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CADTH COMMON DRUG REVIEW

Clinical Review Report

AbobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada, Inc.)

Indication: To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults

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Abbreviations

aboBoNTA	abobotulinumtoxinA (Dysport Therapeutic)
AE	adverse event
ANCOVA	analysis of covariance
BoNT	botulinum neurotoxin
BoNTA	botulinum neurotoxin A
CD	cervical dystonia
CGI-I	Clinical Global Impression – Illness
CI	confidence interval
DB	double-blind
incoBoNTA	incobotulinumtoxinA (Xeomin)
IM	intramuscular
ITC	indirect treatment comparison
ITT	intention-to-treat (population)
MCS	Mental Component Summary (of SF-36)
mITT	modified ITT
onaBoNTA	onabotulinumtoxinA (Botox)
PCS	Physical Component Summary (of SF-36)
PGI-I	Patient Global Impression – Improvement
PP	per-protocol
QoL	quality of life
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey
ST	spasmodic torticollis
TEAE	treatment-emergent adverse event
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
VAS	visual analogue scale

Drug	AbobotulinumtoxinA (Dysport Therapeutic)
Indication	To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults
Listing Request	As per indication
Manufacturer	Ipsen Biopharmaceuticals Canada, Inc.

Executive Summary

Introduction

Cervical dystonia (CD, also known as spasmodic torticollis [ST]) is a movement disorder characterized by involuntary movement causing abnormal movements and awkward posture of the head and neck due to sustained or intermittent muscle contractions. The onset may be acute and painful, or insidious and painless.[1] Incidence is about 1 in 100,000; the usual age of onset is 30 years to 50 years. CD may be idiopathic, genetic, or secondary to multiple different factors such as brain injury, exposure to drugs or toxins, vascular injuries, or tumours.[2] Although CD does not affect mortality, key concerns include chronic pain due to dystonia or strain and social embarrassment, potentially leading to social isolation with depression. Complications of CD include neck pain, disability, and sleep disturbances. The symptoms of CD usually worsen over the first five years before stabilizing. Spontaneous remission is reported in 10% to 20% of patients, but often recurs within several months to years. CD is usually a lifelong chronic condition associated with pain and disability, resulting in significant impact on patient quality of life and associated with significant costs.[3]

Purified botulinum neurotoxin (BoNT) from *Clostridium botulinum* is generally considered the standard of care for the treatment of CD, although treatment can be limited by the potential for dysphagia related to diffusion of the toxin into nearby pharyngeal muscles. Botulinum neurotoxin type A (BoNTA) or botulinum neurotoxin type B (BoNTB), if the patient is resistant to BoNTA, is the first-line treatment for CD.[4,5] There are three botulinum toxin A formulations available in Canada that differ with respect to bacterial strain, dosing, pharmacokinetics, molecular weight, amount of complexing proteins, immunogenicity, manufacturing processes, storage requirements, and chemical properties. In addition to abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic), the other two formulations marketed in Canada are onabotulinumtoxinA (onaBoNTA, Botox) and incobotulinumtoxinA (incoBoNTA, Xeomin). The mechanism of the action of all three botulinum neurotoxin A formulations is the same — that is, to block neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine, thereby reducing the symptoms and signs of CD.[6] IncoBoNTA differs from onaBoNTA in that it is more highly purified and is considered to be free from complexing proteins.[7] AboBoNTA received Notice of Compliance (NOC) on June 15, 2016 to reduce the subjective symptoms and objective signs of CD in adults.[8] Due to differences in specific details, such as vehicle, dilution scheme, and laboratory protocols for various mouse LD50 assays, units of aboBoNTA are not interchangeable with units of any other botulinum toxin A (i.e., onaBoNTA or incoBoNTA).[8] The recommended initial dose of aboBoNTA is 500 U administered by intramuscular (IM) injection. The recommended re-treatment dose, if needed, is 250 U to 1,000 U (≤ 1,000 U). Re-treatment should not occur in intervals of < 12 weeks. The place in therapy for aboBoNTA for CD treatment is consistent with that of other BoNTA therapies that have been recommended by both the American Academy of Neurology and the European Federation of Neurological Societies.[4,5]

The objective of this document is to perform a systematic review of the beneficial and harmful effects of abobotulinumtoxinA (Dysport Therapeutic) for the treatment of CD (spasmodic torticollis) in adults.

Results and Interpretation

Included studies

Two pivotal, placebo-controlled, double-blind (DB), randomized controlled trials (RCTs) (studies 45 and 51)[9,10] met the inclusion criteria. The objective of the two pivotal trials was to assess the efficacy and safety of aboBoNTA versus placebo in the treatment of patients with CD with or without the experience of onaBoNTA treatment previously. Patients were randomized to aboBoNTA (500 U, single intramuscular [IM] injection) or placebo according to a randomization code generated before the study.[9,10] Randomization was stratified by centre, and according to whether or not the patient had previously been treated with botulinum toxin.[9,10] In total, 80 patients and 116 patients were randomized in studies 45 and 51, respectively.

Overall, patients enrolled were adults with a mean age per treatment group ranging from 52 years to 54 years,[10] with a minimum age of 20 years to a maximum age of 79 years (Table 5). The majority of patients (≥ 62%) were female[9,10] and Caucasian (84%[9] to 100%[10]). Greater than 72% of patients in Study 45 and greater than 73% of patients in Study 51 had received botulinum neurotoxin treatment before entering the study. The baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score (mean) was about 45 points in both treatment groups in either Study 45 or Study 51. The primary outcome assessed in the two RCTs was TWSTRS total score at week 4. The secondary or tertiary outcomes (or exploratory outcomes) included the TWSTRS total score assessed at week 8 and week 12, the TWSTRS subscale score, the visual analogue scale (VAS) for pain and symptoms, the Short Form (36) Health Survey (SF-36), the proportion of responders, and overall treatment success. The key efficacy and safety results are summarized in Table 1.

There is a lack of head-to-head clinical trials using the Health Canada–recommended dose (500 U).

Efficacy

TWSTRS total score

In Study 45, the adjusted mean change from baseline (mean ± standard error [SE]) of the TWSTRS total score at week 4 was [redacted] points in the aboBoNTA group compared with [redacted] points in the placebo group. The between-group mean difference of changes from baseline (aboBoNTA minus placebo) was statistically significant (–6.0 points; 95% CI, –10.6 to –1, $P = 0.013$). In Study 51, the adjusted least squares mean ± SE of change from baseline in TWSTRS total score at week 4 were 15.58 ± 1.95 in the aboBoNTA group compared with 6.74 ± 2.03 in the placebo group ($P < 0.0001$; 95% CI, –12.94 to –4.74). The improvement in TWSTRS total score observed for aboBoNTA at week 4 was maintained at week 8 and [redacted] in week 12 in both studies. Subgroup analysis data for TWSTRS total score in Study 51 found that the results for TWSTRS total score at weeks 4, 8, and 12 demonstrated similar efficacy between botulinum neurotoxin-naive and botulinum neurotoxin-experienced patients.[10]

TWSTRS Subscale scores (severity, disability, and pain)

In both Study 45 and Study 51, TWSTRS subscales (severity, disability and pain) demonstrated greater improvement in the aboBoNTA group compared with the placebo group at week 4 to week 12. In Study 45, the between-group difference of change from baseline at week 4, 8, 12 in three TWSTRS subscales was all statistically significant in favour of aboBoNTA treatment. [redacted]

Patient and investigator's VAS symptom assessments

In Study 45, the statistically significant improvement observed in the aboBoNTA group at week 4 was maintained at week 8 and week 12 and results were more toward symptom-free in the aboBoNTA group compared with the placebo group at both week 8 and week 12. [redacted]

Pain (VAS scores for pain)

In both Study 45 and Study 51, pain (VAS scores for pain) showed greater improvement in the aboBoNTA group compared with the placebo group from week 4 to week 12. However, the statistically significant, between-group differences of changes from baseline

were reported in Study 45 only at week 4 and week 8, but not at week 12. By week 12, the VAS pain score had nearly returned to baseline in both treatment groups.

SF-36 health survey

Study 51 reported that the change from baseline for SF-36 scores was not statistically significant in either of the treatment groups.

Treatment response

Responders were defined as those patients who had a decrease in TWSTRS total score of at least 30% and at least 10 points compared with baseline. In Study 45, the proportion of responders in the aboBoNTA group was higher than in the placebo group (aboBoNTA versus placebo) at week 4 (38% versus 16%), week 8 (27% versus 9%), and week 12 (19% versus 7%). In Study 51, the proportion of responders was higher in the aboBoNTA group than in the placebo group at week 4, week 8, and week 12. In both RCTs, there were statistically significantly more responders among patients treated with aboBoNTA compared with those in the placebo group. These effects were reported at week 4 and week 8, but not at week 12.

Investigators global assessment – efficacy and safety/treatment success

In Study 45, numerically more patients in the aboBoNTA group (35%) than patients in the placebo group (23%) were considered treatment successes at week 12; there was no statistically significant difference between aboBoNTA and placebo in treatment success; [redacted]. In Study 51, the treatment success rates were 58% and 16% in aboBoNTA group and the placebo groups respectively.

Duration of effect

In the DB phase of Study 45, it was reported that for the patients who responded to aboBoNTA, the duration of the effect (mean ± standard deviation [SD]) was 22.8 ± 12.5 weeks (range: 9 weeks to 46 weeks). In the open-label extension phase of Study 45,[11] the mean durations of effect in the reported three re-treatments were 18.3 ± 12.0, 19.4 ± 11.4, and 19.6 ± 11.1 weeks, respectively. The range of the duration of effect was from [redacted] to 98 weeks. In the open-label extension phase of Study 51, the mean durations of effect (± SD) were 14.95 ± 4.8, 16.3 ± 6.6, and 15.7 ± 4.24 weeks, respectively, in three treatment cycles (no data were reported for cycle 1). The overall range of the duration of the effect was [redacted] weeks to [redacted] weeks.

Overall, efficacy results from Study 45 and Study 51 indicated a treatment effect, and were consistent across primary and most of the secondary outcomes, demonstrating that aboBoNTA is more effective than placebo for reducing the symptoms and signs of CD (ST). [redacted]

In addition, the two pivotal, placebo-controlled RCTs and the four onaBoNTA-controlled RCTs using dosing outside of Health Canada–approved doses for aboBoNTA reported that aboBoNTA (in a dose ratio of 1.7:1 to 4:1 for aboBoNTA versus onaBoNTA) had similar safety and uncertain comparable efficacy as onaBoNTA in the treatment of patients with CD who had a stable response to onaBoNTA previously. No direct evidence assessed the duration of effect with the aboBoNTA treatment compared with onaBoNTA and incoBoNTA in the treatment of CD. Both the network meta-analysis by Han et al. and an indirect treatment comparison (ITC) submitted by the manufacturer found that the efficacy and safety profile appeared similar in aboBoNTA, onaBoNTA, and incoBoNTA at week 4 after injection.

Harms

In general, the safety profile for aboBoNTA was similar to that for placebo. Study 45 demonstrated a numerically higher incidence (5% greater than placebo) of injection site pain (38% versus 23%), neck or shoulder pain (38% versus 30%), and tiredness (35% versus 30%) in the aboBoNTA groups than in the placebo group in both RCTs. The overall incidence of adverse events (AEs) reported in Study 51 was much lower than that reported in Study 45, which may be due to differences in AE reporting between the two studies. In Study 45, AEs were assessed according to a checklist of 10 adverse effects considered to be associated with botulinum toxin therapy of the neck muscles (dysphagia, dry mouth, voice changes, neck muscle weakness, jaw weakness, limb weakness, tiredness, respiratory difficulties, discomfort at injection site, and visual difficulties). In Study 51, a similar checklist was not described.[9] Serious adverse events (SAEs) were rarely reported in either study. During the DB phase, no patients withdrew due

to an AE. No patients died in either of the studies. After one treatment with aboBoNTA, there was little difference between aboBoNTA and placebo with regard to neutralizing antibody status. However, the data to assess the clinical impact of developing antibodies are limited, as pointed out in the Health Canada review report.[1]

Conclusions

Based on the primary outcome of the two pivotal RCTs (change from baseline in total TWSTRS score) and other outcomes, including patient and investigator VAS cervical dystonia symptom assessment, it was demonstrated that aboBoNTA is statistically significantly more effective than placebo in reducing the symptoms and signs of CD at four weeks to 12 weeks post-treatment. [redacted]. As most patients included in the trials were previously known to have responded to botulinum toxin treatment, the effect in patients who are previous poor or non-responders to treatment is uncertain. The effect of aboBoNTA on quality of life (SF-36), a key outcome in CD, was inconclusive and potentially biased due to missing data. Overall AEs appeared similar in patients who received aboBoNTA and patients in the placebo group. The short duration of the RCTs does not permit adequate assessment of antibody development during the DB phase. Health Canada approved 500 U (dose-equivalency to onaBoNTA of 2.5:1) based on the two pivotal placebo-controlled trials (Study 45 and Study 51). A network meta-analysis by Han and an ITC submitted by the manufacturer found that the efficacy and safety profile are similar in aboBoNTA, onaBoNTA, and incoBoNTA at week 4 after injection. No direct evidence (for the Health Canada–approved dose regimen) assessed the duration of effect with the aboBoNTA treatment compared with [redacted]incoBoNTA in the treatment of CD.

Table 1: Summary of Key Results

	Study 45		Study 51	
	aboBoNTA (n = 37)	**Placebo (n = 43)**	**aboBoNTA (N = 55)**	**Placebo (N = 61)**
TWSTRS Total Score				
Baseline M ± SD	45.1 ± 8.7	46.2 ± 9.4	43.83 ± 7.97	45.81 ± 8.78
Week 4				
M ± SD	35.2 ± 13.8	42.4 ± 12.2	30.04 ± 12.65	40.22 ± 11.75
Change from baseline at wk 4, MD ± SE	–9.6 ± 2.0)	–3.7 ± 1.8	–15.58 ± 1.95	–6.74 ± 2.03
Btw-group MD of change from baseline at wk 4, MD (95% CI), *P* value	–6.0 (–10.6 to –1.3), *P* = 0.013		–8.9 (–12.94 to –4.74) *P* < 0.0001	
Week 12				
M ± SD	39.3 ± 12.9	44.6 ± 11.5	36.04 ± 11.76	40.76 ± 11.08
Change from baseline MD ± SE at wk 12	NR	NR	–9.06 ± 1.66	–4.94 ± 1.66
Btw-group MD of change from baseline at wk 12, MD (95% CI), *P* value	–4.3 (–8.2 to –0.4), *P* = 0.030		MD NR (–7.55 to –0.68) *P* = 0.019	
SF-36				
SF-36 MCS at wk 8, M ± SD,	NR	NR	49.00 ± 8.69	43.41 ± 12.30
P value			NSS	
SF-36 PCS at wk 8, M ± SD,	NR	NR	43.70 ± 8.76	42.49 ± 8.84
P value			NSS	
AEs				
# of patients with ≥ 1 AE n (%)	34 (92)	34 (79)	26 (47)	27 (44)
Withdrawals n (%)	22 (59.5)	36 (84)	10 (18.2)	23 (37.7)
SAE n (%)	5 (13.5)	1 (2.7)	0	1 (1.6)
WDAE	0	0	0	0

	Study 45		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (N = 55)	Placebo (N = 61)
Notable harm				
Dysphagia n (%)	6 (16)	4 (9)	5 (9)	0
Mortality	0	0	0	0

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); AE = adverse event; Btw = between; CI = confidence interval; M = mean; MCS = Mental Component Summary of SF-36; MD = mean difference; NR = not reported; NSS = not statistically significant; PCS = Physical Component Summary of SF-36; SAE = serious adverse events; SD = standard deviation; SF-36 = Short Form (36) Health Survey; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; WDAE = withdrawal due to adverse event; wk = wk.

Source: Study 45 Clinical Study Report [9], Truong et al.; 2005 [12], Study 51 Clinical Study Report; [10] and Truong et al., 2010.[13]

Introduction

Disease Prevalence and Incidence

Cervical dystonia (CD, or spasmodic torticollis [ST]) is a movement disorder characterized by involuntary movement causing abnormal movements and awkward posture of the head and neck due to sustained or intermittent muscle contractions. The onset may be acute and painful, or insidious and painless.[1] The incidence is about 1 in 100,000 and the usual age of onset is 30 years to 50 years. CD may be idiopathic, genetic, or secondary to multiple different factors such as brain injury, exposure to drugs or toxins, vascular injuries, or tumours.[2] Although CD does not affect mortality, key concerns include chronic pain due to dystonia, strain and social embarrassment, and the potential for extreme of social isolation with depression. Dystonia may lessen when the body is at rest and usually disappears during sleep. The diagnosis is made clinically, based on abnormal postures (with or without tremor) and recognition of specific features, such as unintentional muscle contraction. A validated rating scale should be used as part of the assessment if the diagnosis is not clear based on dystonic movements and activation and deactivation features; brain magnetic resonance imaging electromyographic mapping should be considered, and genetic testing performed after establishing a clinical diagnosis. Complications of CD include neck pain, disability, and sleep disturbances. Symptoms of CD usually worsen over the first five years before stabilizing. Spontaneous remission is reported in 10% to 20% of patients, but often recurs within several months to years. CD is usually a lifelong chronic condition associated with pain and disability, has a significant impact on patient quality of life (QoL), and is associated with significant costs.[3] Disability is common in CD and has a substantial, detrimental effect on patient QoL and employment. CD is visible and stigmatizing for affected individuals, and associated with social withdrawal and psychiatric comorbidities.[3]

Standards of Therapy

Botulinum neurotoxin (BoNT) is generally considered the standard of care for treatment of CD, although treatment can be limited by the potential for dysphagia related to diffusion of the toxin into nearby pharyngeal muscles. Botulinum neurotoxin type A (BoNTA) — or botulinum neurotoxin type B (BoNTB) if resistant to BoNTA — is the first-line treatment for CD.[4,5] The addition of physical therapy to BoNTA may be more effective than BoNT alone. For patients with dopa-responsive dystonia, chronic treatment with levodopa after positive diagnostic trial can be used. Bilateral globus pallidus internus deep brain stimulation may reduce the severity of CD. Oral drug therapies (i.e., anticholinergics, benzodiazepines) are used as adjunct therapy to BoNT treatment.

There are three botulinum toxin A formulations available in Canada that differ with respect to bacterial strain, dosing, pharmacokinetics, molecular weight, amount of complexing proteins, immunogenicity, manufacturing processes, storage requirements, and chemical properties. In addition to abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic), the other two formulations marketed in Canada are onabotulinumtoxinA (onaBoNTA, Botox) and incobotulinumtoxinA (incoBoNTA, Xeomin). See Table 2 for more details on the three formulations of BoNTA.

