBoNTA groups at week 4 appeared to be maintained at week 12 to a lesser extent (Table 11). The results of MAS score after week 12 and up to week 24 are presented in Table 19 in Appendix 4.

The subgroup analysis for the MAS assessed for individual muscle groups also showed an improvement in both aboBoNTA groups compared with placebo (Table 20 in Appendix 4). The results for MAS score at weeks 16, 20, and 24 were reported as descriptive statistics; no statistical analysis was performed (see Table 21, Table 22, and Table 23 in Appendix 4). No additional subgroup analyses of interest based on the review protocol were conducted.

Table 11: MAS Score (PTMG)

MAS score	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	80	79	79
Mean (SD)	3.9 (0.5)	3.9 (0.4)	3.9 (0.4)
Week 4			
n	80	79	79
Mean (SD)	2.7 (1.0)	2.6 (1.2)	3.7 (0.7)
CFB to Week 4			
LSM of CFB (95% CI)[a]	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95%CI) (aboBoNTA – placebo)	**–0.9 (–1.2 to –0.6)**	**–1.1 (–1.4 to –0.8)**	NA
P value	< 0.0001	< 0.0001	NA
Week 12 [b]			
n	76	76	75
Mean	NR	NR	NR
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]

MAS score	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
LSM diff CFB (95%CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients in subgroup; NA = not applicable; NR = not reported; PTMG = primary targeted muscle group; SD = standard deviation; U = units.

a LSM was adjusted by baseline MAS, BoNT treatment status at baseline, and the study centre.

b Data at week 12 was an exploratory outcome

Source: Study 145 CSR,[16] Gracies 2015.[17]

Responders based on MAS

A responder was defined as a patient who had at least a one-grade improvement from baseline on the MAS for the PTMG. The percentage of MAS responders for the PTMG at weeks 4 and 12 were 78.5% and 48.1% in the aboBoNTA 1,000 U group, 73.8% and 42.5% in the aboBoNTA 500 U group, and 23% and 14% in the placebo group (Table 24). Responder data in weeks 16, 20, and 24 is presented in Table 24 in Appendix 4.

Tardieu Scale score

The Tardieu Scale (TS) score was analyzed for exploratory purposes only to compare each aboBoNTA dose to placebo. The spasticity angle reduction (calculated by subtraction of angle of catch from angle of arrest presented in Table 26, Table 27 and Table 28 in Appendix 4) is the effect on true spasticity of aboBoNTA, irrespective of muscle length and of spastic dystonia.[17,18] This analysis included patients who had a baseline spasticity angle of at least 10 degrees. At week 4,in **elbow flexors**,[16] the spasticity angle was [redacted] by [redacted] degrees, [redacted] degrees and [redacted] degrees in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups respectively. The spasticity grade at week 4 was also [redacted] by [redacted] points in both aboBoNTA groups and by [redacted] points in placebo groups, respectively (see Table 29). In **wrist flexors**, the spasticity angle was [redacted] by [redacted] in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups respectively. The spasticity grade at week 4 was also [redacted] by [redacted] points in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively (see Table 30). In the extrinsic **finger flexors**, the spasticity angle was [redacted] by [redacted] degrees in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. The spasticity grade at week 4 was also [redacted] by [redacted] points in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively (see Table 31).

Active Range of Motion

AROM was analyzed as a tertiary outcome for exploratory purposes only. The AROM increased for the elbow flexors, wrist flexors, and extrinsic finger flexors at week 4, and the results are presented in Table 32, Table 33, and Table 34 in Appendix 4, respectively. At the baseline, AROM in elbow flexors was [redacted] degrees in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively; AROM in **wrist flexors** was [redacted] degrees in the aboBoNTA 500, aboBoNTA 1,000 U, and placebo groups, respectively; AROM in extrinsic finger flexors was 34 degrees, 48 degrees, and 56 degrees in the aboBoNTA 500, aboBoNTA 1,000 and

placebo groups, respectively. At week 4, compared with placebo, AROM for the elbow flexors [redacted] by [redacted] degrees in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively. AROM wrist flexors [redacted] by [redacted] more in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively. AROM in extrinsic finger flexors increased by 32 degrees and by 18 degrees in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively. AROM data in weeks 16, 20, and 24 was presented in Table 32, Table 33, and Table 34 in Appendix 4.

Disability Assessment Scale

The Disability Assessment Scale (DAS) score for the PTT at week 4 was the second secondary outcome in Study 145. The DAS score for PTT at week 4 and week 12 are presented in Table 12. At baseline, the DAS score for the PTT was [redacted] points in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups respectively. The LSM change from baseline to week 4 compared with placebo was [redacted] in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively. The change from baseline of DAS score at week 12 was similar to that at week 4 (see Table 12) . DAS score for PTT in weeks 16, 20, and 24 is presented in Table 35 in Appendix 4. As tertiary outcomes, DAS score responder for PTT and DAS score responder for individual DAS domain are presented in Table 36 to Table 40 in Appendix 4.

Responders based on DAS

At week 4, the percentage of patients classified as DAS responders for the PTT was [redacted] in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. At week 12, the percentage of patients classified as DAS responders for the PTT was [redacted] in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively (see Table 36 in Appendix 4).

Table 12: Disability Assessment Scale Score for the PTT

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
Mean (SD)	2.6 (0.5)	2.5 (0.5)	2.6 (0.5)
Week 4			
Mean (SD)	1.9 (0.8)	1.8 (0.7)	2.1 (0.8)
CFB to Week 4			
LSM CFB (95% CI) [a]	[redacted]	[redacted]	[redacted]
LSM diff CFB (95% CI) (aboBoNTA – placebo)	**–0.1 (–0.4** to **0.1)**	**–0.2 (–0.4** to **0.0)**	NA
P value	**0.2560**	**0.0772**	NA
Week 12[b]			
n	76	76	75
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = number of patients in group; NA = not applicable; NR = not reported; PTT = principal target of treatment; SD = standard deviation; U = units.

[a] LSM was adjusted with baseline MAS, BoNT treatment status at baseline, and the study centre.

[b] Data at week 12 was an exploratory outcome.

Source: Study 145 CSR,[16] Gracies 2015.[17]

Modified Frenchay Scale

MFS was analyzed as a tertiary outcome for exploratory purposes only in Study 145. The MFS overall score at week 4 and week 12 are presented in Table 41 in Appendix 4. At the baseline, MFS overall scores were [redacted] in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. At week 4, compared with placebo, the treatment group differences (aboBoNTA minus placebo) were [redacted]) in the aboBoNTA 500 U and aboBoNTA 1,000 U groups, respectively; MFS overall score in weeks 16, 20, and 24 is presented Table 41.

Ease of applying a splint

Ease of applying a splint was analyzed as a tertiary outcome for exploratory purposes only in Study 145. The overall score for the ease of applying a splint at week 4 and week 12 is presented in Table 42. At baseline, overall scores for ease of applying a splint were [redacted] in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. At week 4, overall scores were decreased [redacted] in both aboBoNTA groups and increased [redacted] in placebo groups, respectively; Compared with placebo, the ease of applying a splint was decreased by [redacted] in both aboBoNTA groups. Overall score for ease of applying a splint at week 12 was presented in Table 42.

Goal Attainment Scale

GAS was an outcome identified as important to patients according to the clinical expert consulted for this review. This outcome was not assessed in the pivotal Study 145. The limited evidence from non-pivotal placebo-controlled trials was summarized in Appendix 7.

Decreased need for restraints

Decreased need for restraints was an outcome identified as important to patients, according to the patient group input received for this review. This outcome was not assessed in the pivotal Study 145.

Symptom reduction

The DAS, as described in Section 3.6.4 above, includes a pain reduction domain. No other specific symptom reduction outcome was reported in the pivotal Study 145.

Health-related quality of life (SF-36, EQ-5D)

SF-36

SF-36 was reported as a tertiary efficacy outcome for exploratory purposes only in Study 145. There were no statistically significant differences in changes in any of the SF-36 domains between the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups. A summary of baseline scores and change from baseline scores at the end of the study (anytime at or after week 12) or early withdrawal for the SF-36 questionnaire score are provided in Table 43,Table 44, and Table 45 in Appendix 4.

EQ-5D

EQ-5D VAS was reported as a tertiary efficacy outcome for exploratory purposes only in Study 145. There were no statistically significant differences in changes in the EQ-5D VAS between the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups. A summary of baseline scores and change from baseline scores at the end of the study (anytime at or after week 12) or early withdrawal for the EQ-5D VAS are provided in Table 46 of Appendix 4.

Physician Global Assessment

PGA of treatment response at week 4 was analyzed as the first secondary outcome in Study 145. The least square means (LSM) of the PGA at week 4 were [redacted] in the aboBoNTA 1,000 U group, [redacted] in the aboBoNTA 500 U group, and [redacted] in the placebo group respectively (Table 13). The results of the PGA show that aboBoNTA (1,000 U and 500 U) were statistically significantly more effective than placebo (1.1 [95% CI, 0.8 to 1.4, $P < 0.0001$] and 0.6 [95%CI, 0.3 to 1.0, $P = 0.0003$], respectively). PGA assessed at week 12 was analyzed as a tertiary outcome for exploratory purposes only. The improvement in PGA score observed for both aboBoNTA groups at week 4 was maintained at week 12 to a lesser extent (Table 13). PGA findings assessed at weeks 16, 20, and 24 are presented Table 47 in Appendix 4.

Table 13: Physician Global Assessment of Treatment Response

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
n	80	78	78
LSM (95% CI)[a]	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA – placebo)	**0.6 (0.3 to 1.0)**	**1.1 (0.8 to 1.4)**	**NA**
P value	**0.0003**	**< 0.0001**	**NA**
Week 12[b]			
n	76	75	75
LSM (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum neurotoxin; CI = confidence interval; diff = difference; LSM = least squares mean; PGA = Physician Global Assessment of treatment response; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; SD = standard deviation; U = units.

Note: No baseline assessment for PGA.

a LSM was adjusted with BoNT treatment status at baseline and the study centre.

b Data at week 12 was an exploratory outcome.

Source: Study 145 CSR,[16] Gracies 2015.[17,18]

Caregiver Burden Scale

Caregiver Burden Scale (CBS) was an outcome identified as important to patients according to the patient group input received for this review. This outcome was not assessed in the pivotal Study 145. The limited evidence from non-pivotal placebo-controlled trials was summarized in Appendix 7.

Duration of effect (re-treatment intervals)

The duration of effect (estimated as time to re-treatment) was defined as the time between the date of administration of study medication and the date of the need for re-treatment. A patient was deemed eligible for re-treatment if the patient no longer demonstrated a MAS score reduction from baseline of at least one grade in the PTMG, showed no improvement on the PGA (i.e., a score ≤ 0), and there was no unacceptable safety risk identified for the patient. The median (95% CI) time from injection to eligibility for re-treatment was 13.1 weeks (range: 12.9 to 14.1) in the aboBoNTA 500 U group, 14.0 weeks (range: 13.1 to 15.3) in the aboBoNTA 1,000 U group, and 13.0 weeks (range: 12.4 to 13.1) in the placebo group respectively (Table 9). At week 12, 69.4%, 61.3%, and 90.1% patients were eligible for re-treatment in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. The re-treatment was available by entry into the extension phase, for which further results are presented in Table 52 in Appendix 6.

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4 for detailed harms data.

Adverse events

The incidence of TEAEs in Study 145 are presented in Table 14. At least one TEAE was reported in 44%, 42%, and 26% of patients in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively; The most common TEAE was nasopharyngitis (8.6%, 1.2%, and 1.2% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively) and muscular weakness (2.5%, 4.9%, and 2.5% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively). Other TEAEs includes sinusitis, urinary tract infections, and injection site pain, which were all reported by less than 4% of patients (see Table 14).

Table 14: TEAE (≥ 2% of patients) – Safety Population

	aboBoNTA 500 U N = 81	aboBoNTA1000 U N = 81	Placebo N = 81
[redacted]			

aboBoNTA = abobotulinumtoxinA ; N = total number of patients in treatment group; n = number of pts in subgroup (with event); pts = patients; TEAE = treatment-emergent adverse event; U = units.

Source: Study 145 CSR.[16]

Serious adverse events

In Study 145, three SAE were reported in each of the three treatment groups (Table 15).

In the aboBoNTA 500 U group, SAEs included sepsis, muscle spasms, and Behçet's syndrome, cardiovascular disorder, and death and in the aboBoNTA 1,000 U group, SAEs included partial seizures, syncope, ligament sprain, and cerebrovascular accident. In the

placebo group, SAEs included pulmonary edema and death, craniocerebral injury, and muscle weakness, and deep vein thrombosis.[17,18]

Table 15: Serious Adverse Events

	AbobotulinumtoxinA500 U (n = 81)	AbobotulinumtoxinA1000 U (n = 81)	Placebo (n = 81)
Pts with any SAE n (%)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; n = number of pts in subgroup (with event); pts = patients; SAE= serious adverse events; U = units.

Source: Study 145 CSR,[16] additional data from the manufacturer,[43] and Gracies 2015.[17]

Withdrawals due to adverse events

The number of patients who withdrew due adverse events were 1 (1.2%), 1 (1.2%), and 3 (3.7%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively (Table 8).

Mortality

There were two deaths during the study. One patient died in the aboBoNTA 500 U group, and one patient died in the placebo group (Table 1).

Notable harms

Muscular weakness, injection site reaction, dysphagia, and development of antibody were identified as the notable harms of interest based on the review protocol (Objectives and Methods). The number of patients experiencing muscular weakness were 2 (2.5%), 4 (4.9%), and 2 (2.5%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. The number of patients with injection site reactions, including injection site erythema, were 2 (2.4%), 3 (3.7%), and 5 (6.2%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. There were no reports of patients experiencing dysphagia (Table 16).

Table 16: Notable Harms

Pts with notable TEAE, n (%)	aboBoNTA 500 U N = 81	aboBoNTA 1,000 U N = 81	Placebo N=81
Muscular weakness	[redacted]	[redacted]	[redacted]
Injection reaction[a]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; n = number of pts in subgroup (with event); pts = patients; TEAE = treatment-emergent adverse event; U = units.

a The number of injection site reaction events were calculated by CADTH by adding the occurrences of injection site erythema, injection site bruising and injection site pain reported in Table 14

Source: Study 145 CSR,[16] and Gracies 2015.[17]

Discussion

Summary of Available Evidence

One pivotal placebo-controlled RCT (Study 145) met the inclusion criteria for this review. Study 145 enrolled adult patients with ULS (MAS score ≥ 2 in the PTMG for BoNT-naive patients or MAS score ≥ 3 in the PTMG for BoNT-experienced patients; DAS score ≥ 2 on the PTT; spasticity angle ≥ 10° in the PTMG; and MFS overall score [average of all task scores] between 1 and 8). Study 145 assessed the efficacy and the safety of a single aboBoNTA IM injection (500 U or 1,000 U) versus placebo in the treatment of patients with ULS. The primary outcome was the change from baseline in MAS score in the PTMG at week 4. Other outcomes included PGA score (the first secondary outcome) measured at week 4, and change from baseline in the DAS for the PTT assessed at week 4 (the second secondary outcome). MAS, PGA, and DAS measured at week 12, DAS scores within each domain of disability at week 4 to 12; MFS, TS, AROM, the ease of applying a splint and Health-Related Quality of Life Scales (SF-36 and EQ-5D) were assessed as tertiary outcomes for exploratory purposes only. Treatment-emergent adverse events (TEAEs), serious adverse events, and WDAEs were also reported.

In addition to the main pivotal trial reviewed, the long-term efficacy and safety of aboBoNTA treatment in ULS was assessed in the open-label extension phase of Study 145 (i.e., Study 148[22]) (see Appendix 6), and three non-pivotal placebo-controlled studies[44-47] assessed the efficacy of aboBoNTA for clinically relevant outcomes (i.e., GAS and CBS) which were not assessed in the pivotal Study 145 (see Appendix 7). No RCTs were identified that directly compared aboBoNTA with onaBoNTA (Botox) or incoBoNTA (Xeomin) in this review. However, the manufactured submitted an indirect treatment comparison (ITC)[48], which is summarized in Appendix 8: Summary of Indirect Comparisons.

Interpretation of Results

Efficacy

The primary efficacy outcome for the pivotal RCT (Study 145) was the change from baseline in MAS score in the PTMG at week 4. MAS was identified as an important outcome for patients, based on the patient group input. Efficacy results from Study 145 indicated an effect of aboBoNTA in the treatment of ULS consistently across the primary and the first secondary outcome (PGA). It demonstrated that both aboBoNTA doses (1,000 U and 500 U) were more effective than placebo for reducing muscle tone (assessed by MAS) at week 4. This improvement was consistent across individual muscle groups: finger, wrist, and elbow flexors. The between-group mean difference of changes from baseline (aboBoNTA minus placebo) for MAS score was statistically significant. The clinical expert consulted for this review considered the observed difference (–0.9 in the aboBoNTA 500 U group and –1.1 in the aboBoNTA 1,000 U group) to be clinically meaningful, although, in general, a one-point difference in the MAS score is considered to be clinically significant (see Appendix 6). The improvements in muscle tone for both aboBoNTA doses at week 4 were associated with a statistically significant clinical improvement based on the PGA. The between-group mean difference (aboBoNTA minus placebo) for PGA score was statistically significant (1.1 in the aboBoNTA 1,000 U group and 0.6 in the aboBoNTA 500 U group). No validity information and MCID were identified for PGA, however, the clinical expert

consulted in this review indicated that PGA findings reported for both aboBoNTA dose groups in this study showed a clinical benefit compared with placebo. There was a numerically greater reduction in the mean change from baseline in DAS for the PTT at week 4 in the two aboBoNTA groups compared with placebo, but the difference between aboBoNTA groups and placebo was not statistically significant in either group.

Outcomes other than MAS (the primary outcome), PGA (the first secondary outcome), and DAS (the secondary outcome) were treated as tertiary (i.e., exploratory) outcomes. Compared with placebo, at week 4, numerical improvements in aboBoNTA dose groups were observed in tertiary outcomes including: the percentage of responders to MAS assessed for the PTMG or the percentage of responders to DAS; spasticity angle and reduction in spasticity severity grade for elbow flexors, wrist flexors, and extrinsic finger flexors (assessed with TS); the limb active function improvement (measured with MFS); and the AROM for elbow flexors and wrist flexors in aboBoNTA 1,000 U, and for extrinsic finger flexors in both aboBoNTA dose groups were also observed. However, no conclusion could be derived from the aforementioned tertiary outcomes because they were analyzed as tertiary outcomes and for exploratory purpose only. No controls for multiple statistical testing were used to control for the risk of type I error.

The following methodological limitations in study design should be considered when interpreting the results reported in the RCT. First, although the master randomization list was prepared independently and the allocation concealment was sufficient, how the randomization list was generated was not clearly described in the CSR.[16] Second, while identical active and placebo vials were provided to maintain blinding for patients and investigators, there was a risk of unblinding in this trial as overall 55% patients (71% patients in the US study sites) were known to have previously responded to botulinum toxin A. Patients would therefore expect a reduction in symptoms after the injection. Patients with placebo would not experience this reduction in symptoms and therefore patients might be able to identify treatment based on response. Third, except for the primary outcome (MAS) and the first secondary outcome (PGA), the DAS (the secondary second outcome) and other outcomes including TS, AROM, MFS, ease of applying a splint, and quality of life measures, outcomes assessed at week 12, analysis for individual PTMG group and for individual DAS domain, as well as the treatment responder based on MAS or DAS, were all analyzed as tertiary outcomes for exploratory purpose only and not controlled by multiplicity for type I error. Therefore, no statistical significance should be claimed for any tertiary outcomes. Finally, as the patient-related outcomes, GAS, CBS, and decreased need for restraints, were not reported in Study 145.

According to the clinical expert consulted in this review, in Canada, patients with ULS post-stroke or brain trauma usually receive BoNTA treatment within one to two years after stroke or traumatic brain injury. The patients enrolled in the pivotal study were relatively more severe (baseline MAS = 3.9 out of 4) and were at a relatively late stage post-stroke or brain trauma (5 years after stroke or 10 years after brain trauma) than what would typically be seen in Canadian clinical practice. The clinical expert also indicated that clinically, when a patient already had a poor or no response to the current botulinum neurotoxin (onaBoNTA [Botox] or incoBoNTA [Xeomin]) treatment, it is likely that a patient would then be eligible to try aboBoNTA (Dysport). Furthermore, no patients with ULS due to causes other than stroke or TBI were included in Study 145. Patients who were botulinum neurotoxin nonresponders previously and patients with major limitation in the passive ROM at the affected PTMG were excluded. Therefore, it is not clear whether the findings reported in the study can be generalized to patients with less severe ULS, to patients with ULS from

other causes such as MS or cerebral palsy, or to patients who had a poor response to BoNT treatment previously. The clinical expert consulted for this review expected that the efficacy and safety profile of aboBoNTA in the treatment of ULS would be similar regardless of the underlying conditions of the ULS. Input from one patient group Multiple Sclerosis Society of Canada (MS Society) suggested that they expected aboBoNTA to provide patients with an effective therapy for ULS for up to 20 weeks without adverse effects; however, results for the duration of the effect (or time to re-treatment, up to 20 weeks) were not conclusive, based on the evidence reviewed.

Results from the open-label extension study demonstrated that the efficacy of repeated use (up to five treatments) of aboBoNTA in reducing the symptoms and signs of patients with ULS appeared to be maintained, and no new safety signals were identified (Appendix 6). Based on the results reported in the three non-pivotal placebo-controlled studies,[44-47] the aboBoNTA group showed a greater magnitude of improvement in GAS scores and greater reduction in CBS compared with the placebo group at 6 weeks post-injection. However, the findings on GAS and CBS were inconclusive due to various limitations of the study design[44-47] (see Appendix 7).

The manufacturer submitted an indirect treatment comparison (ITC)[48] that suggested the three BoNTAs (aboBoNTA, onaBoNTA, and incoBoNTA) may have similar treatment effects in patients with post-stroke spasticity. These results, however, are limited by the small number of studies available for some outcomes, the high amount of heterogeneity between studies, and the large number of assumptions required to facilitate the pooling of data for analysis (Appendix 8).

Harms

In general, there were no clinically important safety concerns identified for aboBoNTA in the treatment of ULS. In Study 145, there was a numerically higher incidence of TEAEs in the aboBoNTA groups (43%) than in the placebo group (26%). According to the clinical expert consulted in this review, the overall incidence of TEAE reported in the trial was lower than usually observed in clinical practice. The most common TEAE was nasopharyngitis (8.6%, 1.2%, and 1.2% in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively). Other TEAEs included sinusitis and urinary tract infections, which were all less than 4%. Serious adverse event was rarely reported (4% in each group). The number of patients who withdrew due adverse events was 1 (1.2), 1 (1.2%), and 3 (3.7%) in the aboBoNTA 500 U, aboBoNTA 1,000 U, and placebo groups, respectively. There were two deaths during the study. One patient died in the aboBoNTA 500 U group, and one patient died in the placebo group. Notable harms including muscle weakness and injection site pain were less than 5%. No patient with dysphagia was reported. Two patients (one in each aboBoNTA dose group) showed positive for anti-aboBoNTA antibody for binding antibodies and also for neutralizing antibodies. The data to assess the clinical impact of developing antibodies are limited. As there is no means of testing patients for anti-aboBoNTA in clinical practice, the significance of developing these antibodies is likely to be low. The manufacturer submitted an ITC which suggested that the three BoNTAs (aboBoNTA, onaBoNTA, and incoBoNTA) may have a similar safety profile in patients with post-stroke spasticity.

Potential place in therapy[2]

Spasticity is a velocity dependent increase in muscle tone that is commonly seen in neurological disorders affecting the brain and spinal cord, including but not limited to stroke, traumatic brain injury, cerebral palsy, spinal cord injury, and MS.[49,50] ULS can affect patients in various ways, including interfering with active function of the hand and performance of activities of daily living, preventing proper limb positioning, and causing painful muscle spasms. Spasticity is typically a chronic, lifelong condition, and can lead to long-term complications such as skin breakdown and infection, and permanent soft tissue contracture.[49,50]

The approach to spasticity management typically begins with non-pharmacological interventions, namely stretching, splinting, proper positioning, physiotherapy and/or occupational therapy, etc. If these are insufficient to control a patient's spasticity, then pharmacological options would be considered next. The choice of medication depends on the severity of spasticity and the number of limbs or muscle groups affected. For more generalized (i.e., whole body) or regional (e.g., hemibody) spasticity, oral antispasticity medications such as baclofen, dantrolene, or tizanidine can be utilized. For more focal spasticity (i.e., affecting a small number of muscle groups, or one limb only), botulinum toxin injections would be considered as the first-line pharmacological option, as they have the advantage of bypassing systemic side effects typically experienced with the oral agents and allowing the clinician to target the specific muscle groups that are most affected by spasticity. Botulinum toxin injections and oral antispasticity medications can also be combined in cases where suboptimal treatment response is achieved with one or the other alone. Clinical judgment, provider experience, and patient factors (including patient preference, comorbidities and previous treatment exposures) are also factors which inform the decision whether to prescribe oral or injectable medications, or a combination of the two.

Prior to Health Canada's approval of aboBoNTA, there were two formulations of botulinum toxin available in Canada; onaBoNTA (Botox) and incoBoNTA (Xeomin). Botox and Xeomin are generally equivalent in efficacy and safety profile, and if a patient fails treatment with one botulinum toxin, they may be switched to the other in the hopes of achieving a superior treatment effect. A patient who fails both Botox and Xeomin treatment would be deemed a nonresponder to botulinum toxin, and would be limited to managing spasticity with oral medications and non-pharmacological interventions alone.

AboBoNTA (Dysport) is a third formulation of botulinum toxin that has been shown to have similar efficacy and safety results when compared with Botox and Xeomin in the treatment of ULS. Dysport offers patients a third injectable pharmacological option for spasticity, and could be used either as an equivalent first-line alternative to Botox and Xeomin, or as a second- or third-line injection option for patients who do not respond to the others. Any patient who is currently a candidate for Botox or Xeomin treatment would also be a candidate for Dysport, and any patient with ULS, regardless of their underlying neurological diagnosis, could benefit from Dysport. Dysport thus has the potential to significantly improve the function and quality of life for a wide spectrum of patients with diseases of the central nervous system. While not expected to provide superior therapeutic benefit

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

compared with Botox and Xeomin, the availability of Dysport provides patients with an additional choice of botulinum toxin formulation to try for management of their focal ULS.

Conclusions

The CDR systematic review included one double-blind, placebo-controlled study (Study 145; N = 243). Based on the primary outcome (MAS score for the PTMG at week 4), aboBoNTA (1,000 U or 500 U) was statistically and clinically significantly more effective than placebo in reducing muscle tone in patients with ULS. According to the PGA score at week 4 (first secondary outcome), a statistically significant global clinical benefit of aboBoNTA (1,000 U or 500 U) compared with placebo was also achieved. There was no statistically significant difference achieved between aboBoNTA (1,000 U or 500 U) and placebo for the DAS (second secondary outcome). Due to limitations in the design of the study (tertiary outcomes analyzed for exploratory purpose only or not controlled by multiplicity for type I error), the clinical effect of the aboBoNTA compared with placebo was inconclusive for the following outcomes: passive and active function outcomes (TS, AROM, MFS, ease of applying a splint) and health-related quality of life (SF-36, EQ-5D). Outcomes reported as being important to patient groups from patient group input such as GAS, caregiver burden, and decreased needs for restraints, were not measured in the pivotal study. Overall adverse events were low despite a numerically higher incidence of TEAEs in the aboBoNTA groups than that in the placebo group. The open-label uncontrolled extension phase of the trial showed a similar efficacy and safety profile of aboBoNTA (1,000 U and 500 U) as reported in the double-blind phase. A network meta-analysis submitted by the manufacturer suggested that the three BoNTAs (aboBoNTA, onaBoNTA, and incoBoNTA) may have similar treatment effects in patients with post-stroke spasticity, however the statistical analyses are limited by the large number of assumptions required in order to estimate the relative efficacy between toxins.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

Two patient groups submitted input for this review.

The Multiple Sclerosis Society of Canada (MS Society) is a national voluntary organization that supports multiple sclerosis (MS) research and provides services related to MS for patients and their families and caregivers. The MS Society is mainly funded by individuals, companies, and foundations in communities across Canada, and receives almost no funding from government.[51] Between 2016 and 2017, the MS Society received educational grants from the following pharmaceutical companies: Bayer, Biogen, EMD Serono, Novartis, Pfizer, Genzyme – A Sanofi Company, Allergan, Roche, and Teva Neuroscience. All contributions are subject to policies that prevent any control or influence by the donor on the MS Society's decision-making. No conflicts of interest were declared in the preparation of this submission.

The March of Dimes Canada (MDC) is a registered national charity organization that provides a wide range of programs and services to enhance the independence, personal empowerment, and community participation of people with physical disabilities. The MDC receives funds from many individuals and organizations. Major donors include TD Bank Group, Transamerica Life Canada, Drive Medical Canada, Bell, Scotiabank, BMO Financial Group, CIBC, CitiFinancial, Dentons Canada LLP, Green Shield Canada, LCBO, Power Corporation of Canada, Princess of Wales Own Regiment, Proctor & Gamble, Royal Bank of Canada Foundation, Rexall, Sanofi Aventis, Sanofi Pasteur, Shoppers Home Health Care, and Waverley Glenn Systems. MDC's LIFE Toronto program has not received funding from Ipsen Biopharmaceuticals, the manufacturer of aboBoNTA, and Ipsen was not involved in preparing the patient input submission.

2. Condition-Related Information

The MS Society solicited patient input through bilingual (English and French) surveys about upper limb spasticity (ULS) and its management distributed through social media, during May 1 to 7, 2017. In total, 64 people responded to the survey, including four caregivers. Among the patients, approximately 90% of respondents were women with relapsing-remitting MS and with an age ranging from 31 to 70 years. Less than half of all respondents had been living with the disease between 2 to 5 years. About 17% of all respondents stated they had been living with the disease between either 5 to 10 years or 11 to 20 years.

The MDC obtained patient input through the personal experiences of a focus group of six adults with spasticity. This was a convenience sample taken from an MDC life skills program for adults with physical disabilities. The focus group was held on May 2, 2017 in Toronto, Ontario. The age of these patients ranged from 19 to 30 years. Most of them have cerebral palsy. Wheelchairs or walkers are needed by all the patients.

ULS can greatly affect patient's daily living and has been associated with unemployment. More than half of all respondents indicated that ULS affects their recreational activities significantly, as well as the ability to care for children or other family members, driving, self-care (washing, dressing, toileting), mobility, remaining in the work force, socializing, sleep, and living independently.

One patient with ULS from the MS Society stated: “Spasms may seem like a small issue to some but it impacts everything we do every day.” Patients from the MDC also indicated that spasticity negatively affects their daily lives such as the ability to eat meals, difficulty in opening packages or doors, and causes pain. One patient from the MDC indicated that spasticity “makes it difficult for others to help you,” and “when people move me, I’ll jump and move uncontrollably.” Depending on the type and severity of MS, a caregiver’s role can range from providing emotional support and assistance with medication administration, to helping with activities of daily living such as personal care, feeding, and transportation to and from appointments. Caregivers who responded to the MS Society survey stated that they were required to assist the patient they care for with activities of daily living. Input from the MDC identified these challenges for the caregivers when caring for patients with spasticity: time constraints, risk for physical strain, feeling of difficulty and frustration with helping patients during self-care, financial burdens, and finding appropriate treatments.

3. Current Therapy-Related Information

According to the survey conducted by the MS Society, ULS was managed through exercise (approximately 36% of the respondents) or with muscle relaxants and anticonvulsant medications (30%). Twenty per cent of the respondents did not treat this symptom. Of those who stated they use a medication, few patients (less than 5%) were very satisfied with the efficacy of the treatment. Most medications prescribed for the management of ULS carry troublesome side effects including weakness, numbness and tingling, blurred vision, fatigue, and difficulty sleeping. Because these are also common symptoms of MS, it is challenging to identify which is an adverse effect of the medication or a symptom of the disease. Although the medications may manage the spasticity, many of the drug-related adverse events continue to present barriers to employment, driving, and independent living. Two of the six respondents from the MDC had previously received pharmacotherapy for ULS. Both respondents reported reduced spasticity after the medication. Drowsiness was reported at the beginning of the treatment, but went away after the respondents adjusted to the medication.

Respondents from both patient groups expressed concerns about the high cost of the medication therapies. Respondents of the MDC stated “Make sure medications are covered by ODSP [the Ontario Disability Support Program], otherwise we can’t afford it.” In addition, they indicated the challenges that arise when a specialist is required to provide the treatment, as compared with a family doctor.

4. Expectations About the Drug Being Reviewed

None of the respondents had experience with aboBoNTA for ULS. Only one respondent of the MS Society had been made aware of aboBoNTA as a treatment option for ULS by their physician. Respondents of the MDC indicated that they would be willing to experience adverse effects if the drug reduces pain, increases control, reduces the need for straps/restraints, and reduces the need to attend as many other therapies.

Based on clinical trial data, the MS Society suggests that aboBoNTA is expected to provide people with an effective therapy for ULS for up to 20 weeks without the adverse effects that are commonly observed for muscle relaxant or anticonvulsant medications. This may allow patients to remain in the workforce, able to care for their families, continue living independently, and ultimately improving their quality of life.

Appendix 2: Literature Search Strategy

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 15, 2017
Alerts:	Weekly search updates until Sept. 20, 2017
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
Interface:	Ovid

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-Database Strategy
1. exp Botulinum Toxins, Type A/
2. (Abobotulinum* or bobotulinum* or abo botulinum* or Dysport* or Azzalure* or Reloxin* or CNT52120 or CNT 52120 or aboA or abo A or ABO or AboBTXA or aboBoNT A or aboBoNTA or "953397358" or 95339735 8 or 953397 358).ti,ab,kf,ot,hw,rn,nm.
3. (BoNT or BoNTA* or BTA or BTXA or BTX A or BTX).ti,ab,kf,ot,hw,rn,nm.
4. (botulin* adj3 (typeA or type A)).ti,ab,kf,ot,hw,rn,nm.
5. (botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kf,ot,hw,rn,nm.
6. 1 or 2 or 3 or 4 or 5
7. exp Upper extremity/
8. (upper adj2 (limb* or extremit* or bod*)).ti,ab,kf,hw.
9. Membrum superius*.ti,ab,kf,hw.
10. (arm or arms or forearm* or hand or hands or finger* or shoulder* or elbow* or wrist* or metacarpus or thumb*).ti,ab,kf,hw.
11. 7 or 8 or 9 or 10
12. exp Muscle hypertonia/
13. (spas* or torsion* or rigidity* hyperton*).ti,ab,kf,hw.
14. 12 or 13
15. 6 and 11 and 14
16. 15 use ppez
17. *botulinum toxin a/
18. (Abobotulinum* or bobotulinum* or abo botulinum* or Dysport* or Azzalure* or Reloxin* or CNT52120 or CNT 52120 or aboA or abo A or ABO or AboBTXA or aboBoNT A or aboBoNTA or "953397358" or 95339735 8 or 953397 358).ti,ab,kw.
19. (BoNT or BoNTA* or BTA or BTXA or BTX A or BTX).ti,ab,kw.
20. (botulin* adj3 (typeA or type A)).ti,ab,kw.
21. (botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kw.
22. 17 or 18 or 19 or 20 or 21
23. *upper limb/
24. (upper adj2 (limb* or extremit* or bod*)).ti,ab,kw.
25. Membrum superius*.ti,ab,kw.
26. (arm or arms or forearm* or hand or hands or finger* or shoulder* or elbow* or wrist* or metacarpus or thumb*).ti,ab,kw.
27. *Muscle spasm/
28. (spas* or torsion* or rigidity* hyperton*).ti,ab,kw.
29. 23 or 24 or 25 or 26
30. 27 or 28
31. 22 and 29 and 30
32. 31 use oemezd
33. 16 or 32
34. remove duplicates from 33
35. conference abstract.pt.
36. 34 not 35
37. exp animals/
38. exp animal experimentation/ or exp animal experiment/
39. exp models animal/

Multi-Database Strategy
40. nonhuman/
41. exp vertebrate/ or exp vertebrates/
42. or/37-41
43. exp humans/
44. exp human experimentation/ or exp human experiment/
45. or/43-44
46. 42 not 45
47. 36 not 46

Other Databases	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May 2017
Keywords:	Dysport and spasticity
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: a practical tool for searching health-related grey literature (https://www.cadth.ca/grey-matters) were searched:

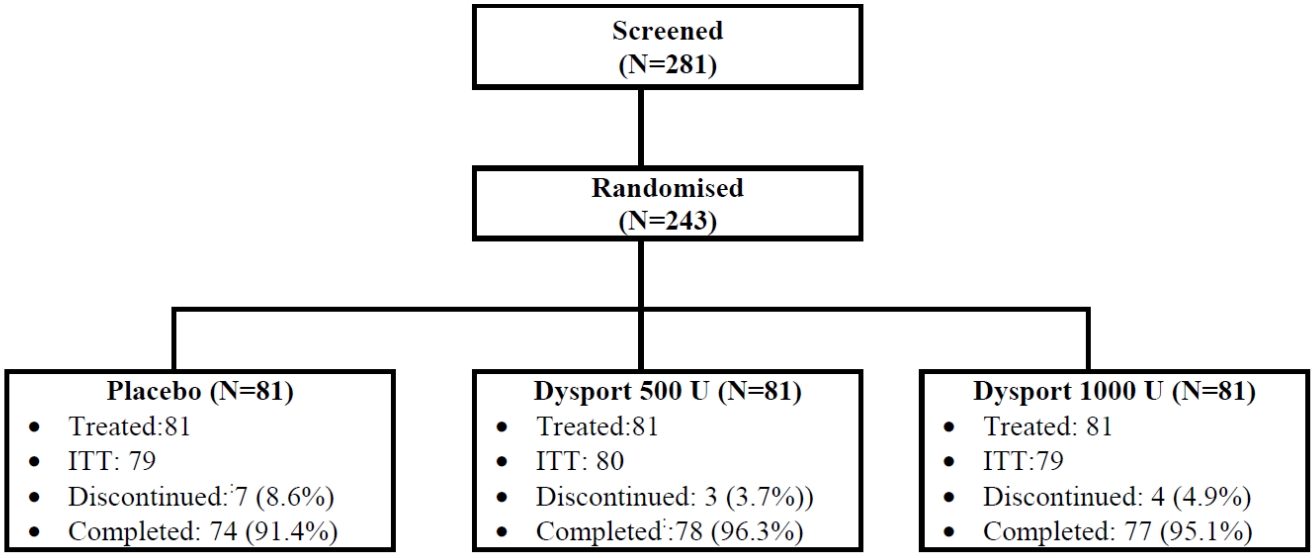
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Jost et al., 2014[2]	Not RCT
Dashtipour et al., 2015[6]	Not RCT

Appendix 4: Detailed Outcome Data

Figure 2: Patient Disposition



ITT = intention-to-treat population; N = total number of patients in treatment group, U = units.

Note: All patients who had completed their treatment cycle irrespective of the re-treatment day were considered to have completed the study.