OnaBoNTA is a purified BoNTA, produced from a culture of the Hall strain of *Clostridium botulinum*. It is purified to a crystalline complex consisting of the neurotoxin, a non-toxic protein, and four major hemagglutinin proteins. OnaBoNTA blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine, thereby reducing the symptoms and signs of CD.[6] IncoBoNTA is also produced by *Clostridium botulinum* bacteria. IncoBoNTA differs from onaBoNTA in that it is more highly purified and considered to be free from complexing proteins.[7]

BoNTA intramuscular (IM) injections are recommended as the therapy of choice for the treatment of CD. However, concerns over lengthy travel represent barriers to desirable outcomes, especially for patients who live in rural areas, where clinics are less easily accessible. Treatment that can provide a long duration of effect and help reduce the frequency of visits would provide patients with the opportunity to exert greater control over their disease. A treatment with long duration of effect will not only help reduce the inconvenience and travel burden for patients, but also potentially reduce wait times in clinics, giving health care providers the opportunity to optimize treatment frequency.[3]

The place in therapy for aboBoNTA for CD treatment is consistent with other BoNTA therapies that have been recommended by both the American Academy of Neurology and the European Federation of Neurological Societies.[4,5]

Drug

AboBoNTA is a BoNTA that blocks neuromuscular transmission by preventing cellular acetylcholine release. It remains the mainstay of treatment for patients with adult-onset CD.[3] AboBoNTA received Notice of Compliance (NOC) on June 15, 2016 to reduce the subjective symptoms and objective signs of CD in adults.[8] 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 that 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.[8] AboBoNTA is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps.[8] 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).[8] The recommended initial dose is 500 U administered by IM injection. The recommended re-treatment dose, if needed, is 250 U to 1,000 U (≤ 1,000 U). Re-treatment should not occur in intervals of < 12 weeks. Together with onaBoNTA and incoBoNTA, aboBoNTA is recommended as the first-line treatment for CD in USA and Europe.[4,5,14,15] 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)[8]	incoBoNTA (Merz)[7]	onaBoNTA (Allergan)[6]
Molecular weight (kD)	500 to 700	900	~150
Complexing proteins	Hemagglutinin/nonhemagglutinin	Hemagglutinin/nonhemagglutinin	None
***Clostridium botulinum* strain**	Hall Strain	Hall A	Hall A
Duration of effect	Up to 20 wks	12 wks to 16 wks	~12 wks to 16 wks
Recommended Re-treatment interval	≥ 12 weeks (3 mos)	≥ 2 mos	≥ 12 wks
Mechanism of action	Botulinum toxin A 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]	To reduce the subjective symptoms and objective signs of CD (spasmodic torticollis) in adults		
Route of administration	For IM injection only		
Recommended dose	• Initial 500 U for pts who are botulinum toxin-naive or treated. • Repeated treatment: 250 U to 1,000 U. Re-treatment interval, if needed, ≥ 12 wks (3 mos).	Individualized, range: 200 U to 360 U. Re-treatment interval, if needed: ≥ 8 wks (2 mos).	200 U. Re-treatment interval, if needed: ≥ 12 wks.
Serious side effects / safety issues	SAEs were very rare. 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; CD = cervical dystonia; IM = intramuscular; incoBoNTA = incobotulinumtoxinA; mos = months; onaBoNTA = onabotulinumtoxinA; pts = patients; SAE = serious adverse events; wk = week.

[a] Health Canada indication.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of aboBoNTA for the treatment of CD (spasmodic torticollis) 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 years) patients with cervical dystonia (spasmodic torticollis) Subgroups: Patients experienced with botulinum toxin (e.g., Dysport) versus Dysport-naive patients Baseline severity of disability (TWSTRS disability subscale) Baseline VAS pain score Anti-Dysport antibodies (+/-)
Intervention	AbobotulinumtoxinA (Dysport Therapeutic) Initial 500 U for botulinum-experienced or -naive patients, IM, as a divided dose among affected muscles Re-treatment dose if needed: 250 U to 1,000 U (≤ 1,000 U). Re-treatment should not occur in intervals of ≤ 12 weeks.
Comparators	IncobotulinumtoxinA (Xeomin) OnabotulinumtoxinA (Botox) RimabotulinumtoxinB (Myobloc)
Outcomes	**Key efficacy outcomes:** • Symptoms (e.g., TWSTRS total score, TWSTRS subscales, patient's and investigator's VAS symptom assessments)[a] • Pain (e.g., VAS pain scores, TWSTRS pain subscale)[a] • Disability (e.g., TWSTRS disability subscale)[a] • HRQoL (e.g., SF-36)[a] **Other efficacy outcomes:** • Treatment response[b] • Investigators global assessment (efficacy and safety) and treatment success[c] • Duration of effect **Harms outcomes:** • AEs, SAEs, WDAEs, mortality, add notable harms and harms of special interest (antibodies, injection site reaction, dysphagia, paralysis, etc.)
Study Design	Published and unpublished phase III RCTs

AE = adverse events; CDR = CADTH Common Drug Review; HRQoL = health-related quality of life; IM = intramuscular; RCT = randomized controlled trial; SAE = serious adverse events; SF-36 = Short Form (36) Health Survey; SAE = serious adverse event; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale; WDAE = withdrawal due to adverse events; yrs. = years.

[a] Identified as an important outcome in the patient input submission to CDR.

[b] Responder defined as ≥ 30% decrease in TWSTRS total score from baseline.

[c] Overall treatment successes assessed by the investigator at week 12 (defined as a global assessment of efficacy rating of "better" or "much better" and a global safety assessment of "no worse than moderate" or "worse than moderate").

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 (abobotulinum) and CD.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 1, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on June 21, 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/resources/finding-evidence/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two 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 585 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in the included studies. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

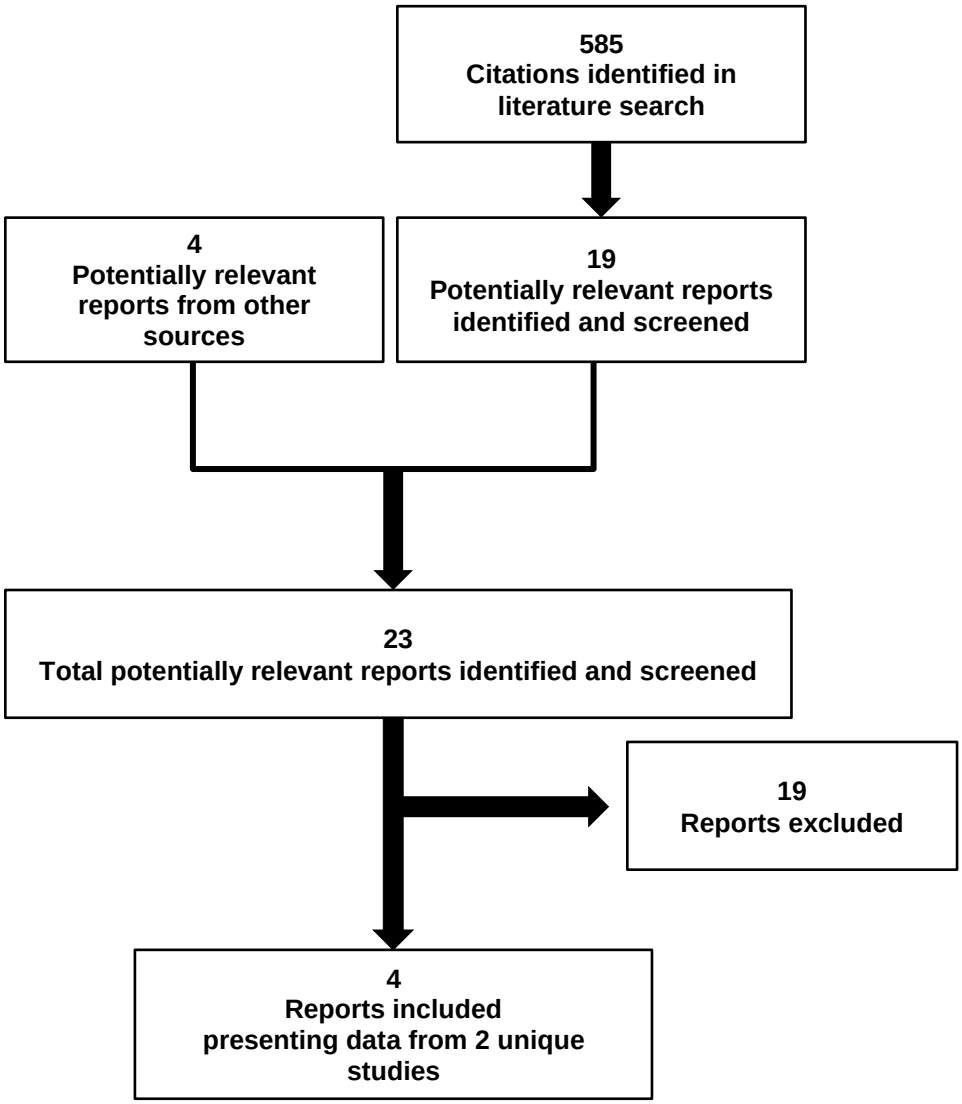


Table 4: Details of Included Studies

		Study 45 [9,12]	Study 51 [10,13]
Designs & Populations	**Study Design**	DB RCT	DB RCT
	Location	USA	USA and Russia
	Randomized (N)	80	116
	Inclusion Criteria	• Male and female patients diagnosed with CD • Symptoms of CD ≥ 18 mos	• Adult patients with CD (≥ 18 years) • Symptoms of CD ≥ 18 mos • TWSTRS total score ≥ 30 • TWSTRS severity subscale score ≥ 15 • TWSTRS disability subscale score ≥ 3 • onaBoNTA naive or if previously treated with BoNTA or BoNTB had ≥ interval of 16 weeks since the last injection or signs and symptoms returned to pre-treatment status
	Exclusion Criteria	• Other forms of CD (anterocollis or pure retrocollis) • Previous poor response to the last 2 botulinum type A toxin treatments (as • determined by standard practice at each site, e.g., < 20% improvement in TWSTRS total score from baseline to wk 4) • Significant dysphagia • Body weight < 100 lb (45.4 kg) • TWSTRS total score < 30, severity score < 15, disability score < 3, and pain score < 1. • Pts treated previously with BoNTA or BoNTB were excluded unless ≥ 16 wks since last injection • Pts required a onaBoNTA dose of < 80 U or > 250 U at baseline • Concomitant medication use (i.e., at entry or an expected requirement) that may have interfered with the evaluation of study treatment (e.g., narcotics)	• Other forms of CD (e.g., anterocollis or retrocollis) • CD symptom remission at screening • Previous poor response to BoNTA or BoNTB treatments • Presence of neutralizing antibodies to BoNTA • Other diseases of the neuromuscular junction, or symptoms that could interfere with TWSTRS scoring • Current or expected requirement for concomitant medication that may have interfered with the evaluation of study treatment (e.g., narcotics) • Body weight ≤ 45.4 kg
Drugs	**Intervention**	aboBoNTA (500 U)	aboBoNTA (500 U)
	Comparator(s)	Placebo	Placebo
Duration	**Phase**		
	Run-in	None	None
	Double-blind	12 wks, but primary outcome assessed at wk 4	12 wks, but primary outcome assessed at wk 4
	Follow-up	4 wks to 20 wks	4 wks to 12 wks
	Open phase	Up to 64 wks	52 wks (range: 4 to 94 wks)
Outcomes	**Primary End Point**	TWSTRS total score at wk 4	TWSTRS total score at wk 4
	Other End Points	**Secondary outcomes:** • Pain VAS at wk 4 **Tertiary outcomes:** • TWSTRS total score, TWSTRS subscale scores, VAS pain scale, proportion of responders, treatment success, duration of effect, VAS symptom score measured after wk 4 • Adverse events	**Secondary outcomes:** • TWSTRS total scores at wks 8 and 12, VAS for symptoms • Investigator's global assessment • SF-36 scores at wk 8 • Treatment successes[a] at wk 12 **Exploratory outcomes:** • VAS for pain, TWSTRS subscales scores (severity, disability, and pain) • Proportion of responders

		Study 45 [9,12]	Study 51 [10,13]
			• Time to re-treatment
NOTES	**Publications**	Truong et al.[12]	Truong et al.[13]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); BoNTA = botulinum neurotoxin A; BoNTB = botulinum neurotoxin B; CD = cervical dystonia; DB = double-blind; onaBoNTA = onabotulinumtoxinA (Botox); RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale; wk = week.

Note: Two additional reports were included: FDA report,[16] and Health Canada report [1]; [redacted]

[a] Treatment successes defined as global assessment of efficacy ratings of "better" or "much better" and a global safety assessment of no worse than moderate.

Source: Study 45 Clinical Study Report [9], Truong et al., 2005[12]; Study 51 Clinical Study Report [10]; and Truong et al., 2010.[13]

Included Studies

Description of studies

A total of two double-blind (DB) RCTs met the inclusion criteria, which were the pivotal placebo-controlled trials (Study 45 and Study 51). In addition, the findings from DB RCTs[17-20] of potential interest that compared aboBoNTA with onaBoNTA are summarized in Appendix 7. These studies did not meet the selection criteria for the systematic review because the aboBoNTA doses used were all below the Health Canada–approved dose of 500 U (Appendix 7, Table 31).

[redacted]9,12

The objective of the two pivotal trials was to assess the efficacy and safety of aboBoNTA versus placebo in the treatment of patients with CD with or without the experience of onaBoNTA treatment previously. Patients were randomized to aboBoNTA (500 U, single IM injection into clinically indicated neck muscles) or placebo according to a randomization code generated before the study.[9,10] Randomization was stratified by centre and according to whether or not the patient had been previously treated with botulinum toxin.[9,10] In Study 45 (group 1), 37 patients and 43 patients were randomized in aboBoNTA and placebo respectively (N = 80). In Study 51, 55 and 61 patients were randomized to aboBoNTA and placebo respectively (N = 116).

Populations

Inclusion and exclusion criteria

The inclusion criteria for the two pivotal placebo-controlled trials were similar, mainly including adult patients with CD (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] ≥ 30) previously treated or untreated with botulinum neurotoxin. If previously treated with botulinum neurotoxin, patients had to have a minimum interval of 16 weeks since the last injection or to have returned to pre-treatment status. Patients with other forms of CD were excluded from all included studies.

Baseline characteristics

Overall, the main baseline patient characteristics were generally balanced between the two treatment groups in the two pivotal placebo-controlled RCTs (Table 5). The patients enrolled were adults, with mean age per treatment group ranging from 52 years to

54 years,[10] with a minimum age of 20 years to a maximum age of 79 years (Table 5). The majority of patients (≥ 62%) were female[9,10] and Caucasian (84%[9] to 100%[10]). In Study 45, numerically more Caucasian patients were included in the placebo group (93%) than in the aboBoNTA group (81%). The mean times since the diagnosis of CD (M ± SD, years) were 12.1 ± 9.5 in the aboBoNTA group and 11.69 ± 9.62 in the placebo group, respectively. More than 72% of patients in Study 45 and more than 73% patients in Study 51 had received botulinum neurotoxin treatment before entering the study. In Study 45, the numbers with prior botulinum toxin treatment were 9.3 ± 9.8 in the aboBoNTA group and 12.3 ± 9.7 in the placebo group, respectively. The most recent doses of onaBoNTA were 232.1 ± 82.4 U in the aboBoNTA group and 210.9 ± 58.6 U in the placebo group, respectively. The baseline TWSTRS total score (mean) was about 45 points in both treatment groups in either Study 45 or Study 51 (see Table 5 and Table 19 in Appendix 4 for more detail).

Table 5: Demographic and Baseline Characteristics

	Study 45 [9,12]		Study 51 [10,13]	
	AboBoNTA (n = 37)	Placebo (n = 43)	AboBoNTA (n = 55)	Placebo (n = 61)
Age (yrs), M ± SD	53.4 ± 11.6	53.6 ± 12.1	51.9 ± 13.4	53.9 ± 12.5
Female, n (%)	23 (62)	27 (63)	37 (67)	38 (62)
Caucasian, n (%)	30 (81)	40 (93)	55 (100)	61 (100)
Weight (kg), M ± SD	76.1± 13.9	74.5 ± 17.7	73.4± 13.8	77.4 ± 15.0
Time since the diagnosis of CD (yrs), M ± SD	7.02 ± 7.12	5.69 ± 5.23	NR	NR
Time since onset of signs/symptoms (yrs), M ± SD	12.1 ± 9.5	11.69 ± 9.62	12.0 ± 8.8	11.8 ± 8.8
Pts without BoNT tx, n (%)	9 (24)	12 (28)	10(18)	10 (16)
Pts previously treated with BoNT, n (%)	28 (76)	31 (72)	45 (82)	51 (84)
Time since first BoNT tx (yrs), M ± SD	4.39 ± 3.24	4.38 ± 2.56	NR	NR
Numbers of BoNT tx, M ± SD	9.3 ± 9.8	12.3 ± 9.7	NR	NR
Time since last BoNT tx (yrs), M ± SD	0.83 ± 0.97	0.60 ± 0.77	NR	NR
Last dose of BoNT (units), M ± SD	232.1 ± 82.4	210.9 ± 58.6	NR	NR
TWSTRS total score, M ± SD	45.1 ± 8.7	46.2 ± 9.4	43.8 ± 8.0	45.8 ± 8.8
Pt's VAS for symptom severity (mm), M ± SD	NR	NR	67.7 ± 19.7	63.6 ± 18.9
Investigator's VAS for symptom severity (mm), M ± SD	NR	NR	62.3 ± 15.8	65.3 ± 18.0
SF-36 MCS, M ± SD	NR	NR	44.5 ± 10.4	43.3 ± 11.1
SF-36 PCS, M ± SD	NR	NR	39.4 ± 8.8	43.2 ± 7.9
Pt VAS for pain severity (mm), M ± SD	NR	NR	47.4 ± 25.0	49.6 ± 24.5
TWSTRS severity score, M ± SD	19.7 ± 2.6	20.5 ± 3.4	20.4 ± 3.0	21.2 ± 2.8
TWSTRS disability score, M ± SD	13.9 ± 4.4	14.1 ± 5.1	12.9 ± 3.8	13.8 ± 4.5
TWSTRS pain score, M ± SD	11.5 ± 3.8	11.7 ± 3.8	10.6 ± 4.2	10.9 ± 4.6

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); BoNT = botulinum neurotoxin; CD = cervical dystonia; M = mean; MCS = Mental Component Summary of SF-36; NR = not reported; PCS = Physical Component Summary of SF-36; Pt = patient; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TWSTRS = Toronto Western Spasmodic Torticollis Scale; tx = treatment; VAS = visual analogue scale; yrs = years.