Source: Study 145 CSR.[16]

Baseline Characteristics

Table 17: Patient Disposition by Visit

	aboBoNTA 500 U	aboBoNTA 1,000 U	Placebo
Screened, N			
Randomized, N			
Baseline, N			
Week 4			
Week 12			
Week 16			
Week 20			
Week 24			

aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; U = units.

Source: Study 145 CSR.[16]

Table 18: Concomitant Medications for ULS (≥ 10% of Pts in Any Group)

	aboBoNTA500 U (N = 80)	aboBoNTA1000 U (N = 79)	Placebo (N = 79)
Any concomitant medication for ULS, n (%)	[redacted]	[redacted]	[redacted]
Muscle relaxants	[redacted]	[redacted]	[redacted]
Baclofen	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; N = total number of pts in treatment group; n = number of pts in subgroup; pts = patients; U = units; ULS = upper limb spasticity.

Source: Study 145 CSR.[16]

Efficacy

MAS

Table 19: Changes from Baseline in MAS Score in the PTMG (Week 16 to 24)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; PTMG = primary targeted muscle group; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 20: MAS Score Change from Baseline to Week 4 in Individual Muscle Groups

MAS	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Elbow Flexors			
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Wrist Flexors			
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

MAS	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Finger Flexors			
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; ND = not determined; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 21: Changes from Baseline in MAS – Elbow Flexors (Week 12 to 24)

Elbow Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]		[redacted]
P value	[redacted]		[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 22: Changes from Baseline in MAS – Wrist Flexors (Week 12 to 24)

Wrist Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 23: Changes from Baseline in MAS – Extrinsic Finger Flexors (Week 12 to 24)

Extrinsic Finger Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFBs (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]

Extrinsic Finger Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 24: MAS Score Responders (PTMG, Week 4 to 24)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4	[redacted]	[redacted]	[redacted]
Responder (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI) (aboBoNTA vs. placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI) (aboBoNTA vs. placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of pts in subgroup (with events); NA = not applicable; pts = patients; U = units; vs. = versus.

Note: The responder was defined as pts with at least one grade reduction from baseline on the MAS in the PTMG.

Source: Study 145 CSR.[16]

Table 25: MAS Score Responders – Individual PTMG

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Elbow Flexors			
Week 4	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI) (aboBoNTA vs. placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI) (aboBoNTA vs. placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 20			
Responder n (%)			
Week 24			
Responders n (%)			
Wrist Flexors			
Week 4			
Responder n (%)			
Odds ratio (95% CI) (aboBoNTA vs. placebo)			
P value			
Week 12			
Responder n (%)			
Odds ratio (95% CI) (aboBoNTA vs. placebo)			
P value			
Week 16			
Responder n (%)			
Week 20			
Responder n (%)			
Week 24			
Responder (%)			
Extrinsic Finger Flexors			
Week 4			
Responder n (%)			
Odds ratio (95% CI) (aboBoNTA vs. placebo)			
P value			
Week 12			
Responder n (%)			
Odds ratio (95% CI) (aboBoNTA vs. placebo)			
P value			
Week 16			
Responder n (%)			
Week 20			
Responder n (%)			
Week 24			
Responder n (%)			

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n = number of patients in subgroup (with events); pts = patients; NA = not applicable; U = units; vs. = versus.

Note: The responder was defined as pts with at least one grade reduction from baseline on the MAS in the PTMG.

Source: Study 145 CSR.[16]

Table 26: Changes from Baseline in the TS – AA and AC (Elbow Flexors)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Angle of Arrest at XV1			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Angle of Catch at XV3			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
LSM CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
LSM CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
LSM CFB (SD)	[redacted]	[redacted]	[redacted]

AA = angle of arrest; AC = angle of catch; aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; TS = Tardieu Scale; U = units; XV1 = angle of arrest at slow speed (TS); XV3 = angle of catch at fast speed (TS).

Note: All angles are measured in degrees.

Source: Study 145 CSR.[16]

Table 27: Changes from Baseline in the TS – AA and AC (Wrist Flexors)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Angle of Arrest at XV1			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB(SD)	[redacted]	[redacted]	[redacted]
Angle of Catch at XV3			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

AA = angle of arrest; AC = angle of catch; aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients subgroup (assessed); NA = not applicable; SD = standard deviation; TS = Tardieu Scale; U = units; XV1 = angle of arrest at slow speed (TS); XV3 = angle of catch at fast speed (TS).

Note: All angles are measured in degrees.

Source: Study 145 CSR.[16]

Table 28: Changes from Baseline in the TS – AA and AC (Extrinsic Finger Flexors)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Angle of Arrest at XV1			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Angle of Catch at XV3			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

AA = angle of arrest; AC = angle of catch; aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; TS= Tardieu Scale; U = units; XV1 = angle of arrest at slow speed (TS); XV3 = angle of catch at fast speed (TS).

Note: All angles are measured in degrees.

Source: Study 145 CSR.[16]

Table 29: Changes from Baseline in the TS – Spasticity Angle and Grade (Elbow Flexors)

Elbow Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Spasticity Angle			
Baseline			
Mean (SD)			
Week 4			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 12			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 16			
Mean CFB (SD)			
Week 20			
Mean CFB (SD)			
Week 24			
Mean CFB (SD)			
Spasticity Grade			
Baseline			
Mean (SD)			
Week 4			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 12			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 16			
Mean CFB (SD)			
Week 20			
Mean CFB (SD)			
Week 24			
Mean CFB (SD)			

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; TS= Tardieu Scale; U = units.

Note: All angles were measured in degrees.

Source: Study 145 CSR.[16]

Table 30: Changes from Baseline in the TS – Spasticity Angle and Grade (Wrist Flexors)

Wrist Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Spasticity Angle			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Spasticity Grade			
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; TS= Tardieu Scale; U = units.

Note: All angles were measured in degrees.

Source: Study 145 CSR.[16]

Table 31: Changes from Baseline in the TS – Spasticity Angle and Grade (Extrinsic Finger Flexors)

Extrinsic Finger Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Spasticity Angle			
Baseline			
Mean (SD)			
Week 4			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 12			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 16			
Mean CFB (SD)			
Week 20			
Mean CFB (SD)			
Week 24			
Mean CFB (SD)			
Spasticity Grade			
Baseline			
Mean (SD)			
Week 4			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 12			
LSM CFB (95% CI)			
LSM diff of CFB (95% CI) (aboBoNTA – placebo)			
P value			
Week 16			
Mean CFB (SD)			
Week 20			
Mean CFB (SD)			
Week 24			
Mean CFB (SD)			

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; TS= Tardieu Scale; U = units.

Note: All angles were measured in degrees.

Source: Study 145 CSR. [16]

Table 32: Changes from Baseline in the AROM (Elbow Flexors)

Elbow Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; AROM = active range of motion; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Note: AROM was measured in degrees.

Source: Study 145 CSR.[16]

Table 33: Changes from Baseline Against the AROM (Wrist Flexors)

Wrist Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]

Wrist Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; AROM = active range of motion; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Note: AROM was measured in degrees.

Source: Study 145 CSR.[16]

Table 34: Changes from Baseline Against the AROM (Extrinsic Finger Flexors)

Extrinsic Finger Flexors	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; AROM = active range of motion; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup (assessed); NA = not applicable; SD = standard deviation; U = units.

Note: AROM was measured in degrees.

Source: Study 145 CSR.[16]

Table 35: Changes from Baseline in the DAS score for the PTT (Week 12 to 24)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; DAS = Disability Assessment Scale; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; PTT = principal target treatment; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 36: DAS Score Responders for the PTT Overall

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
n	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Responder n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; DAS = Disability Assessment Scale; N = total number of patients in treatment group; n = number of patients in subgroup (with events); NA = not applicable; pts = patients; PTT = principal target of treatment; U = units.

Note: Responder was defined as pts with at least one grade reduction from baseline on the DAS for the PTT.

Source: Study 145 CSR.[16]

Table 37: DAS Score Responders for Hygiene

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 20			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 24			
Responders, n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; DAS = Disability Assessment Scale; N = total number of patients in treatment group; n = number of patients in subgroup (with events); NA = not applicable; pts = patients; PTT = principal target of treatment; U = units.

Note: Responder was defined as pts with at least one grade reduction from baseline on the DAS for the PTT.

Source: Study 145 CSR.[16]

Table 38: DAS Score Responders for Dressing

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 20			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 24			
Responders, n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; DAS = Disability Assessment Scale; N = total number of patients in treatment group; n = number of patients in subgroup (with events); NA = not applicable; pts = patients; PTT = principal target of treatment; U = units.

Note: Responder was defined as pts with at least one grade reduction from baseline on the DAS for the PTT.

Source: Study 145 CSR.[16]

Table 39: DAS Score Responders for Limb Position

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 20			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 24			
Responders, n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; DAS = Disability Assessment Scale; N = total number of patients in treatment group; n = number of patients in subgroups (with events); NA = not applicable; pts = patients; PTT = principal target of treatment; U = units.

Note: Responder was defined as pts with at least one grade reduction from baseline on the DAS for the PTT.

Source: Study 145 CSR.[16]

Table 40: DAS Score Responders for Pain

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 4			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
Responders, n (%)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 20			
Responders, n (%)	[redacted]	[redacted]	[redacted]
Week 24			
Responders, n (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; DAS = Disability Assessment Scale; N = total number of patients in treatment group; n = number of patients in subgroups (with events); NA = not applicable; pts = patients; PTT = principal target of treatment; U = units.

Note: Responder was defined as pts with at least one grade reduction from baseline on the DAS for the PTT.

Source: Study 145 CSR.[16]

Table 41: MFS Overall Score

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean CFB (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; MFS = Modified Frenchay Scale; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; PTT = principal target treatment; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 42: Ease of Applying a Splint

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Baseline			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n	[redacted]	[redacted]	[redacted]
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
LSM CFB (95% CI)	[redacted]	[redacted]	[redacted]
LSM diff of CFB (95% CI) (aboBoNTA – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; CI = confidence interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of with data; NA = not applicable; SD = standard deviation; U = units.

Source: Study 145 CSR.[16]

Table 43: SF-36 Mental Component Summary and Physical Component Summary

Study 145		aboBoNTA 500 U (N = 80)		aboBoNTA 1,000 U (N = 79)		Placebo (N = 79)	
		Score	CFB	Score	CFB	Score	CFB
Mental Component Summary							
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical Component Summary							
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CFB = change from baseline; EOS = end of study; N = total number of patients in treatment group; SD = standard deviation; SF-36 = Short Form (36) Health Survey; U = units.

Source: Study 145 CSR;[16] additional data from manufacturer.[52]

Table 44: SF-36 Mental Component Summary (ANCOVA)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
n	**70**	**72**	**73**
LSM (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA dose – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANCOVA = Analysis of Covariance; CI = confidence of interval; diff = difference; LSM = least squares mean; M = mean; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; SE = standard of error; SF-36 = Short Form (36) Health Survey; U = units.

Source: Study 145 CSR;[16] additional data from manufacturer.[52]

Table 45: SF-36 Physical Component Summary (ANCOVA)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
n	**70**	**72**	**73**
LSM (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA dose – placebo)	[redacted]	[redacted]	
P value	[redacted]	[redacted]	

aboBoNTA = abobotulinumtoxinA; ANCOVA = Analysis of Covariance; CI = confidence of interval; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup; SE = standard of error; SF-36 = Short Form (36) Health Survey; U = units.

Source: Study 145 CSR;[16] additional data from manufacturer.[52]

Table 46: EQ-5D – VAS Change from Baseline

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Visual Analogue Scale (VAS)			
n	[redacted]	[redacted]	[redacted]
LSM (SE)	[redacted]	[redacted]	[redacted]
95% CI of LSM	[redacted]	[redacted]	[redacted]
LSM diff (95% CI) (aboBoNTA dose – placebo)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANCOVA = Analysis of Covariance; CI = confidence of interval; EQ-5D = European Quality of Life - 5 Dimensions; diff = difference; LSM = least squares mean; N = total number of patients in treatment group; n = number of patients in subgroup; NA = not applicable; SE = standard of error; U = units; VAS = visual analogue scale.

Source: Study 145 CSR;[16] additional data from manufacturer.[52]

Table 47: Physician Global Assessment of Treatment Response (Week 12 to 24)

	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Week 16			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 20			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 24			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; n = number of patients in subgroup; SD = standard deviation; U = units.

Note: No baseline assessment for PGA.

Source: Study 145 CSR.[16]

Antibodies:

Table 48: Patients Positive for Binding or Neutralizing Antibodies at Baseline

Number of Patients	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Binding Abs	[redacted]	[redacted]	[redacted]
Neutralizing Abs	[redacted]	[redacted]	[redacted]

Ab = antibody; aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; U = units.

Source: Study 145 CSR.[16]

Table 49: Patients Positive for Binding or Neutralizing Antibodies After Injection

Number (%) of Patients	aboBoNTA 500 U (N = 80)	aboBoNTA 1,000 U (N = 79)	Placebo (N = 79)
Binding Abs			
Seroconverters	[redacted]	[redacted]	[redacted]
Neutralizing Abs			
Seroconverters	[redacted]	[redacted]	[redacted]

Ab = antibody; aboBoNTA = abobotulinumtoxinA; N = total number of patients in treatment group; U = units.

Source: Study 145 CSR.[16]

Appendix 5: Validity Of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- MAS
- PGA of Treatment Response
- DAS
- MFS
- Tardieu Scale
- AROM against the PTMG
- Ease of applying a splint
- SF-36
- EQ-5D
- Goal attainment scaling
- Caregiver burden scale

Findings

A focused literature search was conducted to identify the psychometric properties and minimal clinically important difference (MCID) of each of the stated outcome measures. Table 50 summarizes the findings.

Table 50: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
MAS score	condition-specific	Yes	1-point change was considered clinically meaningful; MCID not identified.	Sunnerhagen 2013[25] Biering-Sorensen 2006[26] Rehab Institute of Chicago 1964[31] Royal College of Physicians 2009[53] Kaya 2011[28] Li 2014[29] Mehrholz 2005[30] Fleuren 2010[54]
PGA	condition-specific	No	unknown	CDR submission[14]
DAS score	condition-specific	Yes	unknown	Sunnerhagen 2013[25] Ashford 2013[32] Foley 2013[55] Canadian Partnership for Stroke Recovery, 2017[33]
TS score	condition-specific	Yes	unknown	Haugh 2006[34] Singh 2011[35] Naghdi 2017[36] Rehab Institute of Chicago 2013[56]
MFS score	condition-specific	No	unknown	CDR submission[14]

Instrument	Type	Evidence of Validity	MCID	References
				2017[57]
AROM of the PTMG	condition-specific	No	unknown	CDR submission[14]
Ease of applying a splint	condition-specific	No	unknown	CDR submission[14,53]
SF-36	generic tool to measure multidimensional health concepts and to capture a full-range of health states	Yes	2-point in PCS; 3-point in MCS	User's manual[38]
EQ-5D-5L	generic instrument	Yes	Index score: Summarized mean 0.056 (SD 0.011), summarized median 0.056 (IQR 0.049, to 0.063)	van Reenen 2015[39] Helath Quality Council of Alberta 2014[40] McClure 2017[41]
GAS	generic instrument to evaluate whether the goals have been achieved	Yes	unknown	McCrory 2009[32,45,46]
Caregiver burden	Physiotherapist-rated condition-specific	unknown	unknown	Lam 2012[44]

AROM = active range of motion; CDR = CADTH Common Drug Review; DAS = Disability Assessment Scale; EQ-5D-5L = European Quality of Life - 5 Dimensions – 5 Level; GAS = Goal Attainment Scale; IQR = interquartile range; MAS = Modified Ashworth Scale; MCID = minimal clinically important difference; MCS = Mental Component Summary; MFS = Modified Frenchay Scale; NA = not available; PCS = Physical Component Summary; PGA = Physician Global Assessment; PTMG = primary targeted muscle group; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TS = Tardieu Scale.

MAS

The Ashworth Scale (AS) and the Modified Ashworth Scale (MAS) are commonly used for estimation of muscle tone and spasticity.[25] They provide a semi-quantitative measure of the resistance to passive movement.[26] The original AS for rating spasticity involves manually moving the affected limb passively to stretch the muscle. Bohannon and Smith found that many of their patients demonstrated levels of spasticity toward the lower end of the scale;[26] therefore they modified the original AS by adding an extra category (1+) in order to increase the sensitivity of the measure and facilitate scoring.[58] The currently used modified AS (MAS) is a scale for measuring the degree of spasticity as follows:

- 0: no increase in muscle tone;
- 1: slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part(s) is moved in flexion or extension;
- 1+: slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement;
- 2: more marked increase in muscle tone though most of the range of movement, but the affected part(s) is easily moved;

- 3: considerable increase in muscle tone, passive movement is difficult;
- 4: affected part(s) rigid in flexion or extension.

The validity of the MAS was evaluated in previous studies. Even though the MAS is commonly used for measuring spasticity, evidence suggests that the resistance to passive movement is not an exclusive measure of spasticity (content validity). When comparing it to surface electromyography, which is the gold standard for spasticity, a poor correlation was reported between the MAS and surface electromyography in patients with stroke and in healthy individuals (criterion validity). Estimations of the construct validity of the MAS obtained by comparing it to other objective measures of spasticity (such as electromyography, torque response, pendulum test, etc.) and hyperactive stretch reflex measures (such as the Fugl-Meyer Assessment, the Box and Block test, active range of motion, etc.) varied.[58] The inter-rater and test-retest reliability of the MAS is variable.[53] Different statistics have been used in evaluating reliability in previous studies, such as the percentage agreement (which indicates how often the raters agreed in their scoring on the MAS), the Cohen's Kappa (κ) statistic (which gives a value of agreement corrected for chance where the κ value ranges from 0 [agreement equivalent to chance] to 1 [perfect agreement between raters][59]), Kendall's tau (τ) and Spearman's rank correlation coefficient (ρ) (τ and ρ measure the similarity of the orderings of the data by assuming a rank order between patients). The choice of statistic may also depend on the number of raters included. Although inconsistent results for the reliability of MAS have been reported in patients with spasticity resulting from stroke or severe brain injury (inter-rater reliability: percentage agreement ranged from 55% to 87%, ρ ranged from 0.45 to 0.74, κ ranged from 0.16 to 0.87; intra-rater reliability: percentage agreement ranged from 32% to 72%, ρ ranged from 0.55 to 0.74, κ ranged from 0.29 to 0.83; test-retest reliability: κ ranged from 0.47 to 0.62),[26,28-30] the reliability was generally better in the upper limb than in the lower limb. For intra-rater reliability, there was no information provided with respect to the time points that the assessments were conducted, and it was unclear whether there was a chance that the patient's condition would have changed. Therefore, it is difficult to draw a concrete conclusion from these data. Several factors may contribute to the variability in the reliability scores: different etiology and the circumstances under which the individuals have been tested (such as the time of the day, hours, and type of activity before the test, ambient temperature, emotional status, general health, use of drugs, clothing and especially the testing position), and a lack of standardization of the MAS. Factors such as the velocity and range of motion may affect the perceived resistance, however these have never been quantified for this scale.[26,54] Previous studies also indicated that MAS has an acceptable inter-rater reliability for testing of upper limb spasticity (ULS), but not so for testing of lower limb spasticity.[26] Some researchers stated that AS and MAS are in general use, and their reliability is good in some areas, but their validity in the general application to spasticity assessment is not. It is suggested that MAS should be performed after appropriate training, according to standardized procedures, which take into account the many possible confounding factors, and when used in research one rater only should be applied.

MAS is criticized for the poor criterion validity that has primarily resulted from poor discrimination at the lower end of the scale, between grades 1, 1+, and 2.[60] Its validity has also been questioned as it does not measure the velocity dependent aspect of spasticity.[35] Other limitations of using MAS for spasticity evaluation include: no standardization regarding test position, number of repetitions, testing time (morning/afternoon) or right-left test order in case of bilateral involvement; stimulus not well controlled; may not control the

velocity of passive movement, therefore may be less reliable in clinical practice; cannot distinguish among various neuromuscular components of spasticity across a range of positions and velocities; and does not measure post-stroke spasticity effects on resting posture or the effect of clinically observed associated reactions on spasticity (the remote form of synkinesis due to a failure to inhibit spread of motor activity, i.e., flexion of the elbow simultaneously to flexion of the hip during walking).[25,28]

According to one study enrolling 333 adult patients with ULS and reduced upper limb function due to stroke more than one month previously, a one-point decrease on the MAS was observed as an initial change in muscle tone/spasticity following treatment with Botox. Therefore the Rehabilitation Measures Database suggests that a one-point change on the MAS reflects a clinically significant improvement in patients who receive medication therapy for ULS.[31]

PGA

In the pivotal study of this submission, the PGA of treatment response was conducted by the investigator by scoring responses to the question: "How would you rate the response to treatment in the subject's upper limb since the last injection?" on a 9-point categorical scale that ranged from –4 (markedly worse) to +4 (markedly improved). Assessment of the PGA was undertaken independently, by a different investigator than the investigator who assessed the MAS.[14] Higher scores indicate better results. The psychometric properties (i.e., validity, reliability, and responsiveness) of this tool in the ULS trials have not been assessed, and an MCID for this outcome has not been established.

DAS

The Disability Assessment Scale (DAS) is a questionnaire that measures the degree of the patient's functional impairment in four domains:[61]

- Hygiene: the investigator assesses the extent of maceration, ulceration, and/or palmar infection; palm and hand cleanliness; ease of cleanliness; ease of nail trimming; and the degree of interference caused by hygiene-related disability in the patient's daily life.
- Dressing: the investigator assesses the difficulty or ease with which the patient can put on clothing (e.g., shirts, jackets, gloves) and the degree of interference caused by dressing-related disability in the patient's daily life.
- Limb position: the investigator assesses the amount of abnormal position of the upper limb.
- Pain: the investigator assesses the intensity of pain or discomfort related to ULS.

This scale was specifically developed for the objective measurement of disability in patients with upper limb post-stroke spasticity (although its use is not limited to patients with post-stroke spasticity) and to assess the response to BoNTA treatment. The investigator or rater interviews the patient to determine the extent of functional impairment, mostly perceived passive function, in each domain which is individually rated on a scale of 0 to 3, where:

0 = no disability;

1 = mild disability (noticeable but does not interfere significantly with normal activities);

2 = moderate disability (normal activities required increased effort and/or assistance);

3 = severe disability (normal activities limited).

Many studies of spasticity involving DAS evaluations before and after BoNTA therapy focused on one treatment target from among the four DAS domain to assess the severity of disability, while fewer studies evaluated all four DAS domains.[62] In Study 145, DAS score within each domain of disability as well as four domains for the principal target of treatment (PTT) were obtained at baseline and at the follow-up visits. In this study, DAS was measured as 1) the mean change from baseline in the PTT of the DAS, and 2) the proportion of patients with a decrease from baseline of at least one grade in the PTT and in each domain of disability of the DAS for patients having a baseline score greater than or equal to 2 in the considered domain.[14] A decrease in the DAS score is considered an improvement and is correlated with improvements in the daily activities of the patients.[25,32]

No studies have examined the construct/criterion/content validity of the DAS.[33] It has been shown to have acceptable inter- (Kendall's W=0.494, 0.557, 0.626 and 0.772 for dressing, limb position, hygiene, and pain, respectively) and intra-rater reliability (κ=0.520, 0.530, 0.775 and 0.776 for hygiene, dressing, limb position, and pain, respectively), although its validity has not been established. [25,32,33,55] For intra-rater reliability, there was no information provided with respect to the time points that the assessments were conducted, and it was unclear whether there was a chance that the patient's condition would have changed. Therefore it is difficult to draw a concrete conclusion from these data. No studies have examined the test-retest reliability of the DAS. An MCID for DAS score is not identified from the literature search.

Tardieu Scale Score

The Tardieu Scale (TS) was developed by Tardieu et al. in 1954 to measure spasticity that takes into account resistance to passive movement at both slow and fast speed.[34] Several modifications have been made to the original scale since then. Held and Pierrot-Deseilligny modified the scale by comprising quantitative joint angle measurements taken at three speeds of passive movements: very slow (V1), a passive fall of the limb under gravity (V2), and as fast as possible (V3).[34] The modified TS determines the passive range of movement (PROM) at different movement velocities, with the relative difference between a slow and a fast velocity passive stretch determining the dynamic component of the muscle contracture. With the modified TS, two resulting joint angles are measured by goniometer which includes the R1 angle which is the "angle of catch" after a fast velocity stretch and the R2 angle defined as the passive joint range of movement following a slow velocity stretch. The R2 minus R1 value indicates the level of dynamic component of spasticity in the muscle. A larger difference between R1 and R2 means a large dynamic component, whereas a small difference between R1 and R2 means static contracture in the muscle.[35,36]

There are two measurements in the TS[56]:

- Spasticity angle: measures the angle of muscle reaction (angle of arrest at slow speed V1 *minus* angle of catch at fast speed V3)
- Spasticity grade: measures the quality of muscle reaction (scored 0 to 5 where 0 = no resistance to passive range of movement and 5 = joint is immobile).

A previous review of the published literature suggests that the TS has superior validity and reliability over the Ashworth Scale for the assessment of neural versus peripheral contributions to spasticity.[37] A systematic review published in 2006 indicated that the publications regarding the validity and reliability of the TS were scarce, and in the identified literature, only the range of movement aspect (i.e., the difference between the slow passive range and the "angle of catch") has been used, with no mention of the "rating of the quality

of the muscle reaction" aspect of the scale.[34] It is therefore impossible to make assumptions or draw conclusions as to the validity or reliability of the TS from the literature. Data from a Rehabilitation Measures Database[56] showed an agreement percentage of 94% to 100% between the TS and laboratory measures of contracture or spasticity. Convergent validity was considered excellent (rho 0.86 to 0.89) for elbow flexors. Acceptable test-retest reliability was reported (kappa 0.65 to 0.87 for muscle groups tested; intraclass correlation coefficient [ICC] 0.73 to 0.91) in patients with severe brain injury or stroke. Intra-rater reliability was considered adequate (kappa 0.71 to 0.78 except for shoulders) while poor inter-rater reliability was observed (kappa 0.36 to 0.51).[56] Previous studies suggested that TS is more sensitive than other measures to the change following treatment with BoNTAs.[34] An MCID for the TS was not identified in the literature search for patients with ULS.

Modified Frenchay Scale

The Frenchay Scale was developed to measure upper limb active function. It consists of seven tasks of everyday living (five unimanual and two bimanual), and was a simple and easy-to-conduct test rated as pass or fail by clinicians; however, the binary pass/fail assessment limited the sensitivity of the test (at both ends of the range). The Modified Frenchay Scale (MFS) is an expanded version of the Frenchay Scale and consists of 10 tasks (six bimanual and four unimanual with the affected hand). These 10 tasks consist of asking the patient to reach, grasp, carry, and release different objects, of different sizes, which patients are likely to use in their daily life (such as a bottle, a glass, or a comb). These tasks can only be accomplished by mobilizing the whole affected arm, with or without the contralateral non-affected arm, and involves the fingers, wrist, elbow, and shoulder muscles. Each of these tasks is rated on a 10-point VAS, where 0 = no movement and 10 = task perfectly accomplished. The overall MFS score is defined as the mean of the scores in the 10 tasks. One key advantage of this test is that videos of patients performing the tasks can be recorded and centrally rated, leading to a relatively objective and homogeneous assessment of upper limb active function.[14,57,63]

The intra-and inter-rater reliability were assessed in 10 adult patients with chronic hemiparesis in a cross-sectional study.[57] For the overall scores, the mean intra- and inter-rater intraclass correlation coefficients were 0.99 (95% CI, 0.95 to 1.00) and 0.98 (95% CI, 0.98 to 1.00), respectively. This is considered adequate; however similar to the MAS and DAS, for intra-rater reliability, there was no information provided with respect to the time points that the assessments were conducted, and it was unclear whether there was a chance that the patient's condition would have changed. Therefore it is difficult to draw a concrete conclusion from these data. An MCID of the MFS was not identified from the literature search. This is a tertiary outcome in Study 145.

AROM of the PTMG

The AROM in the PTMG was assessed by asking the patient to move the elbow, wrist, or finger flexors. Goniometry was used for the elbow and wrist flexors but not for the extrinsic finger flexors. This was a tertiary outcome in Study 145.[14]

Easy of Applying a Splint

Improving the ease of applying a splint by the patient would be associated with improving the ease of caring for the affected limb, e.g., in washing and dressing. Furthermore, it can alleviate caregiver burden, and subsequently may have significant cost benefits by reducing the time taken, or the number of people required, to perform care tasks.[53] In

Study 145, the ease of applying a splint was evaluated on a 6-point scale (0 = no splint needed, 1 = splint needed and applied with no difficulty, 2 = splint needed and applied with mild difficulty, 3 = splint needed and applied with moderate difficulty, 4 = splint needed and applied with severe difficulty, 5 = splint needed, but unable to apply).[14] It was unclear whether this outcome was recorded by the patient, caregiver, or physician.

The psychometric properties of this measure have not been evaluated and an MCID is not available to assess the clinically importance of between-group difference. This is a tertiary outcome in the included trial.

Short Form (36) Health Survey (SF-36)

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. SF-36 consists of eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm. The PCS and MCS and eight dimensions are each measured on a scale of 0 to 100, which are t scores (mean of 50 and standard deviation of 10) that have been standardized to the US general population.[38] Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm.[38] An increase in score indicates improvement in health status on any scale. In general use, a change of 2 points in the SF-36 PCS and 3 points in the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient.[38] An MCID for SF-36 was not identified for patients with ULS.

European Quality of Life 5 Dimensions (EQ-5D)

EQ-5D is a generic quality of life instrument developed by the EuroQol Group. It may be applied to a wide range of health conditions and treatments.[39] As a generic measure of health-related quality of life that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[40] The EQ-5D 5 level version (EQ-5D-5L) was introduced in 2005 based on an earlier version (EQ-5D-3L). It consists of an EQ-5D descriptive system and the EQ VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five levels: a level 1 response represents “no problems,” level 2 “slight problems,” level 3 “moderate problems,” level 4 “severe problems,” and level 5 “extreme problems” or “unable to perform,” which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. In total there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to the levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged, for example, to produce an individual dimension “score.” Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore the index score is a country-specific value and a major feature of the EQ-5D instrument.[40] The range of index scores will differ according the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state “dead” and 1.0

reflects “perfect health.” Negative scores are also possible for those health states that society (not the individual patient) considers to be “worse than dead.”

The EQ VAS records the respondent’s self-rated health on a vertical, visual analogue scale where the end points are labelled 0 (“the worst health you can imagine”) and 100 (“the best health you can imagine”). The respondents are asked to mark an X to the point on the VAS which best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[39,41]

Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 21143, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ VAS.

EQ-5D-5L has been validated in a diverse patient population in six countries.[39] However, no studies specifically validating EQ-5D in patients with ULS were identified. The MCID estimates for the index score in Canadian population have a summarized mean (SD) of 0.056 (0.011), and a summarized median of 0.056 (interquartile range 0.049 to 0.063).[41]

Goal Attainment Scaling (GAS)

GAS is a method of integrating achievement in a number of individually-set goals into a single goal attainment score. It has been applied in various areas of complex intervention including spasticity management.[46] Before the treatment, one or more individual goals have been established by the patient or by one or more researchers or practitioners. Clinicians require sufficient knowledge and experience to support patients to set realistic goals. Improvement in GAS is rated from –2 to +2. The expected target of achievement is set by the patient and treating team and given a value of 0. Outcomes less than expected are given values of –1 or –2 and more than expected +1 or +2. It is recommended by the originators of the method that a “t score” is produced. The “t score” is a total score of the composite outcome of all the goals set for an individual patient.

The validity, reliability, and responsiveness of GAS have been demonstrated in rehabilitation and ULS intervention. In the context of spasticity management, GAS was shown to provide a sensitive measure of change for a given individual. The GAS method was found to be valid, reliable and responsive to changes following focal intervention with BoNTA and physical interventions for spasticity at a clinical level.[32] However, limitations have been identified in using the standard GAS approach, which relate to 1) comparison of scores between individuals or groups and 2) data obtained being ordinal rather than interval, undermining the validity of the calculation of the t score.[32]

In supportive studies submitted by the manufacturer, the GAS was used to measure the achievement of individual goals for treatment.[45,46] At baseline, patients, along with their treating team, identified up to two personal goals for treatment and one preferred functional outcome. Goals were weighted by importance and difficulty. Goal attainment was rated at weeks 8 and 20 on a 5-point scale, where “0” denotes the expected level of achievement; “+1” and “+2” are respectively “a little” and “a lot” better than expected, while “–1” and “–2” are correspondingly a little and a lot less than the expected level. These attainment levels were combined in a single total score by applying a formula recommended by Kiresuk and Sherman, which accounts for variable numbers of goals, inter-correlation of goal areas, and

variable weighting. This formula is designed to transform the sum of the attainment levels for each goal (multiplied by their relative weights) into a normal distribution of t scores with a mean of 50 and standard deviation of 10, if the results exceed and fall short of expectation in roughly equal proportions, over a sufficiently large number of patients. Higher GAS t scores indicate greater achievement on the goals. An MCID for the GAS in the ULS population has not been identified from the literature.

Caregiver Burden Scale

Numerous instruments are available to evaluate the caregiver burden from different aspects, such as caregiver willingness to assume care, well-being of the caregiver, perceived challenges (e.g., social isolation, work strain, emotional health/physical health strain, family relationship strain, etc.).[64] One caregiver burden scale was used in manufacturer-submitted supportive studies to measure the impact of the condition on caregivers.[44,47] It consists of four items: cleaning the palm, cutting the fingernails, dressing, cleaning under the armpit. Each item was rated by the research physiotherapist on a 5-point Likert scale:

0 = no disability/carer burden

1 = mild disability/carer burden

2 = moderate disability/carer burden

3 = severe disability/carer burden

4 = maximum disability/carer burden.

Item scores are summed to generate an overall score of the scale with a range of 0 to 16. Higher scores indicate more burden on the carer. The psychometric properties of this instrument is unknown. An MCID of this caregiver burden scale was not reported. A 4-point change in the overall score was considered significant in the study, however a rationale was not provided.[44]

Conclusion

The MAS is a validated and reliable instrument to assess response to treatment for patients with spasticity. No MCID was identified from the literature for this measure, however a one-point change in MAS is commonly considered clinically meaningful. The psychometric properties of the PGA in patients with ULS has not been assessed, and an MCID for this outcome has not been established. The DAS and TS are both instruments with evidence of validity to assess patients' disability or functional status, however no MCIDs were identified. No evidence was identified to assess the validity and reliability of the MFS, ease of applying a splint or AROM in patients with ULS.

Appendix 6: Summary of Other Studies (Open-Label Extension Study)

Aim

To summarize the details and findings of the open-label extension study Y-52-52120-148 (Study 148)[22].

Findings

Study design

Study 148[22] is a multi-centre, prospective, open-label, uncontrolled, rollover, repeated treatment extension of the phase III double-blind (DB) randomized controlled trial (RCT), Study 145[16], for patients with upper limb spasticity (ULS). The study was designed to assess the long-term safety and efficacy of repeated treatments of abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) injections. Patients who completed Study 145 with no major protocol deviations, and no adverse events of unacceptable risk, were eligible to rollover into the extension phase in which all patients were treated with aboBoNTA injections over multiple cycles. The study also enrolled de novo patients to meet a sufficient sample size to assess the long-term safety of aboBoNTA at the highest dosing regimen. De novo patients were eligible for a maximum of five treatments, and rollover patients were eligible for a maximum of four treatments during the extension study. The study inclusion and exclusion criteria were the same as in Study 145,[16,22] Re-treatment was based on a minimum interval of 12 weeks between injections, with four-week study visits from week 12 through week 24 to assess need for re-treatment. At each study visit, a one grade reduction in MAS score and/or an improvement in PGA score greater than or equal to +1, combined with safety data, were used by the investigator to determine whether to postpone re-treatment until next visit. Discretionary, between-visit re-treatment was permitted based on these same criteria.[22]

Population demographics and baseline disease characteristics

More than 90% of the patients enrolled in Study 145 rolled over into the extension study and made up approximately 88% of the extension population, while the de novo patients represented approximately 12%. No major differences were noted for the population demographics and baseline disease characteristics between the two groups entering Study 148 and those described in the DB RCT, Study 145. Briefly, the mean age of participation was 52.4 years and ranged from 18 to 80 years, both sexes participated in the study (64% male) and 85% of patients were white. The cause of ULS was stroke in 89.1% of patients (mean duration of time of 5.1 years since stroke) or traumatic brain injury in 10.9% of patients (mean duration of time of 9.9 years since injury). Approximately half of the rollover and de novo patients had received physiotherapy prior to receiving injections in Study 145 or 148, respectively[16,22].

Intervention

For patients who received aboBoNTA in Study 145, cycle 1 of the extension represented their second dose. De novo patients, and patients who were injected with placebo in Study 145, received their first dose of aboBoNTA in cycle 1 of the extension study. Approximately

half of extension study patients continued to receive physiotherapy in conjunction with study injections. Concomitant oral medications (dantrolene, tizanidine, oral baclofen), opioid, or other antispasticity agents like benzodiazepines, were allowed to be kept at the same dose throughout the study. Additionally, therapy could be initiated or modified during the study after week 4 of any treatment cycle.

Patients were treated for a combined total of five injection cycles over the course of Study 145 and Study 148, with a maximum study duration of 15 months (for rollover patients, this maximum duration included time spent in the DB RCT). Only de novo patients could receive the extension cycle 5 injection. Injections were administered at intervals that spanned 12 weeks (minimum) to 24 weeks (or end of study), according to when patients met the re-treatment criteria. Patients receiving injections in the extension phase were monitored at week 1, week 4, week 12, and in 4-week intervals thereafter, until re-treatment was required. Patients who continued not to require re-treatment were followed until they had been in-study for a total of 12 months. In-study was defined as the baseline of Study 145 for patients who participated in the DB RCT Study 145, or as the baseline of extension Study 148 for de novo patients. For patients who exceeded the 12 months in-study, the minimum follow-up time was 4 or 12 weeks after the last injection (a protocol change affected minimum follow-up time).

Cycle 1 of the extension study treated all patients (rollover or de novo) with 1,000 U aboBoNTA, unless an adverse event (AE) in the previous treatment cycle of the DB RCT required a 500 U injection. The primary targeted muscle group (PTMG) was defined as either extrinsic finger flexors, wrist flexors, or elbow flexors. At least two other upper limb muscles were also injected per cycle (shoulder muscle groups were allowed as secondary targets). In cycles 2, 3, and 4 of the extension, patients could have dose increases or decreases of 500 U from the previous cycle, according to the investigator's judgment, provided doses remained in the range of 500 U to 1,500 U. In cycle 2 and onwards, patients were eligible to receive an additional 500 U injection in the shoulder muscle on an as-needed basis, provided the total dose did not exceed 1,500 U. From cycle 3 onwards, if patients showed improvement in the upper limb, they were eligible to receive a concomitant injection into at least one calf muscle of an affected lower limb, provided their total dose did not exceed 1,500 U.