Note: For Study 45: [redacted]

Source: Study 45 Clinical Study Report[9], Truong 2005,[12] Study 51 Clinical Study Report,[10] and Truong 2010.[13]

Interventions

In the two pivotal RCTs, patients were randomized to aboBoNTA 500 U once or placebo. AboBoNTA was administered by IM injection into clinically indicated neck muscles in a single dosing session. The number of injection sites and the dose at each site were determined by the investigator. Two to four of the indicated muscles (e.g., sternocleidomastoid, splenius capitis, trapezius, and levator scapulae) were injected, with or without electromyogram guidance, according to the investigator's normal practice. In order to maintain blinding, matching placebo was provided in identical clear glass vials and in the same volume containing 125 mcg of human albumin and 2.5 mg of lactose labelled as Dysport.[9,10] Patients were allowed to maintain their concomitant CD medication

throughout the study. The concomitant medications included muscle relaxants and benzodiazepines.[9,10] Adjustment to background medication was permitted during the study in both studies. Concomitant medication use (i.e., at entry or an expected requirement) that may have interfered with the evaluation of study treatment (e.g., narcotics) were prohibited. The concomitant medication (especially analgesic) use was reported and well balanced in Study 51, but such information was not well reported in Study 45.

Outcomes

Efficacy

In the two pivotal RCTs (Study 45 and Study 51), the primary outcome was TWSTRS total score at week 4. The secondary or tertiary outcomes or exploratory outcomes included TWSTRS total score assessed at week 8 and week 12, TWSTRS subscale score, visual analogue scale (VAS) pain scale and VAS symptom scale, SF-36, proportion of responders, and overall treatment success.

TWSTRS (total and subscale)

TWSTRS was developed specifically for clinical trials in CD and is accepted by FDA and Health Canada.[16] The TWSTRS measures three domains in three subscales: symptom severity (11 items, clinician-rated); disability (six items, patient-rated); and pain (three items, patient-rated). The TWSTRS severity (range: 0 to 35), disability (range: 0 to 30), and pain (range: 0 to 20) subscales assessed distinct aspects of CD. The TWSTRS total score (range: 0 to 85) reflected the sum of the three subscale scores. A lower score indicates less severe (mild). The higher the score, the more severe the CD condition.[12] A decrease in TWSTRS total or subscale score indicates an improvement in the patient's CD. A review of the literature evaluating the psychometric properties of the TWSTRS demonstrated that it correlated strongly with the Tsui scale,[21] had positive within-scale correlations, demonstrated responsiveness to clinical changes, and had overall good inter-rater agreement and internal consistency. However, no minimal clinically important difference (MCID) was identified (Appendix 5)

Responders are defined as those patients who had a reduction in TWSTRS total score of at least 30%[9,10] and at least 10 points compared with baseline.[9]

Tsui score

Developed in the 1980s, the Tsui score (assessed by physician) is a scale measure of rotation (0 to 3), tilt (0 to 3), sagittal movements (0 to 3), head tremor (0 to 2), and shoulder elevation (0 to 2). A duration score for sustained movement (1 to 2) and for tremors (1 to 2) can be included in the score. The total Tsui is scored from 0 to 25. The low score indicates less severe or mild condition, while the high score indicates more severe.[17] A decrease in Tsui score indicates an improvement in the patient's CD. Tsui score has shown reproducibility, with acceptable inter-observer correlation. No minimal clinically important difference (MCID) is identified for the Tsui score (Appendix 5).

Visual analogue pain scale:

VAS is a common approach used in measuring pain. The scores range from 0 mm to 100 mm. There is evidence of validity for the use of VAS for muscle pain measurement. However, no information was identified that directly assesses the validity of MCID in CD.

Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) is a patient self-reported questionnaire that assesses aspects of health-related quality of life (HRQoL). The tool allows patients to report, from their perspective, on their health status over the previous four weeks. SF-36 includes eight individual domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, mental health, and role emotional. The eight individual domains can be further aggregated into a physical component summary (SF-36 PCS) and a mental component summary (SF-36 MCS). Each scale ranges from 0 (worst health possible) to 100 (best health possible).[10] No MCID was identified in the clinical research for CD although generally recommended MCID for the SF-36 PCS is 2 points and for the SF-36 MCS is 3 points.

Patient and investigator assessment of change in the signs and symptoms of cervical dystonia:

This was assessed using a VAS with the centre being no change from baseline. VAS ranges from 0 mm to 100 mm, in which 0 mm indicates much worse and 100 mm indicates symptom-free. An assessment of 50 mm indicates no change.[9,12]

Duration of effect or duration of response (time to re-treatment):

This was defined as the time between the date of administration of the study medication and the date of the need for re-treatment. It was only calculated for patients who responded. Re-treatment is indicated if the response to treatment on the TWSTRS total score is no better than a 10% decrease from baseline. Where patients have a censored duration of response, the censored time has been tabulated.[12]

Treatment success and investigator's global assessment – efficacy and safety: As reported by the manufacturer, this measure is an investigator-reported global impression of change. Investigators report their assessment of patients as either positive change or harmful change.[10,22] Patients with a global efficacy assessment of "Better" or "Much better" and a safety assessment of no worse than "Moderate" are defined as treatment successes.[9,10] No additional information was found in the literature that provides evidence on the validity and reliability of such measure.

Harms

Adverse events (AEs) — that is, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable adverse events (i.e., AEs especially particularly relevant for this review) were reported in the two pivotal RCTs.

Statistical analysis

In both Study 45 and Study 51, the primary efficacy outcomes were the changes from baseline in TWSTRS total score at week 4. Other outcomes (secondary or tertiary outcomes) included the TWSTRS total score measured at 8 or 12 weeks, TWSTRS subscales, VAS pain scale, VAS symptom score, proportion of responders, treatment success, and duration of effect. In Study 45, a total of 60 patients (30 in each group) were required for the primary efficacy end point. With 30 patients in each treatment group, there was a likelihood greater than 90% of detecting a significant difference (two-sided significance level: $P = 0.05$) if the true difference in TWSTRS total score was 9 points. This assumes that the standard deviation (SD) of the difference in TWSTRS total score from baseline was 10 points. Considering dropouts, 80 patients were planned. Study 51 was designed to detect a difference of 6.4 points with 90% power using a two-sided test at the 5% significance level. Allowing for dropouts, 120 patients were needed to allow for the completion of 47 patients per treatment group. However, the rationale for the threshold of the between-group difference was not indicated in Study 51, although the rationale for the difference of 9 points in Study 45 was based on a previous study by Lew (see Study 45 Clinical Study Report).[9] Analysis of covariance (ANCOVA) was used for all efficacy analyses. Each analysis was adjusted for centre, treatment history (BoNT-experienced or BoNT-naive), and baseline characteristics (where appropriate). All covariates remained in the final model, regardless of significance. Missing data at weeks 4, 8, and 12 were imputed using the patient's own baseline value for TWSTRS total and subscale analyses and for the pain VAS analyses. However, the patient and investigator assessment of change in signs and symptoms was not assessed at baseline; therefore, missing data were imputed with a value of 40 mm (on a 100-mm scale) to indicate moderate worsening. This conservative approach assumed that there was no dramatic improvement or worsening in withdrawn patients. Statistical testing was performed for the primary and secondary end points, as well as the outcome measured at week 8 and week 12. All statistical testing was two-sided and performed using a 5% significance level. In Study 51, the assessment of treatment successes used a logistics model with treatment and centre as factors. In Study 51, exploratory efficacy (e.g., TWSTRS subscale score) and safety variables were summarized by descriptive statistics.[13] No statistical analysis was performed for between-group difference for the exploratory efficacy outcomes (e.g., TWSTRS subscale) in Study 51.

In Study 45, a rank analysis of covariance for response variables was carried out as a sensitivity analysis. This method uses the ranks of the response variable and the covariates. Rank ANCOVA is an alternative to the classical parametric ANCOVA when the assumptions are not satisfied. This method ranks the data, where the lowest score is given a value of 1, the second lowest a value of 2, and so on. Formulas are provided such that an F statistic can be calculated to test the treatment effect.[9]

Multiplicity testing to control type I error was performed in Study 51,[10,13] but not in Study 45. In Study 51, the primary analysis used hierarchical testing and so no further adjustment for multiple comparisons was necessary within the primary analysis.[10] For secondary outcomes, with all secondary analyses adjusted for multiplicity, if a nonsignificant result was observed on a particular secondary outcome, then no claims were made for significant result(s) from analyses on lower-ranked secondary efficacy end point(s).[10] The ordering of the secondary end point testing is presented in Table 23 in Appendix 4. Based on the data reported in Table 23 in Appendix 4, the hierarchical testing failed at the change from baseline in SF-36 MCS scores at week 8 (P = 0.061). Therefore, no claims should be made for significant result(s) from analyses of any outcomes ranked lower than SF-36 MCS, such as SF-36 PCS. No claims should be made for significant result(s) from analyses for any exploratory outcomes (such as treatment success), which were not adjusted for multiplicity.

Analysis populations

In both Study 45 and Study 51, efficacy outcomes were evaluated based on the intention-to-treat (ITT) population, which included all randomized patients.[9,10,12,13] The per-protocol (PP) population comprised all patients in the ITT population who were not classified as major protocol violators, and was finalized before unblinding in both Study 45 and Study 51.[9,10] Safety was evaluated for all patients who received at least one dose of study medication, which was identical to the ITT population.

Patient Disposition

In Study 45, all 80 patients screened for enrolment (n = 80) were randomized. Discontinuation rates (described as "exited" by the manufacturer) from the DB phase [9,12] were [redacted], [redacted], and [redacted] in the aboBoNTA arm at weeks 4, 8, and 12, respectively. However, discontinuation rates (described as "exited" by the manufacturer) from the DB phase [9,12] were [redacted], [redacted], and [redacted] in the placebo group at weeks 4, 8, and 12, respectively. Thus, while overall discontinuation rates were very high, they were much higher in the placebo group than in the aboBoNTA group (Table 6) in this study. No detailed reason was provided for the discontinuation.

In Study 51, a total of [redacted] patients were screened across 20 centres. A total of [redacted] patients were randomized, with [redacted] patients and [redacted] patients in the aboBoNTA treatment group and placebo treatment groups, respectively. The discontinuation rates from the DB phase[10,13] were [redacted], [redacted], and [redacted] in the aboBoNTA arm at week 4,week 8, and week 12, respectively. However, the discontinuation rates from the DB phase [10,13] were [redacted], [redacted], and [redacted] in the placebo group at week 4, week 8, and week 12, respectively (Table 6). The discontinuation rates at week 8 and week 12 were also higher in the placebo group than in the aboBoNTA group. The most common reason for not completing the study was [redacted]. This was reported in [redacted] patients ([redacted]) in the placebo group compared with [redacted] patients ([redacted]) in the aboBoNTA group. Reasons for withdrawal from the study are also summarized in Table 6.

Table 6: Patient Disposition

	Study 45 Clinical Study Report[9] Truong [12]		Study 51[10] Truong [13]	
	aboBoNTA	Placebo	aboBoNTA	Placebo
Screened, N	[redacted]		[redacted]	
Randomized, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Exited from DB week 4	[redacted]	[redacted]	[redacted]	[redacted]
Exited from DB up to week 8	[redacted]	[redacted]	[redacted]	[redacted]
Exited from DB up to week 12	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from the DB phase up to week 12, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
• *Unspecified reason*	[redacted]	[redacted]		
• *Adverse event*	[redacted]	[redacted]	[redacted]	[redacted]
• *Insufficient clinical response*	[redacted]	[redacted]	[redacted]	[redacted]
• *Protocol violation*	[redacted]	[redacted]	[redacted]	[redacted]
• *Consent withdrawn*	[redacted]	[redacted]	[redacted]	[redacted]
• *Lost to follow-up*	[redacted]	[redacted]	[redacted]	[redacted]

	Study 45 Clinical Study Report[9] Truong [12]		Study 51[10] Truong [13]	
	aboBoNTA	Placebo	aboBoNTA	Placebo
• *PI & pt schedule conflicts*	[redacted]	[redacted]	[redacted]	[redacted]
• *No longer wanted to do blood draws*	[redacted]	[redacted]	[redacted]	[redacted]
Completed the DB				
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N	[redacted]	[redacted]	[redacted]	[redacted]
PP, N	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]	[redacted]

AboBoNTA = abobotulinumtoxinA; DB = double-blind; ITT = intention-to-treat; PI = principal investigator; PP = per-protocol; pt = patient.

[redacted]

Source: Consort table in submission,[3] CSRs,[9,10] Truong, et al.[12,13]

Exposure to Study Treatments

Both Study 45 and Study 51 were designed for a single aboBoNTA IM injection treatment. The dose of aboBoNTA was 500 U for all patients randomized to the aboBoNTA treatment group (Table 7). However, in Study 51, the full prepared injection volume (500 U) was not used in seven patients (three patients in the aboBoNTA group; four patients in the placebo group). Three patients in the aboBoNTA group received 350 U, 425 U, and 450 U, respectively. The four patients in the placebo group received 450 U, 450 U, 400 U, and 300 U of placebo, respectively.[10]

Table 7: Summary of Drug Exposure

	Study 45		Study 51	
	aboBoNTA	Placebo	aboBoNTA	Placebo
Dose (U)	500		500	
# of treatments	1		1	
Total dose (U)	500		500	
Duration of the study	12 wks		12 wks	

AboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); wks = weeks.

Source: Clinical Study Report.[9,10]

Critical Appraisal

Internal validity

The objectives of the studies were well defined. The randomization process was performed based on a randomization code generated a priori with adequate allocation concealment. Randomization was stratified by centre and patient with or without botulinum toxin treatment previously. Identical active and placebo vials were provided to maintain blinding for patients and investigators. However, there was a risk of unblinding in this trial as most patients would have had previous experience with botulinum toxin, were known to have previously responded to botulinum toxin, and would therefore expect a reduction in symptoms after the injection. Placebo patients would not experience this reduction in symptoms and therefore might be able to identify treatment based on response. This may account for a larger dropout rate in the placebo arm than in the treatment arm. Key baseline characteristics were balanced between treatment groups. Concomitant medication (especially analgesic) use was reported and well balanced in Study 51, but such information was not well reported in Study 45.

There is evidence of validation for the primary outcome (TWSTRS total score). The TWSTRS total score has been accepted by FDA and Health Canada for clinical research for CD. The sample sizes were determined based on the power (≥ 90%) to detect a difference of 6.4 points in Study 51,[13] or 9 points in Study 45, [12] on the TWSTRS total scale with a two-sided test at the 5% significance level (*P* = 0.05). However, the rationale for the threshold of the between-group difference was not indicated in Study 51, although the rationale for the difference of 9 points in Study 45 was based on a previous study by Lew (see Study 45 Clinical Study Report). ANOVA analysis was performed on the two RCTs for the primary outcomes. The covariates for ANOVA included study centre, treatment history (BoNT-experienced versus BoNT-naive), and baseline characteristics (such as baseline TWSTRS total score). All efficacy analyses were conducted on the ITT population. Analysis of the primary efficacy end point was also performed on the PP population to assess the robustness of the findings. Multiplicity testing was performed to control for type I error in Study 51, but not in Study 45.

While both studies were well-designed overall, some methodological limitations of the two RCTs (mainly in Study 45) need to be discussed in the interpretation of the results. In Study 45, a total of 15% of patients in the aboBoNTA group and 11% of patients in the placebo group initiated or changed concomitant treatment with benzodiazepines, narcotics, muscle relaxants, or antispasticity agents from six weeks before study entry up to the week 4 assessment. In addition, 5% of patients in the aboBoNTA group, and 1% of patients in the placebo group, initiated or changed concomitant treatment with benzodiazepines, narcotics, muscle relaxants, or antispasticity agents during the course of the study. Whether the concomitant medications were balanced in both treatment groups was not summarized or reported (for group 1 in Study 45, which is relevant to this review). Therefore, it was uncertain whether or not concomitant medication use or change (especially analgesic use) had some impact on the outcome assessment in Study 45.

In Study 45, a total of 60% and 77% of patients discontinued from the DB phase by week 8 in the aboBoNTA and placebo arms respectively. At week 12, 60% and 84% of patients discontinued from the DB phase. In Study 51, 7% of patients discontinued from the DB phase in both treatment groups at week 4; 18% of patients in the aboBoNTA group and 25% of patients in the placebo group discontinued from the DB phase at week 8; and the discontinuation rates were 18% and 38% in the aboBoNTA group and placebo group, respectively, by week 12. The baseline values were imputed for all those missing values at week 4, week 8, and week 12. Even though the majority of patients had an imputed baseline value that assumed no change, statistical significance was achieved. As pointed out in the FDA review report,[16] even though it is difficult to confirm, there might be a potential dropout bias in favour of aboBoNTA, considering that more people in the placebo group dropped out (thus, more people in the placebo group had baseline values imputed at end point). As such, more people in the placebo group showed no change from baseline (not even a placebo effect). This is especially important when interpreting the primary outcome (TWSTRS total score at week 4). In Study 45, a statistical testing hierarchy to control for type I error was not performed. Caution is warranted when interpreting findings for secondary or tertiary outcomes reported in Study 45. In Study 51, the SF-36 analysis was not based on the ITT population. Those who discontinued or had missing data tended to be sicker; therefore, using the available data may have produced a potentially biased estimation. Given the amount of missing data for the SF-36 analysis, the ability to draw conclusions is limited. Furthermore, in Study 51, the hierarchical testing failed at the change from baseline in SF-36 MCS scores at week 8 (*P* = 0.061). Therefore, no claims should be made for significant result(s) from analyses for any outcomes ranked lower than SF-36 MCS, such as SF-36 PCS. No claims should be made for significant result(s) from analyses for any exploratory outcomes (e.g., TWSTRS subscale scores [severity, disability, and pain] and treatment success), which were not adjusted for multiplicity.

External validity

According to the clinical expert consulted for this review, the populations enrolled in the trials would be representative of Canadian patients with mild to moderate CD (spasmodic torticollis). Subpopulation analysis data reported for patients based on previous BoNT treatment experience was reported in Study 51 but not in Study 45. In Study 51, the subgroup analysis showed a similar efficacy between BoNT-naive and BoNT-experienced patients in terms of the results for TWSTRS total score at weeks 4, 8, and 12. However, the two studies excluded patients who had a poor response to botulinum toxin. Therefore, it is not clear whether the findings reported in the two studies can be generalized to patients who had a poor response to BoNT treatment previously.

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.

Not all efficacy outcomes identified in the protocol groups were reported in the included pivotal studies. No data were available on CGI-I and PGI-I; SF-36 and the duration of effect were not assessed in Study 45. It should be noted that in Study 45, [redacted]

TWSTRS total score

In Study 45, the TWSTRS total scores at baseline (mean ± SD) were 45.1 ± 8.7 in the aboBoNTA group and 46.2 ± 9.4 in the placebo group, respectively. The adjusted mean change from baseline (mean ± SE) of TWSTRS total score at week 4 was 9.6 ± 2.0 points in the aboBoNTA group compared with 3.7 ± 1.8 points in the placebo group. The between-group mean difference of changes from baseline (aboBoNTA minus placebo) was statistically significant (–6.0 points; 95% CI, –10.6 to –1.3, *P* = 0.013) (Table 8). In Study 51, the adjusted least squares mean ± SE of change from baseline in TWSTRS total score at week 4 was 15.58 ± 1.95 in the aboBoNTA group compared with 6.74 ± 2.03 in the placebo group (*P* < 0.0001; 95% CI, –12.94 to –4.74). The improvement in TWSTRS total score observed for the aboBoNTA group at week 4 was maintained at week 8 and, to a lesser extent, at week 12 in both studies (Appendix 4, Table 20). [redacted]

Subgroup analysis data for TWSTRS total score in Study 45 and Study 51 are presented in Table 20 and Table 21 in Appendix 4. The results for TWSTRS total score at weeks 4, 8, and 12 demonstrate a similar efficacy between BoNT-naive and BoNT-experienced patients.[3,10]

Table 8: TWSTRS Total Score and Subscale Scores

	Study 45		Study 51	
	aboBoNTA (n = 37)	**Placebo (n = 43)**	**aboBoNTA (N = 55)**	**Placebo (N = 61)**
TWSTRS total score				
Baseline, M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 4				
M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Change from baselineMD ± SE at wk 4	[redacted]	[redacted]	[redacted]	[redacted]
Btw-group MD of change from baseline at wk 4, MD (95% CI), *P* value	[redacted]		[redacted]	
Week 12				
M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline[a] MD ± SE at wk 12	[redacted]	[redacted]	[redacted]	[redacted]
Missing data at week 12	[redacted]	[redacted]		
Btw-group MD of change from baseline at wk 12, MD (95% CI), *P* value	[redacted]		[redacted]	
TWSTRS severity (*P* value, NR)				
Baseline M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline[a] MD ± SD at wk 4	[redacted]	[redacted]	[redacted]	[redacted]
Btw-group MD of change from baseline at wk	[redacted]		[redacted]	

	Study 45		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (N = 55)	Placebo (N = 61)
4 MD (95% CI)				
TWSTRS disability (*P* value, NR)				
Baseline M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline[a] MD ± SD at wk 4	[redacted]	[redacted]	[redacted]	[redacted]
Btw-group MD of change from baseline at wk 4 MD (95% CI)	[redacted]		[redacted]	
TWSTRS pain (*P* value, NR)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline[a] MD ± SD at wk 4	[redacted]	[redacted]	[redacted]	[redacted]
Btw-group MD of change from baseline at wk 4 MD (95% CI)	[redacted]		[redacted]	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); ANCOVA = analysis of covariance; Btw = between; CI = confidence interval; M = mean; MD = mean difference; NR = not reported; SD = standard deviation; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; wk = week.

Note: Mean difference (aboBoNTA minus placebo) from ANCOVA analyses are presented as the difference between the adjusted mean changes from baseline for aboBoNTA and placebo with 95% CI. Inferential statistics were not calculated for the TWSTRS subscale scores.

Note: In Study 51, TWSTRS subscale scores were exploratory outcome and outside of the analysis hierarchy; therefore, no statistical analysis was performed for between-group difference for the TWSTRS subscales.

Source: Study 45 Clinical Study Report,[9] Truong 2005,[12] Study 51 Clinical Study Report,[10] and Truong 2010.[13]

TWSTRS subscale scores (severity, disability, pain)

The TWSTRS subscale scores for severity, disability, and pain were analyzed and reported as tertiary outcomes in Study 45. In Study 51, TWSTRS subscale scores were exploratory outcomes and outside of the analysis hierarchy; therefore, they were summarized by descriptive statistics and no statistical analysis was performed for between-group difference for the TWSTRS subscales. The change from baseline in TWSTRS subscale score for severity, disability, and pain at week 4, week 8, and week 12, reported in both RCTs, is summarized in Table 8 and in Appendix 4, Table 20.

TWSTRS severity scores

In Study 45, the TWSTRS severity subscale scores (mean ± SD) at baseline were 19.7 ± 2.6 in the aboBoNTA group and 20.5 ± 3.4 in the placebo group, respectively. At week 4, the mean TWSTRS severity score improved by 4.6 points from baseline in the aboBoNTA group compared with 2.1 points from baseline in the placebo group. The between-group difference (mean, 95% CI) of changes from baseline at week 4 was –2.5 (–4.5 to –0.5). In the aboBoNTA group, the mean TWSTRS severity score improved by 3.8 points and 2.4 points from baseline at week 8 and week 12, respectively, compared with an improvement of 1.7 points and 1.0 points from baseline at week 8 and week 12, respectively, in the placebo group. The between-group difference of changes from baseline at week 8 and week 12 were –2.1 (–4.0 to –0.2) and –1.3 (–3.0 to –0.4), respectively. In Study 51, the mean TWSTRS severity score at week 4 improved by 6.16 in the aboBoNTA group compared with 2.38 in the placebo group. The mean TWSTRS severity score improved by 6.04 and by 3.13 in the aboBoNTA group at week 8 and week 12, respectively, compared with 2.26 and 1.75 in the placebo group at week 8 and week 12, respectively. No statistical analysis was performed for between-group difference of changes from baseline for TWSTRS severity scores because it was an exploratory outcome and outside of the analysis hierarchy.

TWSTRS disability scores

In Study 45, the mean ± (SD) TWSTRS disability score at baseline was 13.9 ± 4.4 in the aboBoNTA group and 14.1 ±5.1 in the placebo group. At week 4, the mean TWSTRS disability score improved by 2.5 points from baseline in the aboBoNTA group compared with 0.6 points from baseline in the placebo group. The between-group difference (mean, 95% CI) of changes from baseline at week 4 was –1.9 (–3.5 to –0.4). The mean TWSTRS disability score improved by 2.1 points and 1.7 points from baseline

at week 8 and week 12, respectively, in the aboBoNTA group compared with an improvement of 0.2 points from baseline at week 8 and week 12 in the placebo group. The between-group difference of changes from baseline at week 8 and week 12 were –1.9 (–3.2 to –0.5) and –1.5 (–2.8 to –0.2) respectively. In Study 51, the mean TWSTRS disability score at week 4 improved by 3.85 in the aboBoNTA group compared with 1.50 in the placebo group. The mean TWSTRS disability score improved by 3.89 and 2.02 in the aboBoNTA group at week 8 and week 12, respectively, compared with 1.91 and 1.59 in the placebo group at week 8 and week 12, respectively. No statistical analysis was performed for the between-group difference in changes from baseline for TWSTRS disability scores because it was an exploratory outcome and outside of the analysis hierarchy.

TWSTRS pain scores

In Study 45, the mean (SD) TWSTRS pain score at baseline was 11.5 ± 3.8 in the aboBoNTA group and 11.7 ± 3.8 in the placebo group. At week 4, the mean TWSTRS pain score improved by 2.8 points from baseline in the aboBoNTA group compared with 1.2 points from baseline in the placebo group. The between-group difference (mean, 95% CI) of changes from baseline at week 4 was –1.6 (–3.6 to –0.3). Mean (SD) TWSTRS pain score improved by 2.1 points and 1.8 points from baseline at week 8 and week 12, respectively, in the aboBoNTA group compared with an improvement of 0.2 points and 0.4 points from baseline at week 8 and week 12, respectively, in the placebo group. The between-group differences in changes from baseline at week 8 and week 12 were –1.0 (–3.6 to –0.1) and –1.4 (–2.6 to –0.2), respectively. In Study 51, the mean TWSTRS pain score at week 4 improved by 3.74 in the aboBoNTA group compared with 1.35 in the placebo group. The mean TWSTRS pain score improved by 3.88 and 1.72 in the aboBoNTA group at week 8 and week 12, respectively, compared with 1.42 and 1.19 in the placebo group at week 8 and week 12, respectively. No statistical analysis was performed for between-group differences in changes from baseline for TWSTRS pain scores because it was an exploratory outcome and outside of the analysis hierarchy in Study 51, although all subscales showed numerically greater improvement in the aboBoNTA group than that the in placebo group from week 4 to week 12 (see Table 8 and Appendix 4, Table 20).

Patient's and investigator's VAS symptom assessments

The patient and investigator assessment of change in the signs and symptoms of CD at week 4 was a secondary efficacy analysis. It was assessed using a VAS, with the centre being no change from baseline. The VAS score (mean ± SD) at week 4 was 65.0 ± 19.2 mm in the aboBoNTA group compared with 48.6 ± 20.4 in the placebo group (*P* = 0.001) (Table 9). The patient's assessment of change in the signs and symptoms of CD at week 8 and week 12 was a tertiary efficacy end point. The patient assessment (mean ± SD) VAS score at week 8 was 59.8 ± 21.0 in the aboBoNTA group compared with 46.4 ± 13.5 in the placebo group (*P* = 0.002); and at week 12 was 51.9 ± 19.9 in the aboBoNTA group compared with 43.6 ± 9.5 in the placebo group (*P* = 0.022). (Table 9). The statistically significant improvement observed in the aboBoNTA group at week 4 was maintained at week 8 and week 12 and was more toward symptom-free in the aboBoNTA group compared with the placebo group at both week 8 and 12 (Table 9). By week 12, ratings of the signs and symptoms had nearly returned to baseline in the aboBoNTA group but remained significantly worse than baseline in the placebo group. No VAS for changes in signs and symptoms of CD were reported in Study 51.

Table 9: Patient and Investigator Visual Analogue Scale for Changes in the Signs and Symptoms of Cervical Dystonia

Study 45, VAS (mm)	Patient assessment		Investigator assessment	
	aboBoNTA N = 37	Placebo N = 43	aboBoNTA N = 37	Placebo N = 43
Secondary outcome				
Change at wk 4, M ± SD	65.0 ± 19.2	48.6 ± 20.4	66.2 ± 20.3	52.4 ± 14.9
Btw-group diff at wk 4, MD (95% CI), *P* value	15 (6.3 to 23.7), *P* < 0.001		13.8 (5.9 to 21.6)[a]	
Tertiary outcome				
Change at wk 8, M ± SD	59.8 ± 21.0	46.4 ± 13.5	58.0 ± 19.8	47.7 ± 13.9
Btw-group diff at wk 8; MD (95% CI), *P* value	12.9 (4.9 to 20.9); *P* = 0.002		10.4 (2.8 to 17.9)[a]	
Change at wk 12, M ± SD	51.9 ± 19.9	43.6 ± 9.5	51.2 ± 19.5	43.4 ± 10.0
Btw-group diff at wk12; MD (95% CI), *P* value	8.4 (1.2 to 15.5); *P* = 0.022		7.9 (1.1 to 14.6)[a]	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; diff = difference; CI = confidence interval; M = mean; MD = mean difference; SD = standard deviation; VAS = visual analogue scale; wk = week.

[a]No *P* value reported.

Source: Study 45 Clinical Study Report,[9] Truong 2005.[12]

Pain (visual analogue scale scores for pain)

In Study 45, patient VAS pain scale score at week 4 was a secondary efficacy analysis. At week 4, the change from baseline in the patient VAS pain scale score (mean ± SD) was statistically significantly greater in the aboBoNTA group compared with the placebo group (*P* = 0.024). The patient pain VAS improved from 48.6 ± 24.6 at baseline to 35.2 ± 22.3 at week 4 in the aboBoNTA group. In contrast, the patient VAS pain scale score (mean ± SD) was relatively unchanged in the placebo group and only improved from 52.9 ± 25.0 at baseline to 51.0 ± 26.9 at week 4 (Table 10). The mean changes from baseline at week 4 were –13.4 and –1.9 in the aboBoNTA group and the placebo group, respectively. The between-group difference (mean, 95% CI) of changes from baseline at week 4 was –11.4 (–21.3 to –1.5). Patient VAS pain scale score at week 8 and week 12 was a tertiary efficacy analysis. At week 8, the patient VAS pain scale score (mean ± SD) was 41.2 ± 27.2 in the aboBoNTA group, compared with 53.9 ± 26.3 in the placebo group. The between-group difference in change from baseline at week 8 was –8.8 (–16.4 to –1.1), which was statistically significantly (*P* = 0.025). However, at week 12, the patient VAS pain scale score was 45.5 ± 28.5 in the aboBoNTA group compared with 52.0 ± 26.5 in the placebo group. The between-group difference in changes from baseline at week 12 was –2.2 (–8.3 to 3.9), which was not statistically significantly different (*P* = 0.48). These analyses were performed on the ITT population using the patient's own baseline value for missing data. Analyses using different sensitivity analysis of imputing missing data (using a 5 mm increase from baseline) with no replacement of missing data led to similar findings and the same conclusion (data not presented). In Study 51, the VAS pain score change from baseline was an exploratory outcome. The VAS pain score changes from baseline in the aboBoNTA group were –17.7, –15.8, and –7.9 at week 4, 8, and 12 respectively. In the placebo group, the VAS pain score changes from baseline were –4.8, –4.2, and –4.5 at weeks 4, 8, and 12 respectively. No statistical analysis was performed for the between-group difference in changes from baseline for VAS pain scores because it was an exploratory outcome and outside of the analysis hierarchy.

Table 10: Pain Visual Analogue Scale

VAS (mm)	Study 45		Study 51	
	Dysport (n = 37)	Placebo (n = 43)	Dysport (n = 55)	Placebo (n = 61)
Baseline	48.6 ± 24.6	52.9 ± 25.0	47.4 ± 25.0	49.6 ± 24.5
Week 4	35.2 ± 22.3	51.0 ± 26.9	NR	NR
Change from baseline M ± SD at wk 4	–13.4	–1.9	–17.7 ± 24.4	-4.8 ± 24.6
Btw-group MD of change from baseline at wk 4 MD (95% CI), *P* value	–11.4 (–21.3 to –1.5), *P* = 0.024		NR	NR
Week 8	41.2 ± 27.2	53.9 ± 26.3	NR	NR
Change from baseline M ± SD at wk 8	NR	NR	–15.8 ± 30.9	-4.2 ± 23.6
Btw-group MD of change from baseline at wk 8 MD (95% CI), *P* value	–8.8 (–16.4 to –1.1), *P* = 0.025		NR	NR
Week 12	45.5 ± 28.5	52.0 ± 26.5	NR	NR
Change from baseline M ± SD at wk 12	NR	NR	–7.9 ± 27.5	-4.5 ± 31.5
Btw-group MD of change from baseline at wk 12 MD (95% CI), *P* value	–2.2 (–8.3 to 3.9), *P* = 0.48		NR	NR

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CI = confidence interval; M = mean; MD = mean difference; SD = standard deviation; wk = week.

Note: In Study 51, VAS pain score was an exploratory outcome and outside of the analysis hierarchy; therefore, no statistical analysis was performed for between-group difference for VAS pain score.

Source: Study 45 Clinical Study Report[9] and Study 51 Clinical Study Report.[10]

Disability

Disability was assessed with the TWSTRS disability score. See Table 8 in section 3.6.2 and Appendix 4, Table 20.

Short Form 36 Health Survey

In Study 51, at week 8, it was reported that there was no statistically significant change from baseline for the SF-36 MCS (see Table 11 and Appendix 4, Table 22). The SF-36 PCS and SF-36 MCS scores had improved in patients in the aboBoNTA group at week 8. At week 8, patients in the aboBoNTA group scored higher than patients in the placebo group in both the SF-36 PCS (aboBoNTA group mean ± SD: 43.70 ± 8.76; placebo group: 42.49 ± 8.84) and SF-36 MCS (aboBoNTA group mean ± SD: 49.00 ± 8.69; placebo group: 43.41 ± 12.30) scores. In Study 51, the SF-36 was not assessed at week 12. The SF-36 was not assessed in Study 45.

Table 11: SF-36 Data in Study 51

Study 51		aboBoNTA (N = 55)		Placebo (N = 61)	
		Score	Change from baseline	Score	Change from baseline
Mental Health Summary					
Baseline	N	[redacted]	[redacted]	[redacted]	[redacted]
	M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	N	[redacted]	[redacted]	[redacted]	[redacted]
	M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Physical Health Summary					
Baseline	N	[redacted]	[redacted]	[redacted]	[redacted]
	M ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	N	[redacted]	[redacted]	[redacted]	[redacted]
	M ± SD	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; SD = standard deviation.

Source: Study 51 Clinical Study Report.[10]

Treatment response

The proportion of responders was reported in both RCTs. In Study 45, the proportion of treatment responders at weeks 4, 8, and 12 was a tertiary efficacy analysis. Patients were classified as responders if the decrease in TWSTRS total score was ≥ 30% and at least 10 points, compared with the baseline score. All other patients were classified as non-responders. The proportion of responders in the aboBoNTA group was higher than in the placebo group (aboBoNTA versus placebo) at week 4 (38% versus 16%), week 8 (27% versus 9%), and week 12 (19% versus 7%) (Table 12). At week 4, more than twice as many patients in the aboBoNTA group (14 of 37, 38%) as patients in the placebo group (7 of 43, 16%) met the criteria for a therapeutic response (difference in proportion of responders, 22%; 95% CI, 2% to 41%). In Study 51, the proportion of responders was an exploratory end point. The proportion of responders was numerically higher in the aboBoNTA group than in the placebo group at week 4, week 8, and week 12; this was statistically significant at week 4 and week 8 (Table 12).

Table 12: Responders (Intention-to-Treat)

Responder[a]	Study 45		Study 51	
	aboBoNTA N = 37	Placebo N = 43	aboBoNTA N = 55	Placebo N = 61
Week 4				
n (%)	14 (38)	7 (16)	27 (49)	10 (16)
Btw-group difference, % (95% CI)	22 (2 to 41)		33 (17 to 49)	
Week 8				
n (%)	10 (27)	4 (9)	27 (49)	7 (11)
Btw-group difference, % (95% CI)	18 (1 to 34)		38 (22 to 53)	
Week 12				
n (%)	7 (19)	3 (7)	13 (24)	7 (11)
Btw-group difference, % (95% CI)	12 (–3 to 27) NSS		13 (–2 to 26) NSS	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CI = confidence interval; NSS = not statistically significant.

Note: The mean between-group difference (%) was calculated by CADTH. The 95% CI for the mean between-group difference (%) was reported in clinical study reports.

a Responders were those patients who had a decrease in TWSTRS total score of at least 30% in both studies[9,10] and at least 10 points compared with baseline in Study 45.[9]

Source: CSR for studies 45 and 51.[9,10]

Investigator's global assessment – efficacy and safety/treatment success

Investigator global assessment of efficacy and safety and treatment success were determined based on the investigator global assessment of efficacy and safety as presented in Table 13 and Table 14, respectively. In Study 45, a global assessment of efficacy and safety was performed by the investigator at the end of the study (week 12). Overall treatment success was defined as a global efficacy assessment of at least moderate improvement and a global safety assessment of no worse than moderate in regard to AEs. Patients who did not satisfy this definition were classified as treatment failures. More patients in the aboBoNTA group (35%) than patients in the placebo group (23%) were considered treatment successes. At week 12, there was no statistically significant difference between aboBoNTA and placebo in terms of treatment success; however, this should be interpreted with caution due to the very high discontinuation rate in the DB phase.