Patients enrolled in the extension who had received one single dose of aboBoNTA injection in the DB RCT Study 145, but did not require re-treatment at extension study entry, entered an observational phase during which they were monitored every 4 weeks until they required re-treatment. If a patient still did not require re-treatment after 24 weeks of observation in the extension phase, the end of study visit was scheduled for week 28[22].

Outcomes

The primary outcome assessed in this extension study was the safety of repeated cycles of aboBoNTA injections. The secondary outcomes measured efficacy of each injection cycle using the criteria described in the DB RCT Study 145: muscle tone using the MAS in the PTMG; upper limb passive function using the DAS; spasticity using the Tardieu Scale (TS); active range of motion (AROM) against the PTMG; ease of applying a splint; upper limb active function using the MFS; treatment response using the PGA; health-related quality of life using the EQ-5D and SF-36[22].

Patient disposition and exposure

A total of 258 patients were included in the extension study, of whom 227 rolled over from the DB RCT Study 145. The remaining 31 were de novo patients, recruited to begin aboBoNTA injection cycles in the extension study. The total number of patients recruited for the extension study was considered sufficient to analyze the long-term safety of maximum doses of repeated aboBoNTA injections. Four patients from the DB RCT Study 145 were rolled over directly into the observational phase of Study 148 and thus never received an injection in the extension study. Thus, the safety population for the extension study was 258 patients and the ITT population was 254 patients. Upon entering the extension phase, 73 patients had received placebo in the DB RCT, 78 had received aboBoNTA 500 U, and 76 had received aboBoNTA 1,000 U.

The disposition of patients in the extension phase is summarized Table 51: Briefly, 31 patients withdrew from the extension study (14 in cycle 1; 10 in cycle 2; six in cycle 3; and one in cycle 4). A total of 211 patients completed 12 months of follow-up. End of study was recorded after follow-up of cycle 1 for 10 patients; cycle 2 for 44 patients; cycle 3 for 88 patients; cycle 4 for 69 patients; and cycle 5 for 11 patients. Time intervals between injection and cycle completion, as well as the number of patients completing each cycle at the specified interval, are also presented in Table 51:. Mean duration of treatment exposure in each cycle is presented in Table 52, along with the mean injection dose broken down by injection site[22].

Table 51: Patient Disposition and Exposure in ITT population

	Extension Study 148			
	aboBoNTA Injection Dose[a]			All Doses
	500 U	1,000 U	1,500 U	Total
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Completed cycle 1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 12	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 16	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 20	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 24	[redacted]	[redacted]	[redacted]	[redacted]
Entered OP	[redacted]	[redacted]	[redacted]	[redacted]
End of study visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew from cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Completed cycle 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 12	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 16	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 20	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 24	[redacted]	[redacted]	[redacted]	[redacted]
Entered OP	[redacted]	[redacted]	[redacted]	[redacted]
End of study visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew from cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Completed cycle 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Extension Study 148			
	aboBoNTA Injection Dose[a]			All Doses
	500 U	1,000 U	1,500 U	Total
Completed at week 12	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 16	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 20	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 24	[redacted]	[redacted]	[redacted]	[redacted]
Extra visit[b]	[redacted]	[redacted]	[redacted]	[redacted]
End of study visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew from cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Completed cycle 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed at week 12	[redacted]	[redacted]	[redacted]	[redacted]
End of study visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew from cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Completed cycle 5, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed at end of study visit	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew from cycle 5	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ITT = intention-to-treat; n = number of patients in subgroup; NA = not applicable; OP = observational phase; U = units.

aTotal dose per patient (includes additional shoulder injections from cycle 2 onwards and concomitant lower limb injections from cycle 3 onwards).

bA visit between study assessment intervals could be scheduled if patients required an injection.

Source: Study 148, Clinical Study Report.[22]

Table 52: Duration of Treatment Exposure and Site-Specific Doses – Safety Population

Number of Patients, n (%) Duration (wks), Mean (SD)	Study 145	Extension Study 148				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 500 U	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,000 U	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,500 U	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All Doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Site-Specific Doses				Extrinsic Finger Flexors		
aboBoNTA 500 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of Patients, n (%) Duration (wks), Mean (SD)	Study 145	Extension Study 148				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
aboBoNTA 1,000 U						
mean (SD) [range]						
aboBoNTA 1,500 U						
mean (SD) [range]						
Site-Specific Doses				**Wrist Flexors**		
aboBoNTA 500 U						
mean (SD) [range]						
aboBoNTA 1,000 U						
mean (SD) [range]						
aboBoNTA 1,500 U						
mean (SD) [range]						
Site-Specific Doses				**Elbow Flexors**		
aboBoNTA 500 U						
mean (SD) [range]						
aboBoNTA 1,000 U						
mean (SD) [range]						
aboBoNTA 1,500 U						
mean (SD) [range]						
Site-Specific Doses				**Shoulder Extensors**		
aboBoNTA 500 U						
mean (SD) [range]						
aboBoNTA 1,000 U						
mean (SD) [range]						
aboBoNTA 1,500 U						
mean (SD) [range]						

Number of Patients, n (%) Duration (wks), Mean (SD)	Study 145	Extension Study 148				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
			[redacted]	[redacted]	[redacted]	[redacted]
Site-Specific Doses				**Elbow Pronators**		
aboBoNTA 500 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,000 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,500 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Site-Specific Doses				**Other Finger Flexors**		
aboBoNTA 500 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,000 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA 1,500 U		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean (SD) [range]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; n = number of patients in subgroup; NA = not applicable; SD = standard deviation; U = units; wks = weeks.

Note: The original safety population was defined as 258 patients, but four patients were never injected with aboBoNTA in the extension Study 148.

Source: Study 148, Clinical Study Report.[22]

Efficacy

As the extension Study 148 was an open-label, uncontrolled trial, the safety and efficacy outcomes are descriptive in nature and no statistical testing was undertaken. Efficacy was evaluated at week 4 for each injection cycle using the MAS, AROM,TS, and PGA, among other outcomes. No imputations were made for these efficacy end points. Efficacy outcomes for MAS are presented in Table 53 and Table 54; for Tardieu Scale in Table 55; for AROM in Table 56; and for PGA in Table 57.

Overall, the mean changes from baseline to week 4 after injection in MAS scores for the PTMGs for each of the five treatment cycles were similar in magnitude to what was observed during the DB RCT Study 145 (range –1.2 to –1.6) (Table 53). The proportion of responders with at least one grade reduction in MAS score of their PTMG ranged from 75% to 79.5% (Table 54).

As presented in Table 55, each PTMG, as well as the shoulder extensors, were assessed at week 4 after each injection using the Tardieu Scale. There was an improvement from baseline in every muscle group with respect to the angle of spasticity (X). The improvement was highest in cycle 1 for the shoulder extensors, cycle 2 for the wrist flexors, cycle 3 for

the extrinsic finger flexors, and cycle 4 for the elbow flexors. Generally, the changes in the angle of spasticity grade (Y) were similar in each muscle group and treatment cycle.

Improvements in the AROM scores were observed at week 4 after each treatment cycle for the extrinsic finger flexors. The other PTMGs (wrist and elbow) showed variation in the AROM scores across treatment cycles, but did indicate an improvement from baseline for each cycle (Table 56).

Table 57 summarizes the PGA of treatment response at week 4 of Study 145 and throughout extension Study 148. Improvements in mean PGA after each treatment to week 4 after injection ranged from 1.7 to 2.0.

Efficacy was also reported in relation to dosing and treatment exposure duration. A greater proportion of patients receiving the higher dose of aboBoNTA in the upper limb was observed in later treatment cycles. Upper limb injection dosing in cycle 2 was 1,000 U for 172/229 patients (75%) and 1,500 U for 45/229 patients (19%). In cycle 3, 70% (102/145 patients) received 1,000 U while 25% (37/145 patients) received 1,500 U. In cycle 4, 65% (42/64 patients) received 1,000 U while 28% (18/64 patients) received 1,500 U. Shoulder injections were also more common in cycle 4 (40.7%) than in cycle 1 (13.7%).

As shown in Table 52, the mean duration of treatment exposure was 16.4 weeks (SD 7.3) (N = 154) for Study 145, and ranged from 10.6 weeks (SD 4.4) (N = 81) for cycle 4 to 15.6 weeks (SD 5.6) (N = 254) for cycle 1 of the extension study. As summarized in Table 51:, the majority of patients receiving treatment in cycle 1 (59%) and cycle 2 (58%) required re-treatment 12-weeks post-injection. In cycle 3, 41% required re-treatment at the 12-week time point. In contrast, the proportion requiring less frequent injections (16 weeks or more after the last injection), was 35% of patients entering cycle 2 and 24% entering cycle 3. Finally, 4% of patients after cycle 1, 19% of patients after cycle 2, and 50% of patients after cycle 3 completed the study without requiring further re-treatment.[22]

Table 53: MAS and Changes from Baseline – ITT Population at Week 4

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MAS score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ITT = intention-to-treat; N = total number of patients in treatment group; MAS = Modified Ashworth Scale; N = total number of patients; PTMG = primary targeted muscle group; SD = standard deviation.

a Baseline for rollover patients was the baseline measurement from Study 145; for de novo patients baseline was defined as the last available value before the first study injection in any muscle.

b MAS scores and changes from baseline are reported for all injected muscle groups with MAS scores of at least 2 at baseline (irrespective of what muscle group was chosen as PTMG).

Source: Study 148, Clinical Study Report.[22]

Table 54: MAS Responders – ITT Population at Week 4

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ITT = intention-to-treat; MAS = Modified Ashworth Scale; N = total number of patients in treatment group; n=number of patients in subgroup.

a Responders defined as having at least one grade reduction from baseline.

Source: Study 148, Clinical Study Report[22]

Table 55: Changes from Baseline to Week 4 in Tardieu Scale for PTMG and Shoulder Extensors – ITT Population

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity (X): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity Grade (Y): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity (X): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity Grade (Y): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity (X): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity Grade (Y): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity (X): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Angle of Spasticity Grade (Y): mean change[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ITT = intention-to-treat; N = total number of patients in treatment group; PTMG = primary targeted muscle group; SD = standard deviation.

a Mean change is from baseline where baseline refers to baseline from Study 145 for rollover patients, or baseline from Study 148 for de novo patients.

Source: Study 148, Clinical Study Report.[22]

Table 56: Active Range of Motion Scores for PTMG at Week 4 – ITT Population

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]				
All doses of aboBoNTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AROM score, mean change from baseline[a] (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; AROM = active range of motion; ITT = intention-to-treat; N = total number of patients in treatment group; PTMG = primary targeted muscle group; SD = standard deviation.

a Baseline refers to baseline from Study 145 for rollover patients, or baseline from Study 148 for de novo patients.

Source: Study 148, Clinical Study Report.[22]

Table 57: Physician Global Assessment of Treatment Response at Week 4 – ITT Population

	Study 145	Extension Study 148			
	N = 152	Cycle 1 N = 254	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81
aboBoNTA – 1,000 U in upper limb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA – 1,500 U in upper limb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All doses[a] of aboBoNTA - in upper limb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat; N = total number of patients in treatment group; SD = standard deviation; U = units.

[a] All doses include 500 U, 1,000 U, and 1,500 U (when applicable) injected into upper limb.

Source: Study 148, Clinical Study Report.[22]

Harms

The primary outcome of the extension Study 148, was the long-term safety of aboBoNTA over repeated treatment cycles. While the safety population was considered 258 for this extension study, four patients did not receive any injections and thus are not reported in the safety data. Treatment-emergent adverse events (TEAE), by upper limb injection dose, are summarized in Table 58.

Most of these were considered mild to moderate in intensity. Generally, all doses of aboBoNTA (500 U, 1,000 U, and 1,500 U) were considered to be well tolerated. TEAEs occurring at frequencies greater than 5% within a given treatment cycle included musculoskeletal and connective tissue disorders (5.7% to 11.4%), infections and infestations (5.7% to 8.7%), general disorders and administration site conditions (4.4% to 7.1%), injury, poisoning and procedural complications (4.8% to 6.7%), nervous system disorders (3.4% to 9.1%), and investigations (9.1% – one patient was investigated for increased gamma-glutamyl transferase).

The most commonly reported treatment-related AE was localized muscular weakness, experienced by 0.6% to 3.1% of patients across cycles and doses of aboBoNTA. Two patients experienced hemorrhage at the injection site (neither patient was being treated with an anticoagulant). No other AEs deemed to be treatment-related were reported in more than one patient.

Twenty-five AEs of fall were reported. The investigator assessed one case as treatment-related when a patient who received aboBoNTA 1,000 U during cycle 1 tripped and was unable to grab her walker due to weakness in the injected area. The fall resulted in a fracture of the humerus. There was also a higher percentage of falls associated with lower limb injections 5.5% (n = 2/36) compared with 3.6% (n = 5/139) in patients exclusively receiving upper limb injections, but none were considered treatment-related.

Two severe AEs were considered by the investigator to be treatment-related. The first was a case of severe anal sphincter atony six days post-injection of aboBoNTA 1,000 U in cycle 2. The event began as mild in intensity during Study 145 at a dose of 500 U and continued beyond completion of the trial after 12 months in the extension study. The other was a case of peripheral swelling one day following injection of aboBoNTA 1,000 U in cycle 4, which resolved after two days. Thirty-six SAEs were reported, of which one was reported as treatment-related: dizziness in cycle 1.

Two AEs of special interest were considered unrelated to the study drug, according to the investigator, but were suggestive of the pharmacological effect of aboBoNTA due to spread of toxin: severe constipation and short-lasting diplopia. No AEs of special interest related to drug hypersensitivity were reported.

Five withdrawals due to adverse event (WDAEs) were reported over the course of the study. One was due to pregnancy, another due to emotional lability, and three due to death. None of the causes of death were considered related to the study drug. One patient died of untreatable metastatic cancer; one patient with a history of atherosclerosis and hypertension died of cardiopulmonary arrest; and one patient with a history of hypertension and hyperlipidemia died of myocardial infarction.

No significant differences in treatment-related AE were reported for aboBoNTA doses of 1,500 U administered exclusively in the upper limb versus those co-administered at 1,000 U in the upper and 500 U in the lower limbs.

Among the safety population, a total of 20 patients (7.8%) developed binding antibodies, of which 11 patients (4.3%) also had detectable levels of neutralizing antibodies (NAb). Sample volumes were insufficient in two patients with binding antibodies to also analyze for the presence NAb. TEAEs reported by patients with NAb included elevated gamma glutamyl transferase in one patient; pain in extremities and influenza in one patient; and gastrointestinal symptoms, seasonal allergy, muscle weakness, and rash in one patient. AboBoNTA injection efficacy as measured by MAS varied among these patients. No new safety signals were detected among patients with detectable NAb titres.

Table 58: Treatment-Emergent Adverse Events by Upper Limb Dose in the Safety Population

	Extension Study 148				
	Number and Proportion (%) of Patients				
	Cycle 1 N = 254[a]	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81	Cycle 5 N = 11
aboBoNTA – 500 U (upper limb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to WD, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AESI, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA – 1,000 U (upper limb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to WD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	
AESI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
aboBoNTA – 1,500 U (upper limb)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to WD, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Extension Study 148				
	Number and Proportion (%) of Patients				
	Cycle 1 N = 254[a]	Cycle 2 N = 229	Cycle 3 N = 175	Cycle 4 N = 81	Cycle 5 N = 11
AESI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AESI = adverse event of special interest; N = total number of patients in treatment group; n=number of patients in subgroup; NA = not applicable; SAE = serious adverse event; TEAE = treatment-emergent adverse event; U = units; WD = withdrawal

[a] The original safety population was defined as 258 patients, but four patients were never injected with aboBoNTA in the extension Study 148.

Source: Study 148, Clinical Study Report.[22]

Limitations

Overall, a higher proportion of patients received larger doses of aboBoNTA with each treatment cycle. It is difficult to disentangle the exact reasons for this increase as the injection protocol was modified from cycle 1 to cycle 2 to cycle 3, permitting alternate injection locations and changing doses, at the investigator's discretion.

The extension protocol specified a fixed study duration rather than a fixed number of treatment cycles. Thus, patients initially responding to therapy had longer intervals between injection cycles, which reduced the number of injections they could receive. Therefore, it is difficult to determine whether the benefits of aboBoNTA extend beyond the first two to three cycles and whether the observed decline in duration of treatment exposure with each additional cycle is due to declining benefit of the injection over treatment cycles, or due to gradual loss through progressive study cycles of patients responding well to treatment and exiting the study. The study protocol design further obfuscates the effects of the treatment duration by removing patients from the cycle once they reach the fixed study termination time point, regardless of their response time within their last cycle. As a result, cycles 3 through 5 do not accurately reflect the duration of treatment effect (time between injections). For example, the protocol requirement of interval length between injections was set at 12 weeks, but the mean duration of treatment exposure for cycle 4 is only 10.6 weeks.

The extension Study 148 only reports efficacy measures at week 4, such that the mean efficacy at later time points cannot be assessed. Re-treatment criteria were subject to investigator's opinion and not a standardized and well-defined set of requirements, subjecting the "duration of treatment exposure" to potential bias and subjective assessment. While this may be the standard in clinical practice, from a clinical trials perspective, it is an obstacle to the collection of objective data.

The patient input summary for aboBoNTA indicated a desire for reduced need to attend additional therapies. Because the study did not standardize physiotherapy and rehabilitation programs, and allowed for changes according to patients' needs, the effects of, and requirement for, additional therapy cannot be assessed.

Finally, extension Study 148 is an open-label, uncontrolled study design, and as such, the interpretation of the results was limited to descriptive, and non-statistical comparative assessments. Thus, the study design is unable to measure the extent to which the treatment effects observed in the DB RCT Study 145 were maintained[22].

Summary

Study 148 was an open-label, uncontrolled extension study that was designed to assess the long-term safety and efficacy of repeated treatments of aboBoNTA injections in patients with ULS. The extension study followed patients for a maximum of 15 months after their first study injection (whether in DB RCT Study 145 or in extension Study 148) and consisted of patients from Study 145 and a small number of de novo patients to meet a sufficient sample size. De novo patients were eligible for a maximum of five treatments, and rollover patients from Study 145 were eligible for a maximum of four treatments during the extension study. The majority of patients who entered the extension (142 of 254, 56%) completed the study within the first three cycles, and thus did not require their last study protocol injection(s).

Overall, the mean changes from baseline to week 4 in MAS scores for the PTMGs were similar to the DB RCT Study 145 after each cycle of treatment. The proportion of responders with at least one grade reduction in MAS score ranged from 75% to 79.5% across treatment cycles at week 4. There was an improvement from baseline for all PTMGs and for the shoulder extensors with respect to the angle of spasticity (X), on the Tardieu Scale at week 4 after each treatment cycle. Improvement from baseline to week 4 in the AROM scores was observed across treatment cycles for all PTMGs. Similarly, mean PGA scores were similar across treatment cycles. Given that not all patients received each cycle of treatment during the extension phase, it is difficult to make any inference regarding the trends in efficacy across multiple courses of treatment.

No new, carry-over, or cumulative safety concerns for repeated treatment cycles of aboBoNTA emerged from the extension Study 148 at the 500 U, 1,000 U, and 1,500 U doses. Few treatment-related AEs were reported, the most common of which was muscle weakness at injection site/area. The more serious adverse events observed and determined to be treatment-related included anal sphincter atony, peripheral swelling, and dizziness.

Appendix 7: Summary of Other Studies (Non-Pivotal Studies)

Aim

To summarize the details and findings of eight supportive clinical studies assessing the efficacy and safety of abobotulinumtoxinA (aboBoNTA, Dysport).[44-47,65-69]

Findings

Study design

In addition to the pivotal Study 145[16] and the extension Study 148,[22] seven studies did not meet the inclusion criteria of the CDR review, but were identified as non-pivotal supporting studies by Health Canada.[45-47,65-69] An additional study[44], identified in the manufacturer's submission, that provides additional evidence to assess outcomes of interest in the CDR review protocol was also included.