In Study 51, the proportion of patients considered treatment successes, as a secondary end point, was assessed using a logistic model with treatment strata (BoNT-naive or BoNT-treated), and treatment centre as factors in the model. The odds ratio of the number of successes on aboBoNTA versus placebo was summarized for the ITT population. However, treatment successes as an outcome ranked lower than the SF-36 MCS in the hierarchy test, where the hierarchy test was failed (i.e., not significant); therefore, no claim should be made for the statistically significant difference between treatment groups (Table 14).

Table 13: Investigator Global Assessment of Efficacy and Safety

Week 12	Study 45		Study 51	
	aboBoNTA (N = 37)	placebo (N = 43)	aboBoNTA (N = 55)	placebo (N = 61)
Investigator global assessment – *efficacy*, n (%)				
Much better	[redacted]	[redacted]	[redacted]	[redacted]
Better			[redacted]	[redacted]
No change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Worse	[redacted]	[redacted]	[redacted]	[redacted]
Much worse	[redacted]	[redacted]	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]	[redacted]	[redacted]
Investigator global assessment – *safety* n (%)				
None	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]
Extreme	[redacted]	[redacted]	[redacted]	[redacted]
Nor record	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); N = number of patients in a specific group; n = number of patients with event.

Note: Percentages in Study 45 were calculated by CADTH.

[a] Reported as “excellent,” “good,” “moderate,” and “slight” (improvement) and re-grouped by CADTH.

[b] Reported as “slightly worse” and “worse” and re-grouped by CADTH.

Source: CSRs.[9,10]

Table 14: Treatment Successes at Week 12

Treatment successes[a]	Study 45		Study 51	
	aboBoNTA (N = 37)	Placebo (N = 43)	aboBoNTA (N = 55)	placebo (N = 61)
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Btw-group difference (aboBoNTA vs. placebo), % (95% CI)	[redacted]		[redacted]	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CI = confidence interval.

Note: Patients with a global efficacy assessment of “Better” or “Much better” and a safety assessment of no worse than “Moderate” were defined as treatment successes. The odds ratio represents the odds of success on abobotulinumtoxinA versus placebo stratified for strata and country.

[a] Overall treatment success is defined by a global efficacy assessment of at least moderate improvement and a global safety assessment of no worse than moderate.

[b] Logistic regression analysis.

Source: CSRs.[9,10]

Duration of effect

The duration of effect or duration of response (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. It was only calculated for patients who responded. Re-treatment was indicated if the response to treatment on the TWSTRS total score was no better than a 10% decrease from baseline.[12] In Study 45 (Truong 2005[12]), it was reported that for the patients who responded to aboBoNTA, the duration of the effect (mean ± SD) was 22.8 ± 12.5 weeks and the median duration was 18.5 weeks (range: 9 weeks to 46 weeks) (Appendix 4, Table 25). In the open-label extension phase of Study 45,(i.e., Study 45b),[11] all patients received an initial dose of 500 U of aboBoNTA, followed by dose titration up or down based on safety and efficacy response (250 U to 1,000 U), [redacted] (Appendix 4-Table 25. Table 15)

In Study 51, [redacted]. Re-treatments were measured in the open-label phase (Study 731[22]). [redacted] Overall range of the duration of the effect was [redacted] weeks to [redacted] weeks (Table 15 and Appendix 4, Table 25).

Table 15: Duration of Action in Study 45 and Study 51 (Double-Blind and Open-Label Phase)

Study 45	Study 45 (DB)		Study 45b (Study 45 OL phase)		
			re-treatment 1 (N = 131)	re-treatment 2 (N = 121)	re-treatment 3 (N = 111)
	aboBoNTA	Placebo	aboBoNTA		
N of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of action (wks), M ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value (aboBoNTA vs. placebo)	[redacted]		[redacted]		
Study 51	**Study 51 (DB)**		**Study 731 (Study 51 OL phase)**		
			Cycle 2	Cycle 3	Cycle 4
	Dysport	Placebo	aboBoNTA		
N of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of action (wks), M ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value (aboBoNTA vs. placebo)	[redacted]		[redacted]		

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); OL = open-label; M = mean; SD = standard deviation; vs. = versus.

Note: Re-treatment was indicated if the response to treatment on the TWSTRS total score was no better than a 10% decrease from baseline.

Source: CSRs.[9-11,22]

Harms

Only those harms identified in the review protocol are reported here. See Appendix 4 for detailed harms data.

Adverse events

The incidence of TEAEs in Study 45 (Group 1 only) and Study 51 is presented in Table 16. In Study 45, 92% patients in the aboBoNTA group reported at least one TEAE, compared with 79% in the placebo group. The most common TEAEs (≥ 15%) in the aboBoNTA group (and numerically higher than in the placebo group) include injection site pain (38%), neck or shoulder pain (38%), tiredness (35%), headache (24%), dry mouth (22%), dysphagia (16%), and neck muscle weakness (16%). In Study 51, the incidence of TEAEs was much lower compared with that reported in Study 45 (Table 16). A total of 47% patients treated with aboBoNTA reported at least one TEAE, compared with 44% reported in placebo group. The most common TEAEs (≥ 5%) in the aboBoNTA group (and numerically higher than that in the placebo group) include dysphagia (9%) and injection site pain (5%) (Table 16).

Table 16: Adverse Events

AE	Study 45[a]		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (n = 55)	Placebo (n = 61)
# of pts with any TEAE n (%)	34 (92)	34 (79)	26(47)	27(44)
# of pts with AEs (≥ 5% incidence), n (%)	NR	NR	26 (47)	27 (44)
Injection site pain	14 (38)	10 (23)	3 (5)	2 (3)
Neck or shoulder pain	14 (38)	13 (30)	3 (5)	3 (5)
Tiredness	13 (35)	13 (30)	NR	NR
Headache	9 (24)	10 (23)	2 (4)	2 (3)
Dry mouth	8 (22)	8 (19)	NR	NR

AE	Study 45[a]		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (n = 55)	Placebo (n = 61)
Neck muscle weakness	6 (16)	5 (12)	NR	NR
Dysphagia	6 (16)	4 (9)	5 (9)	0
Neck rigidity	5 (14)	4 (9)	NR	NR
Blurred vision	5 (14)	0	NR	NR
Voice alteration	4 (11)	4 (9)	NR	NR
Dyspnea	4 (11)	1 (2)	NR	NR
Insomnia	4 (11)	1 (2)	NR	NR
Muscle weakness	4 (11)	0	NR	NR
Viral infection	4 (11)	2 (5)	NR	NR
Dizziness	3 (8)	2 (5)	NR	NR
Back pain	3 (8)	3 (7)	NR	NR
Sinusitis	3 (8)	1 (2)	NR	NR
Bronchitis	3 (8)	1 (2)	NR	NR
Rhinitis	3 (8)	1 (2)	NR	NR

AE = adverse event; aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); NR = not reported (may include those AEs with incidence ≤ 5%); pts = patients; TEAE = treatment-emergent adverse event.

[a] In Study 45, [redacted]

Source: CSRs.[9,10]

Serious adverse events

In Study 45, SAEs were reported more frequently in the aboBoNTA group (14%) than in the placebo group (2%). In Study 51, only one patient in the placebo group (2%) reported an SAE (Table 17).

Table 17: Serious Adverse Events

SAE	Study 45[a]		Study 51	
	aboBoNTA (N = 37)	Placebo (N = 43)	aboBoNTA (N = 55)	PLACEBO (N = 61)
# of 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]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); pts = patients; SAE = serious adverse event.

[a] In Study 45, [redacted]

Source: CSRs.[9,10]

Withdrawals due to adverse events

No patient withdrawal due to AEs was reported in either of the two RCTs.

Mortality

No death was reported in either of the two RCTs.

Notable harms

Anti-Dysport antibodies, dysphagia, paralysis, and injection site reactions are identified as the notable harms (i.e., the harms of interest to the review). At baseline, in the aboBoNTA group, [redacted]% of patients in Study 51 and [redacted]% of patients in Study 45 showed positive anti- Dysport antibody; [redacted]% of patients in Study 51 and [redacted]% of patients in the placebo group showed positive anti-Dysport antibody. Among those patients with negative antibodies, [redacted] converted from negative to positive at 12 weeks after aboBoNTA treatment in either of the RCTs (Table 18).

Dysphagia and injection site pain were reported more frequently in the aboBoNTA group than in the placebo group (Table 16). No paralysis was reported in either of the two RCTs.

Table 18: Neutralizing Antibody Status

	Study 45		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (n = 55)	Placebo (n = 61)
Negative, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Not recorded, n (%)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic).

Source: CSRs for Study 45 and Study 51.[9,10]

Discussion

Summary of Available Evidence

Two similarly designed, pivotal, placebo-controlled RCTs (Study 45 and Study 51) met the inclusion criteria. Both RCTs enrolled adult patients with CD (TWSTRS total score > 30, TWSTRS severity subscore > 15, TWSTRS disability subscore > 3, TWSTRS pain subscore > 1) who were BoNT-naive or BoNT-experienced. Both RCTs assessed the efficacy and safety of a single aboBoNTA IM injection versus placebo in the treatment of patients with CD. The primary outcome was the TWSTRS total score at week 4 after the treatment. Other outcomes included TWSTRS total score measured at week 8 and week 12, TWSTRS subscale score, patient and investigator assessments (VAS for CD symptoms and signs), VAS pain score, SF-36, investigator's global assessment, treatment response, treatment success, duration of effect, and AEs.

The long-term efficacy and safety findings of the aboBoNTA treatment in CD from the open-label extension phase of Study 45 and Study 51 are presented in Appendix 6. Results from both open-label extension studies demonstrated that the efficacy of repeated use of aboBoNTA in reducing the symptoms and signs of CD appeared to be maintained. No new safety signals were identified.

Four potentially relevant RCTs comparing aboBoNTA with onaBoNTA assessed the clinical dose equivalence of aboBoNTA versus onaBoNTA at various dose ratios (AboBoNTA versus onaBoNTA ratio: 1.7: 1 to 4:1). The objectives of all four RCTs were to establish the appropriate dose ratio for aboBoNTA versus onaBoNTA. The dose used in the trial was not fixed, but based on individual patient needs. The average dose of aboBoNTA in the four RCTs was all lower than the Health Canada–recommended initial dose (i.e., < 500 U). The findings of the four onaBoNTA-controlled RCTs are summarized in Appendix 7, as they did not meet the inclusion criteria for the systematic review.

No RCTs were identified that directly compared aboBoNTA with incoBoNTA in this review. However, the network meta-analysis by Han et al. [23] and the manufacturer's submitted indirect treatment comparisons (ITCs)[24] reported that the efficacy and safety profiles of aboBoNTA, onaBoNTA, and incoBoNTA appeared similar at week 4 after injection in the treatment of patients with CD. The incidences of dysphagia and injection site pain were similar between treatment and placebo groups (Appendix 8).

Interpretation of Results

Efficacy

The primary efficacy outcomes for the two pivotal RCTs (Study 45 and Study 51) were the changes from baseline in TWSTRS total score at week 4. Efficacy results from Study 45 and Study 51 indicated a treatment effect and were consistent across primary and most of the secondary outcomes, demonstrating that aboBoNTA is more effective than placebo for reducing the symptoms and signs of CD (ST). In both studies, a statistically significant greater improvement in TWSTRS total score was reported in the aboBoNTA group than in the placebo group. The between-group mean difference of changes from baseline (aboBoNTA minus placebo) was statistically significant. According to the clinical experts involved in this review, the observed difference (–6.0 in Study 45) was considered clinically meaningful, although no information was found as to what constitutes a clinically meaningful difference in TWSTRS scores. The analyses of the secondary and tertiary efficacy outcomes consistently demonstrated greater improvement for patients with aboBoNTA. Various sensitivity analyses (such as PP analysis) achieved a similar result as the primary analysis. In addition, statistically significantly more patients in the aboBoNTA group than in the placebo group were classified as responders to treatment at week 4 and week 8.

However, the following methodological limitations of the RCTs must be acknowledged. Study 45, in particular, should be considered when interpreting the results reported in the two RCTs.

First, the use of concomitant medication: In Study 45, [redacted]. A total of 15% patients in the aboBoNTA group and 11% in the placebo group started or changed concomitant treatment with

benzodiazepines, narcotics, muscle relaxants, or antispasticity agents from six weeks before study entry up to week 4 after the study; and 5% of patients in the aboBoNTA group and 1% of patients in the placebo group started or changed those concomitant medications during the study. Therefore, it is uncertain whether the concomitant medication use or change of use (especially of analgesics) had an effect on the outcome assessment in Study 45.

Second, in Study 45, a total of 60% and 77% of patients discontinued from the DB phase by week 8 in the aboBoNTA group and in the placebo group, respectively. At week 12, 60% and 84% patients discontinued from the DB phase. In Study 51, 7% of patients discontinued from the DB phase in both treatment groups at week 4. A total of 18% of patients in the aboBoNTA group and 25% of patients in the placebo group discontinued from the DB phase at week 8. The discontinuation rates were 18% and 38% in the aboBoNTA group and placebo group, respectively, by week 12.

The baseline values were imputed for all those missing values at week 4, week 8, and week 12. Even though the majority of patients imputed baseline value, statistical significance was achieved. As pointed out in the FDA review report, [16] there may be a potential dropout bias in favour of aboBoNTA. Since more patients in the placebo group dropped out, more patients in the placebo group had baseline values imputed at end point; thus, more patients in the placebo group showed no change from baseline (not even a placebo effect). This negates the benefit of having a placebo control group, which may be of particular importance in trials with pain as an outcome, as the documented placebo effect in analgesia trials can be meaningful. This is especially important when interpreting the primary outcome for Study 45 (TWSTRS total score at week 4).

Third, in Study 45, a statistical testing hierarchy to control type I error was not performed. Caution is warranted when interpreting findings for secondary or tertiary outcomes reported in Study 45. QoL measured with SF-36 was only reported in Study 51. However, SF-36 was not analyzed based on ITT population. In addition, SF-36 assessment failed in the hierarchical testing; therefore, it is inconclusive for the effect of aboBoNTA on improving QoL, a key outcome to patients with CD. The results reported for the duration of the effect in both studies should be interpreted with caution because of the high dropout rate reported in both studies after week 4.

In both RCTs, patients who were BoNT non-responders previously were excluded and the majority of the patients had a stable therapeutic response to BoNT treatment. However, the clinical expert consulted in this review pointed out that, clinically, it is unlikely that a physician or patient would switch from the current treatment to aboBoNTA if a patient already had a clinical response to the current BoNT (onaBoNTA or incoBoNTA) treatment. Therefore, whether the findings from the two pivotal RCTs can be generalized to patients who are poor or non-responsive to BoNT treatment is uncertain.

Harms

In general, the safety profile for aboBoNTA was similar to that for placebo. In Study 45, it showed a numerically higher incidence in aboBoNTA groups (5% greater than placebo) for injection site pain (38% versus 23%), neck or shoulder pain (38% versus 30%), and tiredness (35% versus 30%) than in the placebo group in both RCTs. The overall incidence of AEs reported in Study 51 was much lower than in Study 45, which may be due to the differences in AE reporting between the two studies. In Study 45, AEs were assessed according to a checklist of 10 conditions considered to be associated with botulinum toxin therapy of neck muscles (dysphagia, dry mouth, voice changes, neck muscle weakness, jaw weakness, limb weakness, tiredness, respiratory difficulties, discomfort at injection site, and visual difficulties). In Study 51, a checklist was not described.[9] In both studies, SAEs were rarely reported. During the DB phase, no patients withdrew due to an AE. No patients died in either of the studies. After one treatment with aboBoNTA, there was little difference between aboBoNTA and placebo with regard to neutralizing antibody status. However, the data to assess the clinical impact of developing antibodies are limited, as pointed out in the Health Canada review report.[1]

Potential place in therapy

CD is the most common focal dystonia and is characterized by sustained involuntary contractions of the cervical muscles, leading to painful and disabling postures. The diagnosis is made clinically without the need for additional laboratory testing or imaging.

BoNT therapies are the gold standard in the treatment of CD[25] and for other focal dystonias. Among therapies, aboBoNTA appears to be comparable to the other approved BoNT therapies for CD. Clinical trial evidence indicates that a starting dose of 500 U of aboBoNTA is clinically and statistically more effective than placebo for reducing the signs and symptoms of CD and is safe and well tolerated. Maximal effect appears to be between four and eight weeks after treatment.

Although doses of 250 U to 500 U are preferred, [26] a much lower dose of aboBoNTA (even as little as 100 units) has also been advocated. If this is confirmed, substantial wastage of the 500 U vial will be likely. However, the availability of 300 U vials of aboBoNTA would minimize wastage of the 500 U vial.

Deficiencies in current therapy include the duration of effect of all BoNT agents, leading to the need for repeated dosing at about three-month intervals, and for doses to be individualized for each patient, which is a clinical judgment.

Conclusions

Based on the primary outcome of the two pivotal RCTs (change from baseline in total TWSTRS score) and other outcomes — including patient and investigator VAS and CD symptom assessment — it was demonstrated that aboBoNTA is statistically significantly more effective than placebo in reducing the symptoms and signs of CD at four weeks to 12 weeks post-treatment. However, high rates of dropouts in the placebo arm and how those patients were handled limits the ability to assess the validity of the difference observed between groups after week 4. As most patients included in the trials were previously known to respond to botulinum toxin treatment, the effect in patients who are previous poor or non-responders to treatment is uncertain. The effect of aboBoNTA on QoL (assessed using the SF-36), a key outcome in CD, was inconclusive and potentially biased due to missing data. Overall AEs appeared similar in patients treated with aboBoNTA and patients in the placebo group. The short duration of the RCTs does not permit adequate assessment of antibody development during the DB phase. The open-label extension phase of the two RCTs showed a similar efficacy and safety profile as reported in the DB phase. Health Canada's approved 500 U dose-equivalency to onaBoNTA (2.5:1) was based on the two pivotal, placebo-controlled trials (Study 45 and Study 51). A network meta-analysis by Han et al. and an ITC submitted by the manufacturer found that the efficacy and safety profiles are similar in aboBoNTA, onaBoNTA, and incoBoNTA at week 4 after injection. No direct evidence (for the Health Canada–approved dose regimen) assessed the duration of effect with the aboBoNTA treatment compared with [redacted] and incoBoNTA in the treatment of CD.

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

The Dystonia Medical Research Foundation Canada (DMRFC) submitted input for this review. The DMRFC is a registered non-profit Canadian charity organization. The organization focuses on dystonia research, education and awareness, and represents the needs of the dystonia patient population in Canada.

In the past 12 months, DMRFC has received financial support from Allergan Inc., Merz Pharma Canada Ltd., and Ipsen Biopharmaceuticals Canada, Inc. for a number of different educational and awareness initiatives. No conflicts of interest were declared for this submission.