Eight supportive studies are summarized in which patients received aboBoNTA via intramuscular injection for the treatment of ULS.[44-47,65-69] Seven of these studies were placebo-controlled, double-blind (DB), randomized control trials (RCTs); one was an open-label single arm prospective study (Study 704)[47]. Two studies assessed the efficacy and safety of repeated treatment over two or three injection cycles (Study 097[45,46] and Study 704[47], respectively). Six studies included or permitted some form of physical therapy or rehabilitation (such as physiotherapy, splinting, occupational therapy).[44,45,47,67-69] However, a standardized, structured physical therapy program was only implemented in conjunction with aboBoNTA injections in two studies[44,67]. Two other studies included a non-structured, non-standard physical therapy component.[68,69] AboBoNTA injections were combined with electrical stimulation in one randomized controlled trial (RCT).[67] Minimum follow-up time for the summarized studies was four weeks, when aboBoNTA efficacy was expected to peak clinically.[47]

Table 59: Characteristics of Supportive Clinical Studies

First Author, Year of Publication, Study Identifier	Study Design, Length, Follow-up, and Location	Population and Disease Characteristics; Sample Size	Intervention & Comparator/s	Clinical Outcomes
Lam, K (2012)[44]	DB RCT; Placebo-controlled; Single injection cycle; Follow-up: 24 wks Multi-centre trial ; Hong Kong	Inclusion: Patients (> 16 years) of long-term care facilities with significant ULS (MAS score > 2) and difficulty in basic upper limb care on CBS; tolerant of limb stretching and splinting; Exclusion: useful movement in affected limb, rigid joints, severe swallowing difficulties, peripheral motor neuropathic, or neuromuscular diseases. Cause of spasticity: not specified. N = 55	Maximum total IM aboBoNTA injection of 1,000 U per patient with individualized muscle dosing (n = 30) or saline placebo injection (n = 25); in conjunction with physiotherapy and splinting of affected upper limb. Single IM injection cycle.	CBS; GAS AE etc.
McCrory, *P* (2009)[45] and Turner-Stokes,	Phase IV; DB RCT; placebo-controlled; 2	Inclusion: Patients (> 18 years) at least 6 months after stroke,	Two cycles of IM injections of aboBoNTA (n = 54) or placebo	CBS; GAS

First Author, Year of Publication, Study Identifier	Study Design, Length, Follow-up, and Location	Population and Disease Characteristics; Sample Size	Intervention & Comparator/s	Clinical Outcomes
L (2010)[46]; Study: A-9B-52120-097	injection cycles; Follow-up: 24 wks Multi-centre; Australia	with moderate to severe spasticity in the arm (≥ 2 on MAS scale for at least 2 muscle groups: elbow, wrist and/or fingers). Exclusion: Patients with severe contracture or other neurological impairments; concurrent aminoglycoside antibiotics; botulinum toxin treatment with 120 days of study, or previously treated with phenol or intrathecal baclofen. Cause of spasticity: stroke. N = 96	(n = 42) with 12 wks apart. First injection at week 0: total dose 750 U to 1,000 U; second injection at week 12: total dose 500 U to 1,000 U; Exact dose, injected muscle groups, the number of sites per group and the use of EMG or muscle stimulation were at injector's discretion. Physiotherapy when possible.	AE etc.
Bakheit, AMO (2004); Study: Y-47-52120-704[47]	Phase III; Prospective, single arm, OL; 3 injection cycles; Follow-up: 12 wks after third injection International trial recruiting from five centres	Inclusion: Adult patients with moderate or severe ULS, ≥ 3 months after cerebrovascular event (≥ 2 on MAS scale for at least 2 joints of the elbow, wrist and/or fingers and a score ≥ 1 in the remaining area; minimum score of 10 on the PD&CBRS. Exclusion: fixed muscle contractures of upper limb; previous treatment with phenol, alcohol nerve blocks, motor point injections and treatment of botulinum toxin within 90 days of study, or treatment with intrathecal baclofen. Cause of spasticity: stroke. N = 51	Three treatment cycles of IM aboBoNTA (N = 51). First treatment total dose was 1,000 U; second and third treatment doses were between 500 U and 1,000 U, repeated every 12, 16, or 20 wks as clinically indicated. Injections placed close to motor endplate zone using anatomical landmarks. Only one site per muscle was injected except for biceps brachii (injected in 2 sites). Concomitant therapies such as physiotherapy, OT, and antispasticity medications were permitted if already in use at study entry. These were continued throughout study.	CBS; GAS AE etc.
Bakheit, AMO (2000); Study: Y-97-52120-016[65]	Phase II; DB RCT; Placebo-controlled; Prospective, dose-ranging study; Follow-up: 16 wks post-injection; 11 West European centres	Inclusion: Patients with hemiplegic stroke and moderate to severe spasticity (≥ 2 on MAS scale in the elbow, wrist and/or fingers). Exclusion: Muscle contracture of upper limb joints; previous treatment with phenol, alcohol nerve blocks, botulinum toxin, or motor point injections for ULS; de novo treatment with antispasticity drugs. Cause of spasticity: stroke. N = 83	One treatment cycle of IM placebo (n = 20) or one of three doses of aboBoNTA: 500 U (n = 22), 1,000 U (n = 22) and 1,500 U (n = 19) into 5 muscles of the affected arm, at fixed doses for each muscle, relative to total dose administered. Injections placed close to motor endplate zone using anatomical landmarks.	AEs, ROM etc.
Bakheit, AMO (2001); Study: Y-97-52120-703[66]	Phase III; DB RCT; Placebo-controlled; Prospective; Follow-up: 16 wks post-injection ; International (multi-centre, n = 7)	Inclusion: Patients with hemiplegic stroke with moderate or severe ULS, ≥ 3 months after cerebrovascular event (≥ 2 on MAS scale for at least 2 joints of the elbow, wrist and/or fingers and a score ≥ 1 in the remaining area. Exclusions: muscle contractures of upper limb; previous treatment with phenol,	One treatment cycle of IM aboBoNTA (1,000 U), or equal volume of placebo; injected into biceps brachii (two sites) and four other muscle groups of forearm (one site each), in fixed dose ranges for each muscle group. Injections placed in muscle belly using anatomical landmarks.	MAS AEs etc.

First Author, Year of Publication, Study Identifier	Study Design, Length, Follow-up, and Location	Population and Disease Characteristics; Sample Size	Intervention & Comparator/s	Clinical Outcomes
		alcohol nerve blocks, motor point injections with neurolytic drugs for ULS and treatment of botulinum toxin within 6 months of study. Cause of spasticity: stroke. N = 59		
Hesse, S (1998); Study: Y-97-52120-109[67]	Phase II; DB RCT; Placebo-controlled multi-arm; Single treatment cycle; Follow-up: 12-wks post-injection; Germany	Indication: Adult patients between 6-12 months post-stroke with a non-functional extremity and severe chronic ULS of grade ≥ 3 MAS for elbow, wrist, and finger joints. Exclusion: Patients with fixed contracture, previous treatment with aboBoNTA, neurolytic, or surgical procedures in study limb. Cause of spasticity: stroke. N = 24	(A) 1,000 U aboBoNTA + electrical stimulation (n = 6); (B) 1,000 U aboBoNTA (n = 6); (C) placebo + electrical stimulation (n = 6); and (D) placebo (n = 6); standardized injection muscles groups of upper limb, receiving 125-250 U/muscle, 2 sites per muscle; injection under EMG guidance near motor point. No individualized injection muscles/doses. Electrical stimulation (where applicable) was applied to arm and forearm muscles 3 times a day for 3 days post-injection (20 Hz, 200 µS, 50-90 mA). Average of 2 concomitant physiotherapy sessions per week with application of Bobath technique.	MAS AEs etc.
Rosales, RL (2012); Study: A-38-52120-713 (ABCDE-S)[68]	Phase IV; DB RCT; Placebo-controlled; 1 injection cycle; Follow-up: 24 wks. Hong Kong, Malaysia, the Philippines, Singapore, and Thailand	Inclusion: Adults (18-80 yrs) within 2-12 wks of first stroke (Asian ethnicity if possible); MAS score ≥1 in elbow or wrist joint; and joint weakness grade ≥2, according to MRC criteria. Exclusions: Pregnancy/lactation, pre-stroke Rankin score > 1, known hypersensitivity to test (or related) compounds, pre-existing neuromuscular junction disease or neurogenic disorders; previous treatment with aboBoNTA. Cause of spasticity: stroke. N = 163	IM injection of aboBoNTA 500 U total dose or placebo into one or more wrist and elbow mover muscles, at discretion of investigator, with unstructured rehabilitation.	MAS AEs etc.
Yelnick (2007); Study: 2-54-52120-048[69]	Phase III, DB RCT; Placebo-controlled; Follow-up: 4 wks , France	Inclusion: hemiplegic patients with ULS at any stage post-stroke; MAS ≥ 1 for medial rotator and elbow flexor; limited range of passive motion of shoulder (10^{o} < 30^{o}). Exclusion: previous traumatic or neurological disease of hemiplegic shoulder; retraction of at least one muscle of elbow, wrist or fingers of hemiplegic	Single dose of aboBoNTA, 500 Speywood units, or placebo was injected into the subscapularis muscle guided by electrical stimulation. All patients received non-standardized physical therapy on weekdays.	MAS AEs

First Author, Year of Publication, Study Identifier	Study Design, Length, Follow-up, and Location	Population and Disease Characteristics; Sample Size	Intervention & Comparator/s	Clinical Outcomes
		limb, previous treatment with aboBoNTA or alcohol of hemiplegic shoulder; neuromuscular disease; pregnancy/lactation. Cause of spasticity: stroke. N = 20		

aboBoNTA = abobotulinum neurotoxin type A; AE = adverse event; CBS = Caregiver Burden Scale; DB = double-blind; EMG = electromyography; GAS = Goal Attainment Scale; Hz = Hertz; IM = intramuscular; mA = milliamperes; MAS = Modified Ashworth Scale; N = total number of patients in sample; OL = open-label; OT = occupational therapy; PD&CBRS = the Patients' Disability and Carer Burden Rating scale; RCT = randomized controlled trial; ROM = range of motion; U = units; ULS = upper limb spasticity; µS = microseconds; VAS = Visual Analogue Scale; wks = weeks; yrs = years.

Source: Lam (2012)[44], McCrory (2009)[45], Turner-Stokes (2010)[46], Bakheit (2004)[47], Bakheit (2000)[65], Bakheit (2001)[66], Hesse (1998)[67], Rosales (2012)[68], Yelnick (2007).[69]

Table 60: Summary of Supportive Study Findings, Author Conclusions, and Limitations

Main Study Findings	Author Conclusion	Limitations
Lam, K (2012)[44]		
Treatment group had a significantly greater reduction in CBS (reduction ≥ 4, $P \leq 0.001$) versus control group, at 6 and 12 weeks post-injection continuing through week 16 ($P = 0.018$). GAS scores for the treatment group showed a greater magnitude of improvement compared with placebo group (12.65, $P = 0.001$) at 6 weeks post-injection: goals set included improving resting positions of limbs (40%); AEs are reported.	**AboBoNTA significantly improved ratings on the CBS for patients of long-term care facilities, mainly owing to its effect on reducing limb spasticity and improving the joint range of movement, but failed to find any difference in pain levels as measured by the PAINAD scale in the treatment group compared with the control group. No treatment-related SAE were reported. aboBoNTA delivered in doses of 1,000 U was safe in the population studied.**	**Some patients in treatment group experienced significant improvements in muscle tone which may have unblinded the caregiver and/or investigator. The study failed to show that the treatment was efficacious in relieving pain in this population. The study was halted before reaching the calculated sample size of 70 as the authors indicated that statistical significance had been achieved. The authors did not provide a rationale for testing at the sample size of 55.**
McCrory, P (2009)[45] and Turner-Stokes, L (2010)[46]; Study: A-9B-52120-097		
Patients completing: aboBoNTA (n = 52); placebo (n = 38). The study failed on its primary end point. The treatment and placebo groups did not differ significantly with respect to the primary outcome (AQoL), or secondary outcomes of pain, mood, disability, or CBS. However, patients treated with BoNTA had significantly greater reduction in MAS scores ($P < 0.001$) at week 8 and week 20, which translated into higher GAS scores ($P = 0.01$) at 20 weeks, GAS t scores for BoNTA effect were statistically significant. GAS t scores correlated with reduction in spasticity (rho = 0.36, $P = 0.001$). GAS t scores were lower than expected (median 32.4, interquartile range 29.6 to 40.6) possibly because goals selected were ambitious. Goals for passive tasks were more often achieved than those for active function. One case each of atopic reaction at injection site and arm numbness was reported as treatment-related.	**Although no change in quality of life was demonstrated using the AQoL, AbobotulinumtoxinA was found to be safe and efficacious in reducing ULS and improving the ability to achieve personal goals and experience a global benefit from treatment. GAS provided a responsive measure for evaluating aboBoNTA therapy for ULS and for identifying outcomes of importance to the individual/carers, which other standardized measures may not be able to identify.**	**The primary outcome measure, AQoL, may have been a poor choice and after taking into consideration baseline AQoL scores, age, and subgroup domain scores, statistical significance was still not achieved. Other study limitations included: a lack of standardization of injection technique; protocol did not require physical therapy and about one-third of patients did not receive any, possibly affecting their outcomes; global benefit includes assessment of goals included in the GAS, therefore the association between these measures should be interpreted with caution; randomization failed despite confirmation of its validity; missing data were imputed using LOCF.**
Bakheit, AMO (2004); Study: Y-47-52120-704[47]		

Main Study Findings	Author Conclusion	Limitations
Patients completing: cycle 1 (n = 47); cycle 2 (n = 43);cycle 3 (n = 41). Improvement from baseline was observed in all outcome measures for all cycles with effect duration between 12 to 20 weeks. Goal achievement ranged from 52% to 58% and mean reduction in CBS ranged from 0.27 to 0.34, across treatment cycles. Mild to moderately severe TEAE were reported in 24% of cases.	**AboBoNTA at a dose of 1,000 U was efficacious in the symptomatic treatment of post-stroke ULS. Study suggests that effect can be maintained with repeated injections for up to at least 3 treatment cycles (duration of cycle effect between 12 and 20 weeks). AboBoNTA was safe in the dose used, did not result in cumulative safety concerns and did not induce the formation of detectable levels of neutralizing anti-BoNTA antibodies over the course of the three treatment cycles.**	**This study was an open-label, uncontrolled study therefore statistical comparisons could not be made and results are subject to patient and investigator bias. While the study did not detect neutralizing anti-BoNTA antibodies, the authors acknowledge that the study length and lower test sensitivity may have played a role in these findings. Standardized physical therapy was not required in study protocol.**
Bakheit, AMO (2000); Study: Y-97-52120-016[65]		
The study goal was to find the optimal, safe dose of aboBoNTA. All doses of aboBoNTA studied showed a significant reduction from baseline compared with placebo in the primary outcome: muscle tone at week 4. Only aboBoNTA 1,000 U showed a significant reduction in MAS score in all muscle groups at week 16. No statistically significant differences detected in AE incidence between study groups.	**AboBoNTA reduced muscle tone in patients with ULS, and was safe and effective in doses used; 1,000 U was the optimal dose. aboBoNTA doses of 1,500 U can reduce ROM possibly due to muscle weakening.**	**The RMA and BI assessments of global functional ability may not be sensitive enough to detect local improvements as detected by spasticity outcomes (MAS) in this study. Individualized goal attainment outcomes might be more appropriate. The population selected for this study was not appropriate for assessing the effect of aboBoNTA on muscle pain, a common symptom of spasticity.**
Bakheit, AMO (2001); Study: Y-97-52120-703[66]		
Statistically significant reduction from baseline in MAS score for patients treated with aboBoNTA versus placebo at 4 weeks (P = 0.004) in any one of three joints; benefit was maintained through 16 weeks in wrist and finger joints, but not in elbow. No statistically significant differences detected in AE incidence between study groups. No SAE or deaths relating to study treatment were reported. AE likely related to aboBoNTA included: fatigue and tiredness, and pain in arm following injection.	**The findings of the present study suggest that treatment with aboBoNTA at a dose of 1,000 U reduces muscle tone in patients with post-stroke ULS. This effect is sustained for at least 16 weeks. AboBoNTA is safe in the dose used in this study.**	**Authors selected "any joint", rather than pre-defining a PTMG. Some outcome measures, such as BI, for global function may not be sensitive enough to detect local improvements in ULS; repeated treatment cycles and longer observations may be required to see improvement in some time-dependent outcomes responding to cumulative effect. AboBoNTA combined with physiotherapy, splints, or other forms of therapy was not studied.**
Hesse, S (1998); Study: Y-97-52120-109[67]		
Group A (aboBoNTA + electrical stimulation) showed most improvement over measured outcomes; including reduction in spasticity. No study-related AE were reported.	**Group A (aboBoNTA + electrical stimulation) showed most improvements over measured outcomes; including reduction in spasticity. Group B (aboBoNTA alone) did not show relevant reduction in spasticity. The placebo-controlled trial is congruent with animal studies showing that electrical**	**Most outcomes measured failed to demonstrate statistical superiority of aboBoNTA + electrical stimulation compared with other treatment groups, possibly because the study was underpowered at 24 patients. The authors did perform alpha level adjustments for multiple dependent variables which can increase the chance of a type II error. The electrical**

Main Study Findings	Author Conclusion	Limitations
	stimulation enhances the effectiveness of BoNTA in the treatment of chronic upper limb flexor spasticity.	**stimulation treatment could not be blinded and was thus subject to bias.**
Rosales, RL (2012); Study: A-38-52120-713 (ABCDE-S)[68]		
AboBoNTA significantly improved MAS scores at 4 weeks post-injection for all baseline MAS scores. The size estimates of treatment effect progressively increased with more severe baseline MAS scores. MAS scores for all secondary end points improved with aboBoNTA versus placebo at all time points, up to 24 weeks ($P < 0.0001$). AboBoNTA decreased spasticity-related pain, but the difference did reach significance. BI, mRS, Functional Motor Assessment, and active ROM of elbow and wrist did not reveal clinically significant differences. Elbow and wrist passive ROM and active finger movements did show significant improvement. No group differences in AE were found. Four aboBoNTA-related AEs were reported: fatigue (2), pyrexia, and muscular weakness. Three deaths occurred: placebo(1), aboBoNTA (2). None was considered treatment-related.	**aboBoNTA 500 U can provide a sustained reduction in post-stroke ULS when combined with rehabilitation in Asian patients who have mild-to-moderate hypertonicity and voluntary movement, within 2 to 12 weeks of stroke. Early treatment may prevent the development of more severe spasticity. Functional use of the arm and hand was not affected.**	**The study did not standardize physiotherapy regimens or the use of antispastic medication. While the trial was randomized, there is still a risk of confounding effects between treatment groups. Trial could not detect functional improvements, possibly because outcome tools were not sensitive enough and/or because a larger trial may be required to detect the small difference expected.**
Yelnick (2007); Study: 2-54-52120-048[69]		
Statistically significant differences were observed between aboBoNTA and placebo : at 4 weeks for pain and at 2 weeks and 4 weeks for lateral rotation. Upper limb MAS scores were improved but only statistically significantly different for fingers at 4 weeks post-injection. No AEs were reported as specifically related to treatment with aboBoNTA.	**The reduction in pain by subscapular injection of aboBoNTA, with a concurrent improvement in shoulder ROM, suggests a BoNTA treatment value in the management of shoulder pain in spastic patients and confirms the role of spasticity in hemiplegic shoulder pain. Authors warn against subscapular injection alone in the treatment of ULS, as injection consideration should be given to all affected muscle groups for optimal results**	**The study failed to recruit the number of patients required, but nonetheless showed a significant reduction in shoulder pain. While all upper limb muscle group spasticities were improved, only spasticity of fingers was statistically significant. In this study of ULS, only one muscle group was injected which was insufficient to improve spasticity of all affected muscle groups of the upper limb.**

aboBoNTA = abobotulinumtoxinA; AE = adverse event; AQoL = Assessment of Quality of Life; BI = Barthel Index; BoNTA = botulinum neurotoxin A; CBS = Caregiver Burden Scale; GAS = Goal Attainment Scale; MAS = Modified Ashworth Scale; mRS = modified Rankin Scale; n = number of patients in treatment group; PAINAD = Pain Assessment in Advanced Dementia; PTMG = primary targeted muscle group; RMA = Rivermead Motor Assessment; ROM = range of motion; SAE = serious adverse events; U = units; ULS = upper limb spasticity.