2. Condition-Related Information

Information for this section was obtained from several sources: an online patient survey conducted between January 23, 2017 and February 9, 2017; three patient questionnaires (February and March 2016) that were administered online via social media channels; and testimonies gathered through social media and online discussion boards. A total of 80 patients (in whole or in part) participated in the survey. In addition, a separate survey was conducted to gain insights into the caregiver experience. This caregiver online survey was launched on January 23, 2017 and ran through February 9, 2017. It was promoted in the same manner as the patient survey. In total, three people participated (in whole or in part) in the caregiver survey.

Patients with cervical dystonia (CD) experience various types of physical and emotional distress as a result of their condition. Physically, patients highlight neck pain as an important symptom to control. Patients also suffer from involuntary muscle action that causes twisting of the torso, shaking and twisting of the head, and general tremors. These physical experiences inadvertently lead to limitations in physical activity; many patients are no longer able to work, are unable to engage in any physical activity, and can no longer enjoy or participate in leisure and social events. The pain, isolation, and physical limitations erode patients' autonomy, confidence, and sense of well-being, and put them at risk of depression and anxiety.

One patient with CD describes the following impacts of the condition: *"lost self-confidence/self-esteem, depression, difficulty to function & do daily simple tasks like eating and enjoying a meal, doing some house cleaning, study for a course or going back to school, difficulty to drive to check turn neck to check blind spot view, being a proactive and active citizen*." Close family members acting as caregivers are also affected; the responders indicated that the condition creates high demands on their personal time. They also identified that frequent visitation to different specialists was a challenge.

3. Current Therapy-Related Information

Information for this section was obtained from an online patient survey conducted between January 23, 2017 and February 9, 2017, from three patient questionnaires (February and March 2016) administered online via social media channels, and from testimonies gathered through social media and online discussion boards.

The majority of the patients who responded to the survey had tried Botox (onaBoNTA, onabotulinumtoxinA) (85.3%), while just over two-thirds had tried some sort of unspecified oral treatment. Patients have attempted a variety of options, including physiotherapy, acupuncture, yoga for dystocia, dry cupping, medical marijuana, and others. This may indicate a strong lack of satisfaction with mainstream therapies and that patients are constantly on the lookout for new therapies.

When they responded to the survey, about three-quarters of the responders were using a neurotoxin (onaBoNTA [62%] or Xeomin [13%]); half were taking an unspecified oral medication; and less than one-third were using other modalities of treatment, such as physiotherapy. However, only a handful of patients (four) reported that their current treatment provided "excellent" control of their headaches, while another six responders reported headache control as "very good." With respect to neck pain, which was described as the most important symptom patients would like to control, just under one-quarter thought their current treatment provided

"excellent" or "very good" control of this symptom. Two adverse events (AEs) were reported frequently by the responders: "muscle weakness near injection area" and "headaches, muscle stiffness, neck or back pain."

Financial difficulty in accessing therapy was a frequent theme among responders, with 59% saying they had experienced financial challenges as a result of their CD therapy. Less than one-quarter of the responders also reported inability to travel to receive treatment. One patient stated: *"I have to travel to Toronto from Sudbury every 3 months."*

4. Expectations About the Drug being Reviewed

Three telephone interviews informed this section.

DMRFC conducted two telephone interviews with patients or their caregivers who had experience with aboBoNTA. In both interviews, the interviewee made positive remarks about the lower frequency of injection with aboBoNTA compared with onaBoNTA. One of the interviewees felt that aboBoNTA helped more with their CD, noting that they had trouble swallowing with onaBoNTA, but not with aboBoNTA. The second interviewee was a caregiver who felt that both aboBoNTA and onaBoNTA had similar efficacy in the management of CD.

A third patient was interviewed regarding their overall experience. This patient mentioned that they live in Sudbury and have to take a trip to Toronto every three weeks for treatment. The patient felt that more support should be available in Sudbury, and that patients should not be expected to travel such long distances.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 1, 2017
Alerts:	Weekly search updates until June 21, 2017
Study Types:	health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and controlled clinical trials
Limits:	No date limits Human only English only Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
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 character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
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
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE SEARCH	
#	**Searches**
1	exp Torticollis/ or exp Dystonia/ or exp Dystonic Disorders/
2	(Torticolli* or wryneck or wry neck).ti,ab,kf,kw,ot,hw.
3	((cervical or neck*) adj3 (dyston* or spasmod*)).ti,ab,kf,kw,ot,hw.
4	((contract* or spasm* or torsion) adj3 (cervical or craniocervical or neck*)).ti,ab,kf,kw,ot,hw.
5	1 or 2 or 3 or 4
6	(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).ti,ab,kf,kw,ot,hw,rn,nm.
7	(CNT52120 or CNT 52120 or "953397358" or 95339735 8 or 953397 358).ti,ab,kf,kw,ot,hw,rn,nm.
8	6 or 7
9	exp Botulinum Toxins, Type A/
10	(BoNT or BoNTA* or BoNT A* or BTA or BTXA or BTX A or BTX).ti,ab,kf,kw,ot,hw,rn,nm.
11	(botulin* adj3 (typeA or type A)).ti,ab,kf,kw,ot,hw,rn,nm.
12	(botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kf,kw,ot,hw,rn,nm.
13	9 or 10 or 11 or 12
14	5 and 8
15	5 and 13
16	14 or 15
17	16 use ppez
18	exp torticollis/ or exp dystonia/ or exp cervical dystonia/ or exp dystonic disorder/
19	(Torticolli* or wryneck or wry neck).ti,ab,kw.
20	((cervical or neck*) adj3 (dyston* or spasmod*)).ti,ab,kw.
21	((contract* or spasm* or torsion) adj3 (cervical or craniocervical or neck*)).ti,ab,kw.
22	18 or 19 or 20 or 21
23	(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).ti,ab,kw.
24	22 and 23
25	exp botulinum toxin A/
26	(BoNT or BoNTA* or BoNT A* or BTA or BTXA or BTX A or BTX).ti,ab,kw.
27	(botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kw.
28	(botulin* adj3 (typeA or type A)).ti,ab,kw.
29	25 or 26 or 27 or 28
30	22 and 29
31	24 or 30
32	31 use oemezd

MULTI-DATABASE SEARCH	
#	**Searches**
33	17 or 32
34	exp animals/
35	exp animal experimentation/ or exp animal experiment/
36	exp models animal/
37	nonhuman/
38	exp vertebrate/ or exp vertebrates/
39	or/34-38
40	exp humans/
41	exp human experimentation/ or exp human experiment/
42	or/40-41
43	39 not 42
44	33 not 43
45	meta-analysis.pt.
46	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
47	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
48	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
49	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
50	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
51	(handsearch* or hand search*).ti,ab,kf,kw.
52	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
53	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
54	(meta regression* or metaregression*).ti,ab,kf,kw.
55	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
56	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
57	(cochrane or (health adj2 technology assessment) or evidence report).jw.
58	(meta-analysis or systematic review).md.
59	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
60	(outcomes research or relative effectiveness).ti,ab,kf,kw.
61	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kf,kw.
62	or/45-61
63	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.

MULTI-DATABASE SEARCH	
#	**Searches**
64	Randomized Controlled Trial/
65	exp Randomized Controlled Trials as Topic/
66	"Randomized Controlled Trial (topic)"/
67	Controlled Clinical Trial/
68	exp Controlled Clinical Trials as Topic/
69	"Controlled Clinical Trial (topic)"/
70	Randomization/
71	Random Allocation/
72	Double-Blind Method/
73	Double Blind Procedure/
74	Double-Blind Studies/
75	Single-Blind Method/
76	Single Blind Procedure/
77	Single-Blind Studies/
78	Placebos/
79	Placebo/
80	Control Groups/
81	Control Group/
82	(random* or sham or placebo*).ti,ab,hw,kf,kw.
83	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
84	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
85	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
86	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
87	allocated.ti,ab,hw.
88	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
89	or/63-88
90	44 and 62
91	44 and 89
92	90 or 91
93	92 not conference abstract.pt.
94	limit 93 to english language
95	remove duplicates from 94

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

Grey Literature

Dates for Search:	February 24, 2017.
Keywords:	Drug name, Indication
Limits:	No date limits used, English language only

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

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

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Study 24[17,27]	Intervention not of interest (dose lower than recommended dose)
Study 227 (Yun et al.)[18]	Intervention not of interest (dose lower than recommended dose)
Study by Rystedt et al.[19]	Intervention not of interest (dose lower than recommended dose)
Study by Ranoux et al.[20]	Intervention not of interest (dose lower than recommended dose)
POEWE et al. (2016) [28]	Comparator not of interest (non-pivotal placebo control; intervention not the approved dose form [liquid solution Dysport])
BARBOSA et al.[29]	Comparator not of interest (Prosigne)
MORDIN et al.[30]	Comparator not of interest (placebo)
PAPPERT et al.[31]	Intervention not of the interest (Botox, not Dysport)
COMELLA et al.[32]	Intervention not of the interest (Botox, not Dysport)
NAUMANN et al.[33]	Comparator not of interest (BoNT-A versus BoNT-A)
POEWE et al. (1998)[34]	Comparator not of interest (non-pivotal placebo RCT)
WISSEL et al.[35]	Comparator not of interest (non-pivotal placebo RCT)
BRANS et al.[36]	Comparator not of interest (trihexyphenidyl, anticholinergics)
LORENTZ et al.[37]	Comparator not of interest (non-pivotal placebo RCT)
HEFTER et al. 2013[38]	Study design not of interest (not RCT)
HEFTER et al. 2011[39]	Study design not of interest (not RCT)
HAUSER et al.[40]	Study design not of interest not RCT)
BRASHEAR et al.[41]	Intervention and comparator not of interest (toxin B versus placebo)

Botox = onabotulinumtoxinA (onaBoNTA); BoNTA = botulinum toxin A; Prosigne = Chinese botulinum toxin serotype A; RCT = randomized controlled trial.

Appendix 4: Detailed Outcome Data

Baseline Characteristics

Table 19: Detailed Demographic and Baseline Characteristics

	Study 45		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (n = 55)	Placebo (n = 61)
Age (yrs)				
M ± SD	53.4 ± 11.6	53.6 ± 12.1	51.9 ± 13.4	53.9 ± 12.5
Median (range)	56.0 (27 to 78)	53.0 (27 to 76)	53.0 (20 to 79)	56.0 (28 to 78)
Female, n (%)	23 (62)	27 (63)	37 (67)	38 (62)
Caucasian, n (%)	30 (81)	40 (93)	55 (100)	61 (100)
Weight (kg), M ± SD	76.1 ± 13.9	74.5 ± 17.7	73.4 ± 13.8	77.4 ± 15.0
Height (cm), M ± SD	167.5 ± 10.7	169.2 ± 10.2	167 ± 10.3	170 ± 8.5
Time since the diagnosis of CD (yrs)				
M ± SD	7.02 ± 7.12	5.69 ± 5.23	NR	NR
Median (range)	5.75 (0.17 to 24)	5.33 (0 to 25.58)	NR	NR
Time since onset of signs/symptoms (yrs)				
Mean (SD)	12.1 ± 9.5	11.69 ± 9.62	12.0 ± 8.8	11.8 ± 8.8
Median (range)	9.5 (1.08 to 33.25)	10 (1.75 to 47)	NR	NR
De novo pts, n (%)	9 (24)	12 (28)	10 (18)	10 (16)
Pts previously treated with botulinum toxin, n (%)	28 (76)	31 (72)	45 (82)	51 (84)
Time since first botulinum toxin treatment (yrs)				
M ± SD	4.39 ± 3.24	4.38 ± 2.56	NR	NR
Median (range)	3.88 (0.25 to 13)	4.92 (0.75 to 9.0)	NR	NR
Number of botulinum toxin treatments				
M ± SD	9.3 ± 9.8	12.3 ± 9.7	NR	NR
Median (range)	6.0 (1 to 35)	9.0 (2 to 35)	NR	NR
Time since most recent botulinum toxin treatment (yrs)				
M ± SD	0.83 ± 0.97	0.60 ± 0.77	NR	NR
Median (range)	0.43 (0.30 to 4.02)	0.39 (0.29 to 4.33)	NR	NR
Most recent dose of botulinum toxin (units)				
M ± SD	232.1 ± 82.4	210.9 ± 58.6	NR	NR
Median (range)	252.5 (65 to 400)	200.0 (100 to 300)	NR	NR
TWSTRS total score (M ± SD)	45.1 ± 8.7	46.2 ± 9.4	43.8 ± 8.0	45.8 ± 8.8
Pt VAS for symptom severity (mm) (M ± SD)	NR	NR	67.7 ± 19.7	63.6 ± 18.9
Investigator VAS for symptom severity (mm) (M ± SD)	NR	NR	62.3 ± 15.8	65.3 ± 18.0
SF-36 MCS score (M ± SD)	NR	NR	44.5 ± 10.4	43.3 ± 11.1

	Study 45		Study 51	
SF-36 PCS (M ± SD)	NR	NR	39.4 ± 8.8	43.2 ± 7.9
Pt VAS for pain severity (mm) (M ± SD)	NR	NR	47.4 ± 25.0	49.6 ± 24.5
TWSTRS severity subscale score (M ± SD)	19.7 ± 2.6	20.5 ± 3.4	20.4 ± 3.0	21.2 ± 2.8
TWSTRS disability subscale score (M ± SD)	13.9 ± 4.4	14.1 ± 5.1	12.9 ± 3.8	13.8 ± 4.5
TWSTRS pain subscale score (M ± SD)	11.5 ± 3.8	11.7 ± 3.8	10.6 ± 4.2	10.9 ± 4.6

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CD = cervical dystonia; M = mean; MCS = Mental Component Summary of SF-36; NR = not reported; PCS = Physical Component Summary of SF-36; pts = patients; SD = standard deviation; SF-36 = Short Form (36) Health Survey; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale; yrs = years.

Note: For Study 45: [redacted] (Clinical Study Report p. 42);[9] Thoung 2005 [12] only reported the group 1 info.[12]

Source: Study 45 Clinical Study Report; [9] Truong 2005;[12] Study 51 Clinical Study Report; [10] Truong 2010.[13]

Efficacy

Table 20: TWSTRS Total Score and Subscale Scores

	Study 45		Study 51	
	aboBoNTA (n = 37)	**Placebo (n = 43)**	**aboBoNTA (N = 55)**	**Placebo (N = 61)**
TWSTRS Totals				
Baseline M ± SD	45.1 ± 8.7	46.2 ± 9.4	43.83 ± 7.97	45.81 ± 8.78
Week 4				
M ± SD	35.2 ± 13.8	42.4 ± 12.2	30.04 ± 12.65	40.22 ± 11.75
Change from baseline, MD ± SE at wk 4	–9.6 (2.0)	–3.7 (1.8)	–15.58 ± 1.95	–6.74 ± 2.03
Btw-group MD of change from baseline at wk 4, MD (95% CI), *P* value	–6.0 (–10.6 to –1.3) *P* = 0.013		–8.9 (–12.94 to –4.74) *P* < 0.0001	
Week 8				
M ± SD	37.0 ± 13.8	44.0 ± 11.6	29.31 ± 10.99	39.64 ± 13.50
Change from baseline, MD ± SE at wk 8	–7.5 (1.8)	–1.7 (1.6)	–14.70 ± 1.98	–5.89 ± 1.98
Missing data at week 8	15	29	NR	NR
Btw-group MD of change from baseline at wk 8, MD (95% CI), *P* value	–5.8 (–9.9 to –1.6), *P* = 0.007		MD NR (–12.91 to –4.71) *P* < 0.0001	
Week 12				
M ± SD	39.3 ± 12.9	44.6 ± 11.5	36.04 ± 11.76	40.76 ± 11.08
Change from baseline, MD ± SE at wk 12	–5.2 (1.6)	–0.8 (1.5)	–9.06 ± 1.66	–4.94 ± 1.66
Missing data at week 12	35	23		
Btw-group MD of change from baseline at wk 12, MD (95% CI), *P* value	–4.3 (–8.2 to –0.4), *P* = 0.030		MD NR (–7.55 to –0.68) *P* = 0.019	
TWSTRS – Severity (*P* value, NR)				
Baseline M ± SD	19.7 ± 2.6	20.5 ± 3.4	20.38 ± 3.04	21.15 ± 2.76
Week 4	15.1 ± 5.8	18.4 ± 4.8	14.51 ± 5.86	18.67 ± 5.16
Change from baseline, MD ± SD at wk 4	–4.6 (5.1)	–2.1 (3.9)	–6.16 ± 5.42	–2.38 ± 3.83
Btw-group MD of change from baseline at wk 4 MD (95% CI),	–2.5 (–4.5 to –0.5)		NR	
Week 8	15.9 ± 6.1	18.8 ± 4.6	14.04 ± 5.80	18.41 ± 5.57
Change from baseline, MD ± SD at wk 8	–3.8 (5.2)	–1.7 (3.2)	–6.04 ± 5.32	–2.26 ± 4.88

	Study 45		Study 51	
	aboBoNTA (n = 37)	Placebo (n = 43)	aboBoNTA (N = 55)	Placebo (N = 61)
Btw-group MD of change from baseline at wk 4, MD (95% CI)	–2.1 (–4.0 to –0.2)		NR	
Week 12	17.4 ± 5.2	19.5 ± 4.5	17.09 ± 5.57	19.14 ± 4.54
Change from baseline MD ± SD at wk 12	–2.4 (4.4)	–1.0 (3.2)	–3.13 ± 4.92	–1.75 ± 3.70
Btw-group MD of change from baseline at wk 4, MD (95% CI)	–1.3 (–3.0 to –0.4)		NR	
TWSTRS – Disability (*P* value NR)				
Baseline Mean ± SD	13.9 ± 4.4	14.1 ± 5.1	12.87 ± 3.83	13.79 ± 4.51
Week 4	11.4 ± 5.6	13.5 ± 4.9	8.96 ± 5.02	12.21 ± 4.49
Change from baseline, MD ± SD at wk 4	–2.5 (4.2)	–0.6 (2.6)	–3.85 ± 4.94	–1.50 ± 3.61
Btw-group MD of change from baseline at wk 4, MD (95% CI)	–1.9 (–3.5 to –0.4)		NR	
Week 8	11.8 ± 5.5	13.8 ± 5.4	9.09 ± 4.55	12.09 ± 5.32
Change from baseline[a] MD ± SD at wk 8	–2.1 (4.2)	–0.2 (1.4)	–3.89 ± 4.63	–1.91 ± 4.21
Btw-group MD of change from baseline at wk 8, MD (95% CI)	–1.9 (–3.2 to –0.5)		NR	
Week 12	12.2 ± 5.2	13.9 ± 5.2	10.73 ± 4.29	12.09 ± 4.59
Change from baseline, MD ± SD at wk 12	–1.7 (4.1)	–0.2 (1.0)	–2.02 ± 4.14	–1.59 ± 2.86
Btw-group MD of change from baseline at wk 12, MD (95% CI)	–1.5 (–2.8 to –0.2)		NR	
TWSTRS – Pain (*P* value NR)				
Baseline	11.5 ± 3.8	11.7 ± 3.8	10.57 ± 4.23	10.88 ± 4.61
Week 4	8.7 ± 5.5	10.5 ± 4.8	6.79 ± 5.09	9.34 ± 4.89
Change from baseline, MD ± SD at wk 4	–2.8 (5.0)	–1.2 (3.9)	–3.74 ± 4.69	–1.35 ± 3.81
Btw-group MD of change from baseline at wk 4, MD (95% CI)	–1.6 (–3.6 to –0.3)		NR	
Week 8	9.4 ± 5.5	11.4 ± 4.4	6.18 ± 4.32	9.14 ± 4.83
Change from baseline, MD ± SD at wk 8	–2.1 (5.4)	–0.2 (1.9)	–3.88 ± 4.56	–1.42 ± 3.86
Btw-group MD of change from baseline at wk 8, MD (95% CI)	–1.0 (–3.6 to –0.1)		NR	
Week 12	9.7 ±4.9	11.2 ± 4.4	8.45 ± 4.50	9.53 ± 5.01
Change from baseline, MD ± SD at wk 12	–1.8 (3.7)	–0.4 (1.3)	–1.72 ± 3.58	–1.19 ± 3.54
Btw-group MD of change from baseline at wk 12, MD (95% CI)	–1.4 (–2.6 to –0.2)		NR	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CD = cervical dystonia; CI = confidence interval; M = mean; MD = mean difference; NR = not reported; SD = standard deviation; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; wk = week.