Sources: Lam (2012)[44], McCrory (2009)[45], Turner-Stokes (2010)[46], Bakheit (2004)[47], Bakheit (2000)[65], Bakheit (2001)[66], Hesse (1998)[67], Rosales (2012)[68], Yelnick (2007).[69]

Results

Two clinically relevant outcome measures, Caregiver Burden Scale (CBS) and Goal Attainment Scale (GAS), not assessed in pivotal Study 145,[16] were identified as providing additional support to the use of aboBoNTA in the treatment of ULS. Additionally, when available, information on dosing, on duration of treatment effect, on re-treatment cycles, and on safety outcomes was summarized. Table 59 provides a summary of the study

design, the population and disease characteristics (inclusion/exclusion criteria), the sample size, the intervention and comparators, and the measured outcomes, while Table 60 provides a summary of the findings, author conclusions, and study limitations.

The clinically relevant outcomes of CBS and GAS were assessed in three supportive studies: placebo-controlled DB RCTs (Lam 2012)[44] and Study 097,[45,46] and the open-label Study 704.[47]

Significantly improved ratings were reported on the CBS for patients of long-term care facilities treated with aboBoNTA versus placebo at 6 and 12 weeks post-injection ($P \leq 0.001$), through week 16 ($P = 0.018$). where the maximum benefit was seen at 8 weeks.[44] Another non-pivotal, placebo-controlled RCT[45,46], reported no statistically significant difference between aboBoNTA group and placebo group in caregiver burden (CBS). Finally, the open-label, uncontrolled study[47] reported that aboBoNTA at a dose of 1,000 U, afforded a mean reduction in CBS ranging from 0.27 to 0.34, across three treatment cycles.

Goal attainment was also evaluated in the aforementioned studies. In the first study, GAS scores for the aboBoNTA group showed a greater magnitude of improvement compared with placebo group at six weeks post-injection (12.65, $P = 0.001$). The goals set in this study included improving resting positions of limbs (40%); range of motion (ROM) of joints (32%); decreasing pain during limb stretching (16%) and promoting healing skin (11%).[44] In the non-pivotal, placebo-controlled RCT, Study 097[45,46], it was reported that patients treated with aboBoNTA achieved higher GAS scores ($P = 0.01$) at 20 weeks compared with placebo, and that these correlated with significant reductions in MAS scores. In two other studies, goal attainment was assessed although this outcome was not reported using GAS scores. In the open-label, uncontrolled Study 704[47], it was reported that the aboBoNTA dose of 1,000 U led to goal achievement ranging from 52% to 58% across treatment cycles. In the placebo-controlled DB RCT, Study 703[66], goal attainment was not statistically significant in the treatment group compared with the placebo group.

Additionally, Study 097[45,46] and Study 704[47] assessed the outcomes of patients after re-treatment cycles of aboBoNTA (see Table 59). Placebo-controlled DB RCT Study 097 failed on its primary outcome (Assessment of Quality of Life [AQoL]) and other secondary outcomes, but did show a sustained effect on MAS scores across both treatment cycles ($P < 0.001$) and an improvement in GAS scores after the second treatment cycle at week 20 ($P = 0.01$).[45,46] The open-label Study 704 reported that the majority of patients completed all three treatment cycles (41/51), that an improvement from baseline was observed for all measured outcomes across treatment cycles and that 90% or patients perceived a treatment benefit.[47]

Overall, doses of 500 U[45-47,65,68,69], 1,000 U[44-47,65-67] and 1,500 U[65] were administered in the eight summarized supportive trials. Generally, 500 U and 1,000 U were found to be effective, albeit targeted muscle groups and appropriate selection of measured outcomes had an impact on study findings (Table 60) The higher dose of 1,500 U was found to be somewhat effective, but could also lead to a loss of ability to extend fingers.[65] This dose is not recommended, as per the product monograph for aboBoNTA.[15]

No serious adverse events were reported in the non-pivotal studies as related to aboBoNTA. AEs deemed possibly or likely related to treatment with aboBoNTA included: of atopic reaction at injection site and arm numbness,[45,46] pain at injection site,[47,66] fatigue and tiredness,[47,66,68] dysphagia,[47] skin rashes and flu-like symptoms,[65] pyrexia, and muscular weakness.[68]

Limitations

The reported findings on CBS and GAS in the above-mentioned non-pivotal studies should be interpreted with caution given various limitations of study design, such as relatively small sample size, varying number aboBoNTA treatment cycles received and outcome measures at different time points,[44-47]. Further study limitations included: the potential bias of unblinded caregiver and/or investigator and a failure to report rationale for determining the sample size[44]; a lack of standardization of injection technique and the failure of randomization[45,46]; an open-label and uncontrolled study design[47]; and poor or inappropriate study design[66]. Furthermore, possibly due to differences in study design and population, the aboBoNTA treatment effect on the significance of these measured outcomes was inconsistent and inconclusive between studies.

Summary

The non-pivotal studies summarized provide limited information that can be used to further assess the efficacy of aboBoNTA in the treatment of ULS. The overall study design and outcomes measured differed from one trial to the next and each study presented unique limitations. The interventions also varied between studies, including variable doses of aboBoNTA, with or without supplemental electrical stimulation, and the presence or absence of physical and rehabilitative therapies. There were insufficient data to support the extended effect of aboBoNTA beyond the 12-week re-treatment interval. None of the studies compared aboBoNTA to the other commercially-available forms of botulinumtoxinA (onaBoNTA[19] and incoBoNTA[20]), or included patients who were refractory to treatment with other BoNTAs. No serious adverse events were reported to be treatment-related in any of the eight studies.

Appendix 8: Summary of Indirect Comparisons

Background

Given the absence of head-to-head studies comparing Dysport Therapeutic with other botulinum toxin type A (BoNTA) drugs in the study population in this CADTH Common Drug Review (CDR) review, indirect comparisons (ITCs) that include Dysport Therapeutic can provide information on the comparative effectiveness and safety of this drug to existing therapies. This section of the report provides a summary and critical appraisal of the methods and results of any ITCs that compare Dysport Therapeutic to Botox or Xeomin in adults with upper limb spasticity (ULS).

Methods

An ITC submitted by the manufacturer was reviewed and critically appraised. Also, a comprehensive literature search was undertaken by CDR to identify any additional relevant published ITCs.

Description of ITCs Identified

There were no published ITCs identified from the literature search conducted by CDR.

The manufacturer submitted an ITC as part of their economic evaluation.[48] They previously performed an ITC based on a systematic review (SR) of relevant literature of upper and lower limb spasticity up to August 31, 2015 for the purpose of a National Institute for Health and Care Excellence (NICE) review, and a Bayesian-based network meta-analysis (NMA) approach and a Bucher approach were adopted to assess the efficacy, as measured by DAS and MAS at 4 to 6 weeks, and 12 weeks after the baseline, of Dysport Therapeutic compared with Xeomin and Botox in patients with ULS. The current ITC is informed by an update of the earlier SR.

Review of Manufacturer-Submitted ITC

Objectives and rationale

The objectives of the previous SR were to identify the evidence describing the clinical efficacy and safety of currently available BoNTA therapies (Botox, Xeomin, and Dysport Therapeutic) in adult upper and lower limb spasticity associated with stroke, to compare the relative efficacy and safety of these treatments where data were available, and to inform an economic model of Dysport for BoNTAs in stroke-related spasticity. All three BoNTAs have been approved by Health Canada for use in patients with ULS.

The ITC presented in this CDR review was an update of the aforementioned ITC, based on an updated SR up to March 3, 2017 for the purpose of revising the ITC to support their CDR submission. New evidence regarding the clinical efficacy and safety of BoNTA therapies in adult ULS associated with stroke that may be added to the network was searched and analyzed in the Canadian setting. The results exclusive for ULS are presented in this Appendix.

Methods

Study eligibility and selection process

Multiple electronic databases such as MEDLINE, Embase, and the Cochrane Library were searched, as well as the reference lists of the included systematic reviews and meta-analyses in the original SR. Grey literature search was also performed. The search covered articles from the database inception up to August 31, 2015, and had no language restrictions. Search for recent studies was undertaken between August 31, 2015 and March 3, 2017 in the updated SR. Study selection was conducted by two independent reviewers using the pre-specified selection criteria in both the original and updated SR. Any disagreements were settled by consensus.

The population of interest for the manufacturer's SR was patients with muscle spasticity post-stroke, including both upper and lower limb spasticity. Studies of patients with muscle spasticity not associated with stroke were excluded in general, although studies with a small proportion of patients (not defined in the manufacturer's report) with spasticity from other causes, such as traumatic brain injury, may be allowed to be included. The interventions and comparators of interest are BoNTAs, including onabotulinumtoxinA (Botox, onaBoNTA), incobotulinumtoxinA (Xeomin, incoBoNTA) and abobotulinumtoxinA (Dysport Therapeutic, aboBoNTA), as monotherapy or in combination with existing therapies such as oral muscle relaxants, anxiolytics, nerve blockade, and physiotherapy. All trials that included one of the three BoNTA treatments in at least one of the treatment arms were included. Eligible study designs were randomized controlled trials (RCTs), SRs, and meta-analyses. Non-randomized studies or narrative reviews were excluded.

In the updated SR, the same inclusion/exclusion criteria as the original review were applied, except that only studies of patients with ULS were included.

Data extraction

Data were extracted from the included full text of articles by one reviewer, and were quality checked by a second reviewer.

Comparators

The comparator in all included studies in the SR and the related ITC were Botox (doses ranging from 75 units [U] to 500 U), Xeomin (doses ranging from 150 U to 400 U) and placebo. Placebo may comprise treatment with oral muscle relaxants, nerve blockades, and physiotherapy, and may be considered to be standard of care without toxin therapy.

Outcomes

In the SR, studies were not excluded based on outcomes of interest. Selection of the clinical outcomes to the ITC was based on the end points reported in the Dysport Therapeutic trials and how widely reported these outcomes were in comparator trials and whether or not links could be formed between treatments. The primary outcome in each included study was captured as well as key characteristics. Clinical outcomes and key baseline characteristics of interest were discussed and agreed with the manufacturer prior to commencing data extraction. The key outcomes included in the ITC were DAS score, MAS score, and AEs.

Clinical outcomes were measured at week 4 to 6 and week 12, post-baseline. The rationale for the time point selection is that BoNTAs are likely to yield a peak effect at week 4. In

addition, for the three BoNTAs, the injection intervals should be at least 12 weeks, according to the respective Health Canada product monographs.

A total of 11 separate NMAs were performed for the following outcome measures:

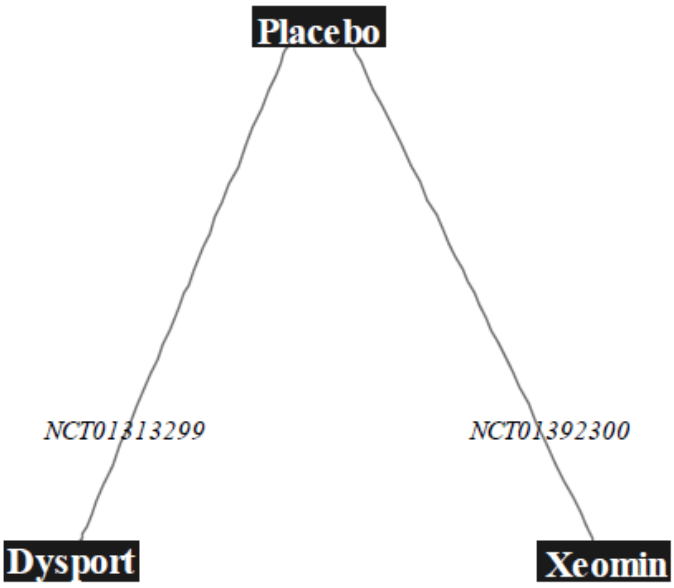
- DAS (reduction of ≥ 1 at 4 weeks post-baseline) (4-item scale) – upper limb
- DAS change from baseline at 4 to 6 weeks (4-item scale) – upper limb
- DAS change from baseline at 12 weeks (4-item scale) – upper limb
- MAS shoulder change from baseline at 4 weeks
- MAS shoulder change from baseline at 12 weeks
- MAS overall upper limb (finger, wrist, elbow) change from baseline at 4 to 6 weeks
- MAS overall upper limb (finger, wrist, elbow) change from baseline at 12 weeks
- Occurrence of AEs at 12 weeks – upper limb

Quality assessment of included studies

The quality of the RCTs selected for inclusion in the NMA were assessed using a quality assessment tool recommended by NICE and adapted from the Centre for Reviews and Dissemination systematic review guidance. The tool considers the appropriateness of randomization and allocation concealment, the method of blinding, similarity at baseline across treatment groups, methods of statistical analysis, and the appropriateness of result reporting.

Evidence network

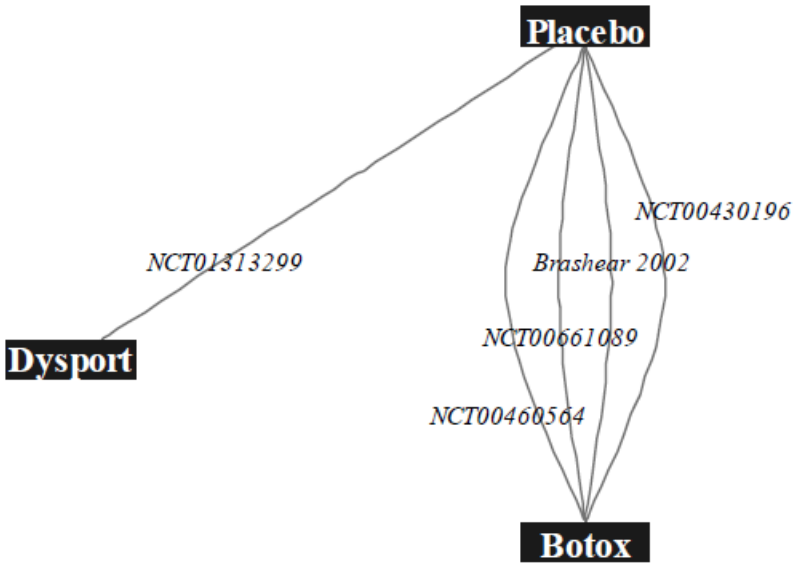
Figure 3: Network of DAS Scores (Achieving a Reduction of ≥ 1), 4 Wks Post-Baseline



DAS = Disability Assessment Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

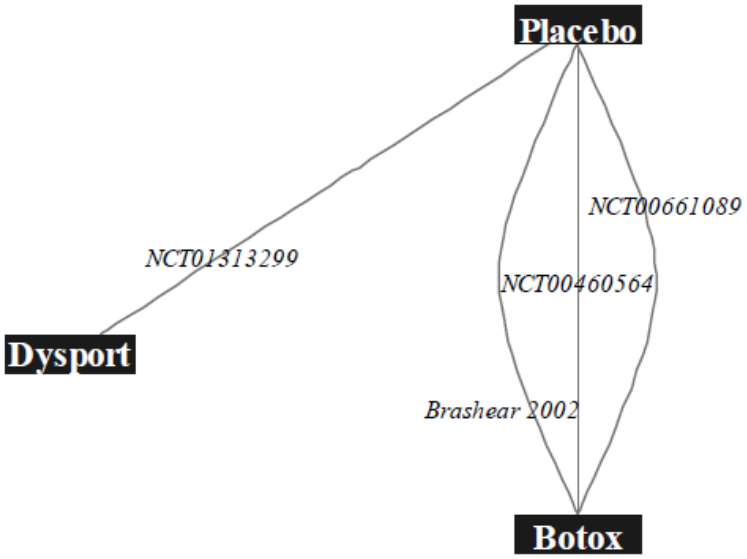
Figure 4: Network of DAS Scores (Change from Baseline), 4 to 6 Wks Post-Baseline



DAS = Disability Assessment Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

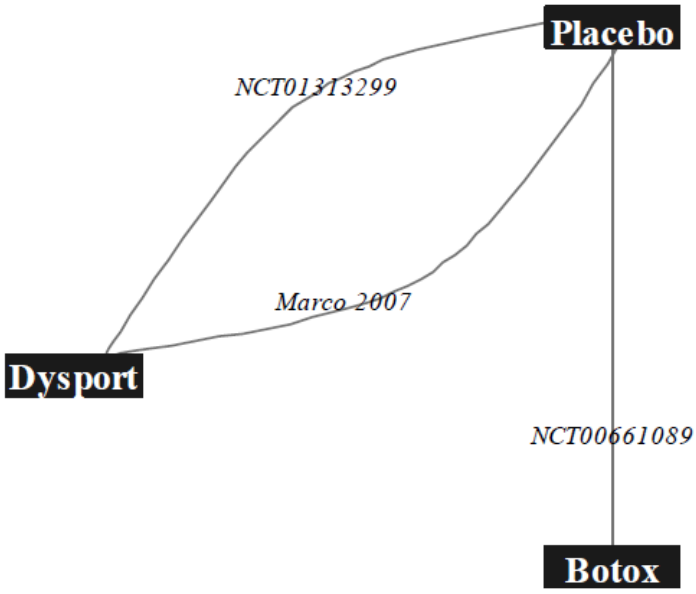
Figure 5: Network of DAS Scores (Change from Baseline), 12 Wks Post-Baseline



DAS = Disability Assessment Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

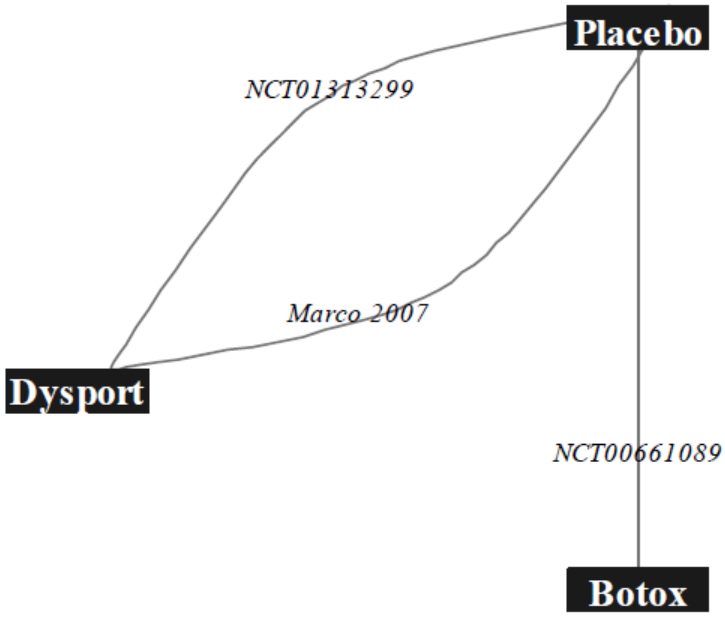
Figure 6: Network of MAS Scores (Change from Baseline), Shoulder, 4 Wks Post-Baseline