Note: The mean difference (aboBoNTA minus placebo) from ANCOVA analyses is presented as the difference between the adjusted mean changes from baseline for aboBoNTA and placebo with 95% confidence interval. Statistical analyses of between-group differences in changes from baseline were not performed for the TWSTRS subscale scores.

Source: Study 45 Clinical Study Report;[9] Truong 2005;[12] Study 51 Clinical Study Report;[10] and Truong 2010.[13]

Table 21: Subgroup Analysis for TWSTRS Total Score (BoNT-Naive/ BoNT-Experienced in Study 45)

	Mean TWSTRS Total Score (SD)			
	BoNT-Naive		BoNT-Experienced	
	aboBoNTA	Placebo	aboBoNTA	Placebo
n	9	12	28	31
Baseline	43.7 (9.6)	49.1 (9.6)	45.5 (8.5)	45.1 (9.2)
Change from baseline to:				
Week 4	–10.5 (13.7)	–5 (11.2)	–9.7 (11.4)	–3.3 (7.4)
Week 8	–5.6 (11.4)	–0.8 (3.5)	–8.8 (12.8)	–2.8 (5.1)
Week 12	–7.6 (13.7)	–1.1 (3.9)	–5.2 (10.4)	–1.8 (5)

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); BoNT = botulinum neurotoxin; SD = standard deviation; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

Source: Clinical Study Report[3]

[redacted]

Table 22: Short Form (36) Health Survey Data in Study 51

Study 51		aboBoNTA (N = 55)		Placebo (N = 61)		*P* value for treatment difference
		Score	Change from baseline	Score	Change from baseline	
SF-36 MCS						
Baseline	N	[redacted]				
	M ± SD					
	Median					
	Range					
Week 8	N					
	Mean ± SD					
	Median					
	Range					
SF-36 PCS						
Baseline	N					
	M ± SD					
	Median					
	Range					
Week 8	N					
	M ± SD					
	Median					
	Range					

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; MCS = Mental Component Summary of SF-36; PCS = Physical Component Summary of SF-36; SD = standard deviation; SF-36 = Short Form (36) Health Survey.

[a] For this outcome, the hierarchical testing was non-significant.[10] Therefore, it was considered not statistically significant, even though *P* = 0.002 based on the protocol (see Table 23 below).

Source: Study 51 Clinical Study Report.[10]

Table 23: Significance in Hierarchical Testing in Study 51

Rank	Outcomes	*P* value for paired testing	Significance in hierarchical testing
1°	Change from baseline in TWSTRS total score at wk 4	$P < 0.0001$	Yes, $P < 0.05$
2°	1 Change from baseline in TWSTRS total score at wk 8	$P < 0.0001$	Yes, $P < 0.05$
2°	2 Change from baseline in TWSTRS total score at wk 12	$P = 0.019$	Yes, $P < 0.05$
2°	3 Change from baseline in pt's VAS for symptom of CD at wk 4	$P < 0.001$	Yes, $P < 0.05$
2°	4 Change from baseline in investigator's VAS for symptom of CD at wk 4	$P < 0.001$	Yes, $P < 0.05$
2°	5 Change from baseline in pts' VAS for symptom of CD at wk 8	$P < 0.001$	Yes, $P < 0.05$
2°	6 Change from baseline in investigator's VAS for symptom of CD at wk 8	$P < 0.001$	Yes, $P < 0.05$
2°	7 Change from baseline in pts' VAS for symptom of CD at wk 12	$P = 0.007$	Yes, $P < 0.05$
2°	8 Change from baseline in investigator VAS for symptom of CD at wk 12	$P = 0.028$	Yes, $P < 0.05$
2°	9a Change from baseline in MCS-36 at wk 8	$P = 0.061$	Not significant
2°	9b Change from baseline in PCS-36 at wk 8	Should not be claimed[b]	Not significant
2°	10 Overall treatment successes[a] at wk 12	Should not be claimed[b]	Not significant

CD = cervical dystonia; MCS = Mental Component Summary of SF-36; PCS = Physical Component Summary of SF-36; pt = patient; SF-36 = Short Form (36) Health Survey; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale; wk = week.

Note: 1° = primary end point; 2° = secondary end point.

[a] Treatment successes were defined by a global efficacy assessment of "better" or "much better" and a global safety assessment of no worse than "moderate."

[b] No statistical significance should be claimed for SF-36 PCS or treatment success because both ranked lower than the SF-36 MCS in the hierarchical testing, where significance in hierarchical testing failed.

Source: Study 51 Clinical Study Report.[10]

Table 24: Exploratory Efficacy Outcomes in Study 51

Exploratory efficacy outcomes	aboBoNTA (n = 55)	Placebo (n = 61)
Pt's M (SD) change from baseline in VAS pain scores (mm) at wk 4	–17.7 (24.4)	–4.8 (24.6)
TWSTRS severity score, M (SD) change from baseline at wk 4	–6.2 (5.4)	–2.4 (3.8)
TWSTRS disability score, M (SD) change from baseline at wk 4	–3.9 (4.9)	–1.5 (3.6)
TWSTRS pain score, M (SD) change from baseline at wk 4	–3.7 (4.7)	–1.4 (3.8)
Pt's M (SD) change from baseline in VAS pain scores (mm) at wk 8	–15.8 (30.9)	–4.2 (23.6)
TWSTRS severity score, M (SD) change from baseline at wk 8	–6.0 (5.3)	–2.3 (4.9)
TWSTRS disability score, M (SD) change from baseline at wk 8	–3.9 (4.6)	–1.9 (4.2)
TWSTRS pain score, M (SD) change from baseline at wk 8	–3.9 (4.6)	–1.4 (3.9)
Pt's M (SD) change from baseline in VAS pain scores (mm) at wk 12	–7.9 (27.5)	–4.5 (31.5)
TWSTRS severity score, M (SD) change from baseline at wk 12	–3.1 (4.9)	–1.8 (3.7)
TWSTRS disability score, M (SD) change from baseline at wk 12	–2.0 (4.1)	–1.6 (2.9)
TWSTRS pain score, M (SD) change from baseline at wk 12	–1.7 (3.6)	–1.2 (3.5)
Pt's change in VAS pain scores (mm) for subgroups with VAS > 40 mm at baseline at wk 4, M (SD)	–26.5 (25.1)	–10.8 (25.1)
Pt's change in VAS pain scores (mm) for subgroups with VAS > 40 mm at baseline at wk 8, M (SD)	–29.7 (30.0)	–8.4 (23.2)
Pt's change in VAS pain scores (mm) for subgroups with VAS > 40 mm at baseline at wk 12, M (SD)	–18.4 (26.1)	–14.6 (29.6)
Proportion of responders at wk 4	49%	16%

Exploratory efficacy outcomes	aboBoNTA (n = 55)	Placebo (n = 61)
Proportion of responders (decrease in TWSTRS total score of at least 30% compared with baseline) at wk 8	49%	11%
Proportion of responders (decrease in TWSTRS total score of at least 30% compared with baseline) at wk 12	24%	11%

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; pts = patients; SD = standard deviation; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale; wk = week.

Note: These were assessed as exploratory efficacy outcomes; no statistical comparison between treatment groups was conducted.

Note: Responders were defined as pts with reduction in TWSTRS total score of at least 30% from baseline.

Source: Study 51 Clinical Study Report.[10]

Table 25: Duration of Response (Double-Blind Phase and Open-Label Phase)

Study 45	Study 45 (DB)		Study 45b (Study 45 OL phase)		
			re-treatment 1 (N = 131)	re-treatment 2 (N = 121)	re-treatment 3 (N = 111)
	aboBoNTA	Placebo	aboBoNTA		
N of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of response (wks) M ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N of patients not recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value (aboBoNTA vs. placebo)	[redacted]		[redacted]		
Study 51	**Study 51 (DB)**		**Study 731 (Study 51 OL phase)**		
			Cycle 2	Cycle 3	Cycle 4
	aboBoNTA	Placebo	aboBoNTA		
N of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of response (wks) Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value (aboBoNTA vs. placebo)	[redacted]		[redacted]		

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; SD = standard deviation; vs. = versus; wks = weeks.

Notes:

Duration of response (time to re-treatment eligibility) was only calculated for patients who responded and was defined as the time between the date of administration of study medication and the date of the need for re-treatment. Re-treatment was indicated if the response to treatment on the TWSTRS total score was no better than a 10% decrease from baseline. Where patients have a censored duration of response, the censored time has been tabulated.

Duration of action was not assessed for cycle 1 in study 731.

In the open-label study, all patients received an initial dose of 500 U of aboBoNTA, followed by dose titration up or down, based on safety and efficacy response.

Source: Study 45 Clinical Study Report, [9] Truong 2005;[12] Study 51 Clinical Study Report; [10] Truong 2010.[13]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
- Tsui score
- Visual Analogue Scale (VAS) pain scale and VAS symptom scale
- Short Form (36) Health Survey (SF-36)
- Global Efficacy Assessment and Global Safety Assessment for cervical dystonia (CD)

Findings

We conducted a focused literature search for the psychometric properties and minimum clinically important difference (MCID) of each of the stated outcome measures. We retrieved 221 results, only four of which were directly informative. Table 26 summarizes the findings.

Table 26: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of validation	MCID	References
TWSTRS	Three subscales to measure pain, disability, and severity	Yes	Unknown	Consky 1994,[21] Albanese 2013,[42] Consky 1990, Tarsy 1997 [43]
Tsui score	A scale measure of rotation, tilt, sagittal movement, head tremor, and shoulder elevation	Yes	Unknown	Jost 2013,[44] Tarsy 1997 [43]
VAS pain scale and VAS symptom scale	A psychometric response scale used as a measuring instrument for symptom intensity	Unknown in cervical dystocia	Unknown in cervical dystonia	
SF-36	A 36-item survey to measure multi-dimensional health concepts and capture a full range of health states	Unknown in cervical dystonia	Unknown in cervical dystonia	
Global Efficacy Assessment and Global Safety Assessment for cervical dystonia	Investigator subjective assessment of change in efficacy on a three-point scale or presence of safety issues on a two-point scale	Unknown	Unknown	

SF-36 = Short Form (36) Health Survey; MCID = minimal clinically important difference; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; VAS = visual analogue scale.

Toronto Western Spasmodic Torticollis Rating Scale

Developed in the early 1990s, TWSTRS is a composite scale used to measure three aspects of CD: severity, disability, and pain. TWSTRS total score falls within the range of 0 to 85, where a higher score indicates a more severe condition.[44]

Torticollis Severity Scale (maximum subtotal score 35)

The severity subscore is a maximum of 35 and consists of 11 items scored on scales ranging from either 0 to 1, 0 to 3, 0 to 4, or 0 to 5, also emphasizing the duration of the symptoms by weighting them with a factor of 2.

A. Maximal Excursion
    1. Rotation, score range 0 to 4
    2. Laterocollis, score range 0 to 3
    3. Anterocollis, score range 0 to 3
    4. Retrocollis, score range 0 to 3
    5. Lateral shift, score range 0 to 1
    6. Sagittal shift, 0 to 1
B. Duration Factor (weighted by a factor of 2), score range 0 to 5
C. Effect of Sensory Tricks score range 0 to 2
D. Shoulder Elevation/ Anterior Displacement, score range 0 to 3
E. Range of Motion, score range 0 to 4
F. Time, score range 0 to 4

Disability Scale (maximum subtotal score 30)

The disability subscore has a maximum of 30 and consists of six items scored on scales from 0 to 5.

A. Work, score range 0 to 5
B. Activities of Daily Living, score range 0 to 5
C. Driving, score range 0 to 5
D. Reading, score range 0 to 5
E. Television, score range 0 to 5
F. Activities Outside the Home, score range 0 to 5

Pain Scale (maximum subtotal score 20)

The pain subscore has a maximum of 20 and consists of three patient-rated items, two of which are scored on a range from 0 to 5, while the third depends on patients' score of their usual pain (factored by 2), worst pain, and best pain, on a range of 0 to 10, all divided by 4 to reach a total ranging from 0 to 10.

A. Severity of Pain (best + worst + ((2×usual)÷4)), score range 0 to 10
    a. Best, score range 0 to 10
    b. Worst, score range 0 to 10
    c. Usual, score range 0 to 10
B. Duration of Pain, score range 0 to 5
C. Disability Due to Pain, score range 0 to 5

Using the TWSTRS videotape protocol, researchers filmed 200 CD patients and asked three independent movement disorders specialists to watch the videos and provide TWSTRS scores for them.[45] The researchers found a substantial degree of concordance among the raters' scores for all of the TWSTRS components of the tool (Kendall's coefficient of concordance *W* range: 0.76 to 0.98). Also, the concordance between total TWSTRS score for raters was high (Kendall's coefficient of concordance *W* = 0.85).[45] In addition to the assessment of inter-rater agreement, construct validity was assessed in two studies where TWSTRS scores were measured for patients with CD; the researchers also recorded patient and clinician perceptions before and after treatment.[21,46] Both studies have shown high correlation between the change in TWSTRS score and overall patient and clinician perception of improvement, with a reported Pearson correlation coefficient between the change in total severity score and patient perception of 0.68, and a reported Pearson correlation between the changes in the severity score and changes in disability and pain scores of 0.65 in TWSTRS and patient perception.[47] Also, as a measure of score responsiveness, the TWSTRS and the Tsui scores were measured for 76 patients with CD before and after treatment with botulium neurotoxin A (BoNTA) along with a recorded global assessment scale, where assessments were conducted by the treating physician.[43] This study showed a large Pearson correlation

coefficient of 0.71 in the reduction of the TWSTRS total score and global assessment scale, and a large Pearson correlation coefficient of 0.57 between the TWSTRS total score and Tsui score.[43]

We were not able to find any study to inform us about a potential MCID for the TWSTRS score.

Tsui score

Developed in the 1980s for assessing efficacy in CD clinical trials, the Tsui score is an impairment scale that assesses the extent and duration of neck, head, and shoulder movement in patients with CD. In essence, the tool consists of four categories: amplitude of sustained movement, duration of sustained movement, shoulder elevation, and tremors. The combination of these four categories gives rise to the total Tsui score, which can be in the range of 1 to 25. The higher the score, the more aggressive the condition.[48] The exact scoring algorithm is as follows:

A. **Amplitude of sustained movements**: combined score ranges from 0 to 9 by adding the following:
    1. Rotation: score of 0, 1, 2, or 3 based on a degree of rotation of absent, less than 15 degrees, 15 degrees to 30 degrees, and more than 30 degrees, respectively
    2. Tilt: score of 0, 1, 2, or 3 based on a degree of rotation of absent, less than 15 degrees, 15 degrees to 30 degrees, and more than 30 degrees, respectively
    3. Sagittal movements: score of 0, 1, 2, or 3 based on a severity of absent, mild, moderate, or severe, respectively
B. **Duration of sustained movement**: score of either 1 or 2 based on intermittent or constant duration, respectively
C. **Shoulder elevation**: score of 0, 1, 2, or 3 based on the duration and severity of shoulder elevation where 0 = absent, 1 = mild and intermittent, 2 = mild and constant or severe and intermittent, and 3 = severe and constant.
D. **Tremor**: combined score ranges from 1 to 4 by multiplying the following:
    1. Severity: score of 1 or 2 based on either mild or severe tremor
    2. Duration: score of 1 or 2 based on either occasional or continuous tremor

Total Tsui score = (amplitude of sustained movements × duration of sustained movement) + shoulder elevation + tremor

Inter-observer variability in the Tsui score was assessed in a randomized, double-blind (DB) trial of CD patients who underwent an injection of BoNTA or placebo.[48] The clinical encounter with enrolled patients was filmed, and an assessment of the CD severity was carried out by two independent and blinded movement specialists using Tsui scoring.[48] The agreement between raters was expressed as a large correlation coefficient of 0.86.[48] Additionally, the Tsui score was measured in 76 patients with CD before and after treatment with botulinum toxin A; a recorded global assessment scale was also recorded and TWSTRS assessments were conducted by the treating physician.[21] The results of the study showed a strong correlation between the Tsui and TWSTRS total scores (Pearson correlation coefficient of 0.57), a strong correlation between the Tsui score and the TWSTRS severity subscore (Pearson correlation coefficient of 0.69), and a weak correlation between the Tsui score and the TWSTRS pain subscore (Pearson correlation coefficient = 0.27). Correlation between the Tsui and the global impression of change was not reported.

Also, one study has demonstrated differences between the Tsui score and the patient's reported subjective perception.[49] The study enrolled 60 patients with CD to a randomized trial to receive BoNTA or placebo. The clinical encounter was filmed four weeks before and after the injection, and a blinded assessor provided a Tsui score of the patient. In addition, patients were asked to provide an assessment of symptoms change (nil, mild, moderate, marked) and a pain score on a scale from 0 to 10 where 10 was most severe.[49] The correlation between the patients' reported scores and Tsui scores was strong (0.64).[49]

We were not able to find any study to inform us about a potential MCID for the Tsui scores.

Visual analogue scale pain and symptom scale

This tool was used in Study 45 and 51. In both, for pain and symptom assessment, the patient was asked to draw a line on a 100 mm scale that represented the severity of the patient's pain or symptom; the longer the line, the higher the severity. Thus, at 0 mm there would be an absence of pain or symptoms.[9,10] We found no published evidence to support the validity, reliability, responsiveness, or MCID of these particular VASs for pain or symptoms in patients with CD.