MAS = Modified Ashworth Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

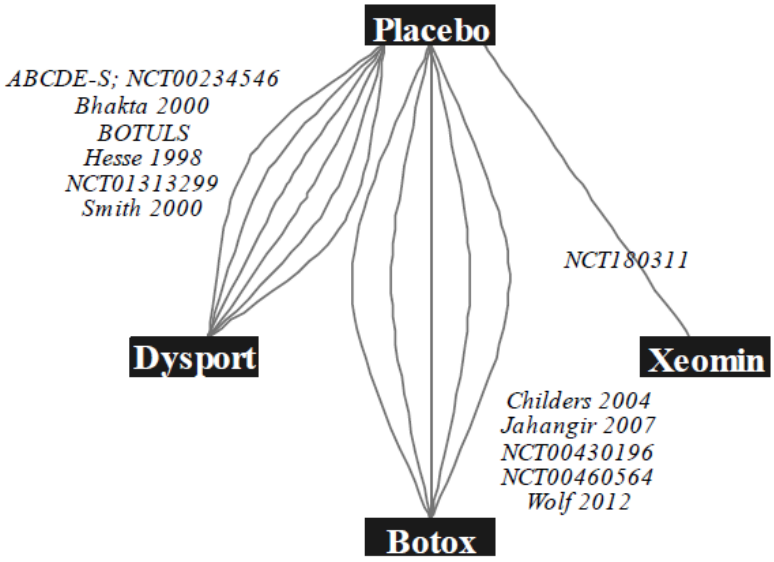
Figure 7: Network of MAS Scores (Change from Baseline), Shoulder, 12 Wks Post-Baseline



MAS = Modified Ashworth Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

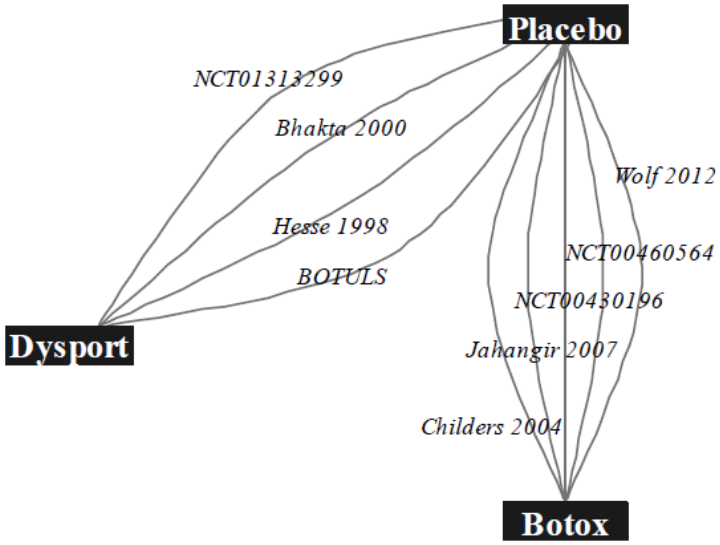
Figure 8: Network of MAS Scores (Change From Baseline), Overall Upper Limb, 4-6 Wks Post-Baseline



MAS = Modified Ashworth Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

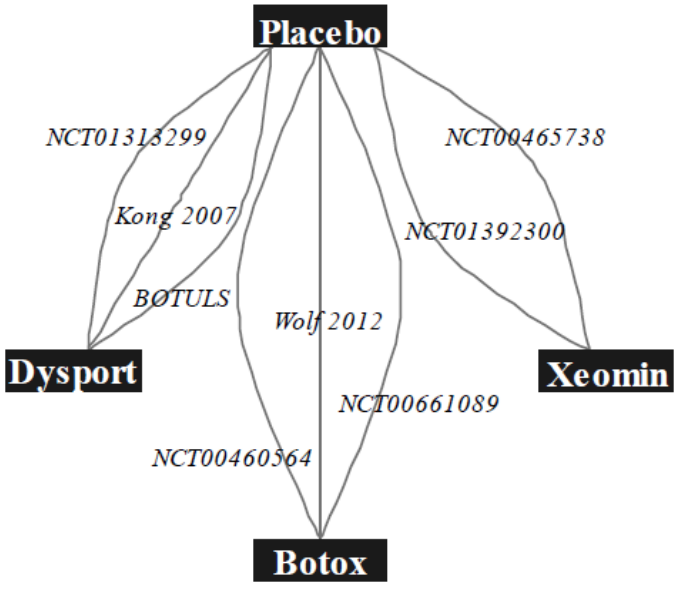
Figure 9: Network of MAS Scores (Change from Baseline), Overall Upper Limb, 12 Wks Post-Baseline



MAS = Modified Ashworth Scale; wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

Figure 10: Occurrence of Adverse Events, Upper Limb, 12 Wks Post-Baseline



Wks = weeks.

Source: Manufacturer-submitted indirect comparison.[48]

Indirect Comparison Methods

End points evaluated in the ITC included DAS score, MAS score, and occurrence of AEs at 4 to 6 weeks and 12 weeks post-baseline. A series of Bucher indirect comparisons and Bayesian NMAs were performed to estimate the relative treatment effects between treatments. Odds ratio (OR), mean difference (MD), or proportion of responders along with the associated 95% confidence intervals (CIs) or 95% credible intervals (CrIs) were generated from the ITC, for dichotomous or continuous outcomes, as appropriate.

The Bucher approach was performed for each of the end points in order to assess the relative efficacy between Dysport Therapeutic and Botox and/or Xeomin via a common comparator (placebo), where data were available. Results and conclusions drawn from Bucher ITCs are limited as they do not account for any statistical heterogeneity between studies. While the uncertainty is likely to be underestimated, results from the Bucher indirect comparison may be compared with those obtained from each corresponding NMA in order to check consistency in point estimates.

A Bayesian NMA was used because of its ability to include multiple pairwise comparisons across a range of interventions and provides estimates of relative treatment effects on multiple treatment comparisons for comparative effectiveness purposes, by combining both direct and indirect evidence.[70] Both fixed effect (FE) and random-effect (RE) models were fitted to the data. Due to the heterogeneous nature of the data, it is likely that RE models may be a more appropriate choice compared with FE models. The overall goodness-of-fit of the model was assessed using the total residual deviance. The Deviance Information Criterion (DIC) was used to compare fit between FE and RE models. The majority of the FE and RE models showed a reasonably good fit to the data, while the most notable deviation was for the pooled overall upper limb MAS analysis at week 4 to 6 post-baseline, particularly for the FE model. The DIC indicates no significant differences in model fit when comparing RE and FE models except for MAS overall upper limb at week 4 to 6 post-baseline. The DIC is much lower for the RE model versus the FE model. For all other end points, the DIC value is very similar for both models, further suggesting that RE models may be a more appropriate choice of model in order to account for the differences between the studies included in the analyses. Bayesian analyses rely upon the use of Markov chain Monte Carlo (MCMC) methods, combining prior distributions with the data to construct a posterior distribution upon which to base summary results.

A number of assumptions were made in the NMA to facilitate the use of certain data from the trials and treatments in the statistical analyses:

- Median value = mean value
- Week 6 data were used in instances where week 4 data were unavailable; or a combined time point of 4 to 6 weeks was used
- Missing change from baseline data were calculated for each arm in the respective study as the difference between baseline and follow-up data; when variation around the change from baseline data (i.e., SD) was missing, it could be calculated using the equations described in the ITC
- Pooling data across doses of interventions to obtain a series of two-arm studies (active arm versus placebo)
- Pooling data across joints within upper limb, up to three separate joints (fingers, wrist, and elbow). Note that treatment effects for the shoulder joint were not

considered to be consistent with finger, wrist, and elbow and therefore was not included in the overall upper limb analysis, and was reported separately.

Results

From the original SR, 41 publications for 29 unique studies in ULS were included for consideration in the NMA. No new studies were added to the NMA from the updated SR.

According to the authors of this ITC, the included studies had a low risk of bias overall, with the main potential for bias coming from the absence of an intention-to-treat (ITT) analysis within a number of trials.

In total, 18 trials reported data for at least one end point in the upper limb and were included in the NMA. Botox (seven trials) and Dysport Therapeutic (eight trials) were involved in most analyses, while Xeomin was included in three analyses. Many of the outcome data of Dysport on DAS and MAS mainly came from one single trial (Study 145). Week 12 was the most frequently evaluated time point. The doses of Dysport ranged from 500 U to 1,500 U, Botox from 80 U to 500 U, and Xeomin 150 U to 400 U. The baseline characteristics across trials varied, in particular for mean time since stroke (Dysport 57.3 months, Botox 54.4 months, Xeomin 37.8 months, and placebo 47.9 months), concomitant physiotherapy (Dysport 71.8%, Botox 100%, Xeomin 100%, and placebo 80.3%), and the proportion of BoNTA-naive patients (Dysport 63.4%, Botox 100%, Xeomin 74.4%, and placebo 81.5%). The baseline MAS and DAS data were not available for the three Xeomin trials. Patients' baseline characteristics are briefly summarized in the manufacturer-submitted ITC (Table 61). Details of individual studies were not reported. Outcome measures were presented in various manners, such as proportion of patients with greater than or equal to 1-point reduction in DAS, change from baseline in DAS or MAS, or the occurrence of AEs.

Table 61: Baseline Characteristics of the Trials of ULS Included in NMA

Treatment	Total number of studies	Age (years) mean (range)	Weight (kg) mean (range)	Male (%) mean (range)	Time since stroke (months) mean (range)	Stroke (%) mean (range)	Time since TBI (months) mean (range)	TBI (%) mean (range)	DAS mean (range)	MAS (Overall) mean (range)	MAS (Shoulder) mean (range)	Concomitant physio-therapy (%) mean (range)	Toxin-naïve (%) mean (range)
PBO	18	58.8	74.8	61.7	47.9	98.0	10.9	14.1	2.4	2.9	3.4	80.3	81.5
		(42.7 - 67.2)	(58.6 - 79.4)	(33.3 - 73.3)	(26.6 - 79.2)	(73.7 - 100.0)	(8.4 - 44.0)	(11.0 - 26.3)	(1.5 - 2.6)	(2.0 - 3.9)	(3.0 - 3.5)	(0.0 - 100.0)	(47.0 - 100.0)
		(n=16)	(n=5)	(n=16)	(n=9)	(n=17)	(n=2)	(n=3)	(n=4)	(n=2)	(n=3)	(n=6)	(n=6)
B	7	60.1	72.0	64.7	54.4	98.9	NAv	15.0	2.5	NAv	3.5	100.0	100.0
		(48.8 - 63.3)	(61.2 - 79.4)	(44.0 - 76.4)	(25.6 - 84.9)	(85.0 - 100.0)		(NAv)	(2.2 - 2.7)		(NAv)	(100.0 - 100.0)	(100.0 - 100.0)
		(n=7)	(n=4)	(n=7)	(n=5)	(n=7)		(n=1)	(n=4)		(n=1)	(n=2)	(n=2)
D	8	59.0	82.2	64.8	57.3	96.4	13.7	9.2	2.6	3.2	2.9	71.8	63.4
		(51.8 - 67.0)	(NAv)	(42.1 - 71.4)	(9.3 - 62.4)	(89.5 - 100.0)	(11.5 - 32.1)	(9.0 - 10.5)	(NAv)	(1.9 - 3.9)	(2.9 - 3.1)	(0.0 - 100.0)	(45.0 - 100.0)
		(n=7)	(n=1)	(n=6)	(n=3)	(n=7)	(n=2)	(n=2)	(n=1)	(n=2)	(n=2)	(n=3)	(n=2)
X	3	56.2	NAv	57.4	37.8	100.0	NAv	NAv	NAv	NAv	NAv	100.0	74.4
		(55.4 - 58.1)		(33.3 - 62.0)	(28.0 - 60.9)	(100.0 - 100.0)						(NAv)	(71.2 - 100.0)
		(n=3)		(n=3)	(n=2)	(n=3)						(n=1)	(n=2)

Key: AUL, adult upper limb; B, Botox; D, Dysport; DAS, Disability Assessment Scale; kg, kilogram; MAS, Modified Ashworth Scale; n, number of studies reporting data; NAv, no study data available; (NAv), only one study reported data, min and max values are equal to the mean; PBO, placebo; TBI, traumatic brain injury; X, Xeomin.

Source: Manufacturer-submitted indirect comparison.[48]

The Bucher approach and the RE Bayesian models produced similar point estimates for the relative efficacy and harm of the active treatments for ULS, although the latter show more uncertainty in the results with wider credible intervals, when heterogeneity between trials were accounted for. The differences in all the outcome measures did not reach statistical significance between the three active interventions. Placebo responses across trials were explored for each outcome synthesized in the ITC, and the results were presented graphically (actual data were not reported). There are variations in the placebo responses. In particular, for the outcomes of change from baseline in DAS (week 4 to 6), change from baseline in MAS (week 12, shoulder), and change from baseline in MAS (Week 4 to 6 and Week 12, overall upper limb), different directions of change were observed. This suggested heterogeneity in patient baseline characteristics between the trials, or that the outcome measures may not be sensitive enough to capture change in spasticity and other related symptoms over time after the treatment. Bucher adjusted ITC results and the Bayesian NMA results of RE models are summarized in Table 62.

Table 62: Summary of Clinical Effectiveness and Harm Results in the ITC

	Bucher Approach	Bayesian NMA Approach (RE Models)	Evidence Base
DAS scores (achieving a reduction of ≥ 1), 4 wks post-baseline *OR (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: no data		From 2 trials: 1 D trial 1 X trial
	D vs. X: 0.91 (0.42 to 1.98)	X vs. D: 1.11 (0.34 to 3.51)	
DAS scores (CFB), 4-6 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: 0.42 (0.16 to 0.67)	D vs. B: 0.44 (–0.67 to 1.69)	From 5 trials: 1 D trial 4 B trials
	D vs. X: no data		
DAS scores (CFB), 12 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: 0.27 (0.01 to 0.53)	D vs. B: 0.23 (–1.95 to 2.50)	From 4 trials: 1 D trial 3 B trials
	D vs. X: no data		
MAS scores (CFB), shoulder, 4 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: 0.42 (–0.43 to 1.28)	D vs. B: 0.42 (–2.10 to 2.94)	From 3 trials: 2 D trials 1 B trial
	D vs. X: no data		
MAS scores (CFB), shoulder, 12 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: –0.14 (–0.95 to 0.66)	D vs. B: –0.14 (–2.61 to 2.32)	From 3 trials: 2 D trials 1 B trial
	D vs. X: no data		
MAS scores (CFB), overall upper limb, 4-6 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: –0.40 (–0.95 to 0.15)	D vs. B: –0.25 (–0.96 to 0.34)	From 12 trials: 6 D trials 5 B trials 1 X trial
	D vs. X: 0.66 (–0.08 to 1.41)	X vs. D: –0.75 (–1.84 to 0.44)	
MAS scores (CFB), overall upper limb, 12 wks post-baseline *MD (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: 0.10 (–0.15 to 0.36) Not SS	D vs. B: 0.07 (–0.34 to 0.42)	From 9 trials: 4 D trials 5 B trials
	D vs. X: no data		
Occurrence of AEs, AUL, 12 wks post-baseline *OR (95% CI for Bucher or 95% CrI for Bayesian NMA approach)*	D vs. B: 2.33 (0.96 to 5.63) Not SS	D vs. B: 2.38 (0.68 to 8.88)	From 8 trials: 3 D trials 3 B trials 2 X trials
	D vs. X: 1.27 (0.66 to 2.46)	X vs. D: 0.77 (0.20 to 2.66)	

AE = adverse event; AUL = adult upper limb; B = Botox; CFB = change from baseline; CI = confidence interval; CrI = credible interval; D = Dysport Therapeutic; DAS = Disability Assessment Scale; MAS = Modified Ashworth Scale; MD = mean difference; NMA = network meta-analysis; OR = odds ratio; RE = random-effect; SS = statistically significant; vs. = versus; wks = weeks; X = Xeomin.

Critical Appraisal

The research questions were clear in this study. The authors were transparent with the methods that were taken with regard to literature search strategy, study selection, data extraction, quality assessment of the included studies, and statistical analysis. The literature search was conducted using a systematic review approach to identify relevant studies. The comparators were relevant; in addition, according to the clinical expert consulted for this review, the dosages of the BoNTAs that were included in this ITC were consistent with clinical practice. The indirect comparisons were performed with appropriate approaches, and the results from two ITC approaches were similar.

Several limitations were identified with the manufacturer-submitted ITC, which include:

- Limited number of studies were included in the NMA for some outcome measures. For example, there were only three studies of Xeomin identified. Thus, the relative effectiveness of Xeomin to Dysport Therapeutic is uncertain.
- Insufficient information regarding some of the characteristics of the included studies was provided in the ITC. Although the ITC indicated that many of the study sample sizes were small and resulted in large standard deviations around the point estimates, sample size of the individual trials was lacking, which leads to additional uncertainty in the relative treatment effects. The inclusion and exclusion criteria of the individual trials was not provided. Such information is important in assessing potential methodological and clinical heterogeneity (for instance, treatment experience, disease severity, and background therapy) between the included studies. Definitions of the outcome measures were not reported; it is uncertain whether the definitions of the outcomes were similar across the trials.
- For the study characteristics that were reported, heterogeneity was observed across studies in population, intervention (varying doses of each intervention were pooled in the NMA and classified as one intervention) and outcome measures (measured differently across the studies identified in the SR, e.g., change from baseline, or achieving a reduction above a particular value; some studies reported MAS scores by specific joints, and each of these were analyzed separately and pooled to provide an overall upper limb measure). The potential impact of such heterogeneity on treatment effects is unknown as it was not explored or described in sufficient detail.
- A number of assumptions were made in the NMA to facilitate the pooling of data. For example, median values were assumed to be the same as the mean values when the latter was not reported; however, it is unknown whether the sample data were normally distributed to support this assumption. Data across various doses of interventions were allowed to be pooled; yet the evidence to support this assumption is lacking and a dose effect may exist in these individual trials. In addition, the validity of pooling data across joints within the upper limb (fingers, wrist, and elbow) was uncertain, and makes data interpretation challenging.
- Sensitivity analysis and subgroup analysis were not performed to assess the validity of the assumptions or address heterogeneity. But, given the paucity of trials, this may not have been feasible.
- Variation was observed in the placebo responses between trials, suggesting heterogeneous patient populations or study designs (hence yielding a different placebo response).

Discussion and Conclusion

The manufacturer-submitted ITC is summarized and critically appraised in this review. In total 18 trials (eight for Dysport Therapeutic, seven for Botox and three for Xeomin) were included in the ITC to examine the relative benefits and harms of three BoNTAs for the treatment of adult patients with ULS. The reported outcomes of interest included the change in MAS score measured at week 4 to 6 and week 12, change in DAS scores measured at week 4 to 6 and week 12, and rates of AEs at week 12.Limited number of studies were available for some outcome measures, therefore the treatment effect of Dysport Therapeutic versus Botox or Xeomin may not be estimated. Several key baseline patient characteristics (treatment experience, disease severity and background therapy) were not reported in sufficient detail to allow for a comprehensive assessment of the clinical heterogeneity between trials. Where trial characteristics were reported, and heterogeneity was identified (for example, with interventions and outcome measures

assessed), the potential impact of such heterogeneity on treatment effects is unknown as it was not explored or described in sufficient detail.

None of the differences between Dysport Therapeutic, Botox, and Xeomin reached statistical significance. The results suggest the three BoNTAs may have similar treatment effects in patients with post-stroke spasticity, although the noted limitations increase the uncertainty in the comparisons.

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