Short Form (36) Health Survey

The 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 (HRQoL). The SF-36 consists of eight domains: 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 SF-36 PCS, SF-36 MCS, and eight domains 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, while a score 10 points less (i.e., 40) would be one standard deviation below the norm. An increase in score indicates an improvement in health status on any scale. In general, when using the SF-36, a change of 2 points on the SF-36 PCS and 3 points on the SF-36 MCS indicates a clinically meaningful improvement as determined by the patient.[50]

We found no published evidence to support the validity or the MCID of the SF-36 in patients with CD.

Global Efficacy Assessment and Global Safety Assessment for cervical dystonia

As reported by the manufacturer, this measure is an investigator-reported global impression of change related to either CD symptoms or safety. For efficacy, this was carried out on a five-point ordinal scale on the change in CD symptoms (i.e., much better, better, no change from baseline, worse, or much worse), where the investigator chose one category based on their assessment during the assessment visit. With safety, the investigator assessed the safety profile (any AE or complication) on a five-point ordinal scale (i.e., none, mild, moderate, severe, or extreme). We were not able to find any literature that provides evidence on the validity, reliability, and MCID of such a measure.

Conclusion

The TWSTRS is a validated and reliable instrument to report on the outcome of patients with CD. The Tsui score has shown good inter-rater agreement, but had a less-than-ideal correlation with patients' perceptions. We did not find evidence supporting the validity and reliability in the population of CD patients with the use of SF-36, VAS pain and symptom scale, and Global Efficacy Assessment and Global Safety Assessment. Also, we were not able to identify evidence regarding the MCID that was specific to CD on any of the reviewed measures.

Appendix 6: Summary of Other Studies

Study design

Extension studies 45b and 731 were open-label continuations of Study 45 and Study 51, respectively. The original double-blind (DB) studies compared Dysport (aboBoNTA) versus placebo and were reviewed in detail in the main body of this report. All patients who completed the DB phase were eligible to participate in the open-label phase. A washout period of four weeks was designated for Study 45b while a washout period of 12 weeks was designated for Study 731. In both extension studies, original treatment assignment remained unknown and all patients entering the open-label phase received aboBoNTA. Patients on both extension studies were initiated on a dose of 500 U. Subsequent treatments could vary from 250 U to 1,000 U by increments of 250 U from the previous dose, based on the assessment of the treating physician. Study 45b was designed to allow patients to receive a maximum of three treatments with a minimum of a four-week period between treatments, up to a period of two years (104 weeks). Study 731 was designed to allow patients to receive a maximum of four treatments with a designed period between treatments ranging from 12 to 16 weeks, but ultimately determined by the treating physician.

An additional 'extended phase' was designed in Study 45b.This phase allowed patients to receive any number of treatments at any dose as decided by the patient and the treating physician. This phase of Study 45b was meant to mimic clinical practice. Participation in the 'extended phase' of Study 45b was optional, but it excluded patients who showed no improvement in the open-label phase of Study 45b, as well as patients who experienced an unacceptable side effect, as determined by the study investigators.

Both studies aimed to describe the long-term safety and efficacy of aboBoNTA given in a setting similar to normal clinical practice. Efficacy was reported on a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scale while safety was captured as adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs). The "extended phase" of Study 45b used an overall subjective assessment of the treating investigator regarding efficacy. The analysis in both Study 45b and study 731 was reported using all patients that received at least one dose of the treatment.

Both extension studies are descriptive in nature, with no comparison group. All results were reported using general descriptive statistics (e.g., mean, median, standard deviation [SD], range, etc.). Missing or incomplete data were not imputed.

Patient disposition

Study 45b enrolled 132 patients while study 731 enrolled 108 patients. Patients' disposition during each treatment phase of the studies is detailed in Table 27. Of the 132 patients enrolled in the 45b extension study, 104 patients (78.8%) finished the three designated treatments, with no WDAEs. Only 58 patients continued to the extended phase of the 45b study. Extension study 731 had 108 patients initially enrolled, 80 completed the four designated treatments (74.1%), while one patient withdrew due to AEs.

Table 27: Patients' Disposition Throughout the Extension Studies

	Study	
	45b	731
Treatment 1		
N	132	108
Received study medication, N (%)	131 (99.2%)	108 (100.0%)
Completed treatment cycle	NR	102 (94.4%)
Withdrawals	10 (7.6%)	8 (7.4%)
Adverse event	0 (0.0%)	1 (0.9%)
Insufficient clinical response	2 (1.5%)	3 (2.8%)
Consent withdrawn	5 (3.8%)	1 (0.9%)
Lost to follow-up	1 (0.8%)	2 (1.8%)
Other	2 (1.5%)	1 (0.9%)

	Study	
	45b	731
Treatment 2		
N	121	100
Received study medication, N (%)	121 (100.0%)	100 (100.0%)
Completed treatment cycle	NR	97 (97.0%)
Withdrawals	10 (8.3%)	4 (4.0%)
Adverse event	0 (0.0%)	0 (0.0%)
Insufficient clinical response	0 (0.0%)	2 (2.0%)
Consent withdrawn	4 (3.3%)	2 (2.0%)
Lost to follow-up	2 (1.6%)	0 (0.0%)
Other	4 (3.3%)	0 (0.0%)
Treatment 3		
N	111	96
Received study medication, N (%)	111 (100.0%)	96 (100%)
Completed treatment cycle	NR	91 (94.8%)
Withdrawals	7 (6.3%)	8 (8.3%)
Adverse event	0 (0.0%)	0 (0.0%)
Insufficient clinical response	0 (0.0%)	1 (1.0%)
Consent withdrawn	2 (1.8%)	1 (1.0%)
Lost to follow-up	1 (0.9%)	2 (2.1%)
Other	5 (4.5)	4 (4.2%)
Treatment 4 / extended phase		
N	59	88
Received study medication, N (%)	NR	88 (100%)
Completed treatment cycle	NR	80 (90.9%)
Withdrawals	NR	8 (9.1%)
Adverse event	NR	0 (0.0%)
Insufficient clinical response	NR	0 (0.0%)
Consent withdrawn	NR	3 (3.4%)
Lost to follow-up	NR	4 (4.5%)
Other	NR	1 (1.1%)

NR = not reported

Source: CSRs [11,22]

Demographic characteristics

Both extension studies had similar patient characteristics in term of age, race, and weight (Table 28).

Table 28: Demographics of Studies' Population

Characteristic	Study 45b (N = 131)	Study 731 (N = 108)
Age (yrs), mean (SD)	54.0 (12.3)	53.5 (13.0)
Number of females (%)	81 (61.8)	67 (62.0)
Race		
Caucasian, N (%)	118 (90.1)	108 (100.0)
Hispanic, N (%)	10 (7.6)	0 (0.0)
Black, N (%)	2 (1.5)	0 (0.0)
Other, N (%)	1 (0.7)	0 (0.0)
Weight (kg), mean (SD)	74.0 (15.4)	76.2 (14.7)

SD = standard deviation; yrs = years.

Source: Clinical Study Reports.[11,22]

Drug exposure

In the open-label phase of Study 45b, patients underwent three treatments by study design: the first treatment had a fixed dose of 500 U with an actual given mean dose of 498.1 (SD = [redacted]); the second treatment allowed for dose adjustment at an increment of 250 U with an actual given mean dose of 615 (SD = [redacted]); the third treatment allowed for further dose adjustment at an increment of 250 U, with an actual given mean dose of 701.5 (SD = [redacted]). [redacted]

Efficacy results

Both extension studies demonstrate that at four weeks post assessment, the TWSTRS score lay in the range of 21 to 31. [redacted]. (See Table 29)

Table 29: Summary of Efficacy Results

	Study 45b	Study 731
Treatment 1		
TWSTRS total score at baseline of treatment 1, mean (SD)	44.5 (8.8)	42.5 (10.2)
TWSTRS total score at Wk 4 post-treatment 1, mean (SD)	31.0 (12.9)	25.8 (12.8)
Treatment 2		
TWSTRS total score at baseline of treatment 2, mean (SD)	41.7 (11.3)	34.7 (11.1)
TWSTRS total score at Wk 4 post-treatment 2, mean (SD)	30.3 (12.8)	23.4 (12.6)
Treatment 3		
TWSTRS total score at baseline of treatment 3, mean (SD)	41.0 (10.7)	32.7 (11.7)
TWSTRS total score at Wk 4 post-treatment 3, mean (SD)	28.9 (11.9)	21.8 (20.6)
Treatment 4		
TWSTRS total score at baseline of treatment 4, mean (SD)	NA	34.4 (12.8)
TWSTRS total score at Wk 4 post-treatment 4, mean (SD)	NA	23.1 (12.6)

SD = standard deviation; Wk = Week

Source: CSRs [11,22]

Safety Results

Safety analysis is summarized in Table 30.

Table 30: Summary of Safety Analysis Results

	Study 45b N = 131	Study 731 N = 108
Participants reporting > 0 AEs, n (%)	[redacted]	[redacted]
Most common AEs[a], n (%)		
Myasthenia/neck	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Neck/shoulder pain	[redacted]	[redacted]
Voice alteration	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Myasthenia	[redacted]	[redacted]
Dyspnea	[redacted]	-
Back pain	[redacted]	-
Nausea	[redacted]	-
Myasthenia/jaw	[redacted]	-
Tremor	[redacted]	-
Viral infection	[redacted]	-
Dizziness	[redacted]	-
Hypertension	[redacted]	-
Accidental injury	[redacted]	-
Amblyopia (blurred vision)	[redacted]	-
Hyperesthesia	[redacted]	-
Abdominal pain	[redacted]	-

	Study 45b N = 131	Study 731 N = 108
Insomnia	[redacted]	-
Pharyngitis	[redacted]	-
Influenza	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event.

a Common AEs are defined as those with 5% or more occurrences.

Source: Clinical Study Reports.[11,22]

Limitations

The open-label extension studies have several limitations imposed by the overall design; the lack of a comparison group to provide context and control for potential confounders, the open-label design may influence the perception of improvement in patients and clinicians, and the descriptive nature of the statistical results prevent any valid inferences. Specific limitations to these two extension studies include: short washout period in Study 45b where some of the effects of the treatment in the DB study may have lingered, and the proportion of withdrawals in both studies (in the range of 4% to10% after each treatment cycle) may indicate a potential bias in favour of the intervention as patients who are unhappy with the trial or the treatment choose to remove themselves from the study.

Summary

Efficacy outcomes showed a TWSTRS score lying in the range of 21 to 31 at four weeks of post-treatment assessment. Safety results did not show a gross sign of concern. However, the study only reported efficacy and safety in a descriptive, non-comparative manner. As such, the study design cannot inform onto the consistency of the treatment and safety effects.

Appendix 7: Summary of OnabotulinumtoxinA-Controlled Studies

Aim

To summarize the efficacy and safety outcomes of abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) compared with onabotulinumtoxinA (onaBoNTA, Botox) from the four onaBoNTA-controlled randomized controlled trials (RCTs).[17-20]

Study Design

All four onaBoNTA-controlled studies were double-blind (DB), randomized controlled studies. The study by Yun et al. was a non-inferiority design. The non-inferiority of aboBoNTA/onaBoNTA dosed at a ratio of 2.5:1 was determined if the upper limit of the one-sided 95% confidence interval (CI) for the difference in Tsui scores in change from baseline between treatments (aboBoNTA minus onaBoNTA) was ≤ 1.5 points. The study by Ranoux et al. was a well defined equivalency study design. The equivalence between treatments was defined as a difference in the post-treatment Tsui score of 1.5 points or less. Study 24 and the study by Rystedt et al. were designed as superiority studies with the two-sided $P < 0.05$. Study 24 was a parallel-controlled study. The other three studies (by Yun et al.,[18], Rystedt et al.,[19] and Ranoux et al.)[20] were crossover studies. Study duration ranged from 12 weeks [17,19] to 16 weeks.[18,20] The four RCTs were designed to compare a clinically-established dose of onaBoNTA used in the treatment of patients with cervical dystonia (CD), with various dose ratios of aboBoNTA from 1.7 times the dose of onaBoNTA in the study by Rystedt et al.,[19] to 4 times the dose of onaBoNTA in the study by Ranoux et al.[20]. The inclusion criteria were also similar across the four studies and mainly included adult patients with CD[17-20] treated with onaBoNTA[17,20] or aboBoNTA[19],with a stable response to onaBoNTA[17,20] or aboBoNTA.[19] Previous onaBoNTA treatment was an inclusion criteria for all studies except the study by Yun et al., in which it was not required.[18] Patients with other forms of CD were excluded in all four studies. Tsui score was the primary outcome in three studies[17,18,20], and Toronto Western Spasmodic Torticollis Rating Score (TWSTRS) total score was the primary outcome in the study by Rystedt et al.[20] The secondary outcomes included TWSTRS subscales, among others (Table 31).

Baseline Characteristics and Patient Disposition

Baseline characteristics are summarized in Table 32. The patients enrolled were adults with a mean age per treatment group of 51[17] and 62 years,[19] and ranging in age from 24 years to 78 years old. The majority of patients were female (56%[18] to 74%[20]). The patients had a CD diagnosis on average for 9 years[27] to 17 years.[19] All patients received onaBoNTA[17,18] or aboBoNTA[20], except in the study by Yun et al., in which about 45 patients had received the onaBoNTA treatment before entering the study.[19] The TWSTRS mean total score was 33 in the studies by Yun et al.[18] and Rystedt et al.[19] TWSTRS total score was not reported in Study 24 [17] or by Ranoux et al.[20]. The Tsui score was 8 points and 10 points in Study 24[17] and in the study by Yun et al.,[18] respectively. Concomitant medication use was only reported in the study by Ranoux et al.[20] The main baseline patient characteristics were generally balanced between groups within all included studies. In the study by Yun et al., the discontinuation rate was similar in both group sequences (< 10% in both group sequence). The main reason for discontinuation was protocol violation in both group sequences. No discontinuation was reported in the remaining studies (Table 33).[17,19,20]

Exposure to the study treatment

The dose of aboBoNTA or onaBoNTA was not fixed, but was based on each individual patient's needs. The mean aboBoNTA dose (mean ± SD) varied from 169 ± 63 in the study by Rystedt et al.,[19] to 477 ± 131 in Study 24.[17] The dose range was from 50 U to 720 U. The mean onaBoNTA dose (mean ± SD) varied from 56.33 ± 21 in the study by Rystedt et al.,[19] to 152 ± 45 in Study 24.[17] The onaBoNTA dose ranged from 17 U to 240 U across all four RCTs. (Table 34).

Critical Appraisal

Randomization was done based on a predetermined randomization table in Study 24 and the study by Yun et al. However, the method used to generate randomization codes (i.e., computer generated or randomization table) was not described in either the study by Rystedt et al., or the study by Ranoux et al. The randomization allocation concealment described was adequate. DB methods were well described in all four studies. The demographic and clinical baseline characteristics were well matched in both treatment groups,[17,18] but the demographic and clinical baseline characteristics of the included patients was reported as total, and no comparison between the two treatment groups was made.

The aboBoNTA doses used in the four RCTs were all below the Health Canada–recommended dose (i.e., < 500 U), however, the clinical experts CADTH consulted in the review indicated that the majority of those patients had been previously onaBoNTA or aboBoNTA treated, therefore the individualized dose range reflects the routine clinical practice. Furthermore, the clinical expert also mentioned that, clinically, if a patient has already responded well to the existing botulinum toxin treatment, it is unlikely for a physician or patients to switch from onaBoNTA to aboBoNTA treatment.

Primary outcomes (Tsui or TWSTRS total score) are well-validated outcomes used in clinical studies on CD. ANOVA analysis was performed in all RCTs for the primary outcomes except for in the study by Yun et al.[18] Only a few dropouts (< 10%) were reported in the study by Yun et al. No dropouts occurred in the other studies. Intention-to-treat (ITT) population analysis was performed in Study 224 [17] and in the study by Ranoux et al.[20] A modified ITT (mITT) was performed in the study by Yun et al. Per-protocol (PP) analysis was also reported.

Several potential methodologic limitations need to be considered when interpreting the findings of these studies:

- The study by Yun et al. was a non-inferiority design and the study by Ranoux et al. was designed as an equivalence study. While the non-inferiority margin in the study by Yun et al. and the equivalence margin in the study by Ranoux et al. were well defined, the rationale for the choice of the non-inferiority or equivalence margins was not provided. In general, non-inferiority should be tested using the PP population, as using ITT will bias toward no-difference and could lead to a false conclusion of non-inferiority.
- Concomitant medications (such as analgesics, antidepressants, or antiepileptics) were allowed, but whether the concomitant medication use was balanced in the two treatment groups was not well described.[17,18,20] Concomitant medication information was not reported in the study by Rystedt et al.[19] Therefore, whether or not concomitant medication use had some impact on the outcome assessment is uncertain in this study.
- No multiplicity test was used to control for type I error in any of the four RCTs for secondary outcomes. Therefore, all findings of secondary outcomes need to be interpreted with caution where differences are found to be statistically significant. Furthermore, among the three crossover study design RCTs, only the study by Yun et al. included a washout period to reduce the potential carry-over effect. The study by Ranoux et al. was 16 weeks' trial duration for each period; the authors claimed that 16 weeks should be long enough to avoid the potential carry-over effect, considering that the usual duration of effect of aboBoNTA was 12 weeks. The clinical expert CADTH consulted in the review also agreed that the 16 weeks' duration is reasonable to avoid carry-over effect. However, the duration of the study by Rystedt et al. was only 12 weeks. Therefore, potential carry-over effect should be considered when interpreting the findings of the study by Rystedt et al.
- None of the four RCTs was conducted in North America. One was conducted in Korea. Whether the findings from the study by Yun et al. conducted in Korea can be generalized to a Canadian setting is uncertain.

Results

TWSTRS total score

TWSTRS total score was assessed in the study by Yun et al. as the secondary outcome[18] and in the study by Rystedt et al. as the primary outcome.[19] (Table 35) At week 4, there was no statistically significant difference between aboBoNTA and onaBoNTA in the results of the study by Yun et al. (mean –0.97, 95% CI [–3.39 to 1.45], *P* = 0.43), and in the study by Rystedt et al. (mean 0.98, 95% CI [−1.72, 3.67], *P* = 0.47). (Table 35).

Tsui score

Tsui score was reported as the primary outcome in all four studies except for the study by Rystedt et al., in which Tsui score was assessed as the secondary outcome (Table 36).

In Study 24, both groups showed substantial improvement in Tsui score at week 4 with Tsui score improvement (mean ± SD [%]) of 49% ± 29% for aboBoNTA versus 44% ± 28% for onaBoNTA. The Tsui score (mean ± SE) at week 4 for the aboBoNTA group was 4.8 ± 0.3, and for the onaBoNTA group, was 5.0 ± 0.3. However, the adjusted between-group difference (adjusted for baseline and centre effects) was not statistically significantly different (P = 0.66).[17] (Table 36)

In the study by Yun et al., the between-group difference of changes from baseline at week 4 for Tsui score (MD [95% CI]) was 0.8 (–0.20 to 1.80) in PP analysis (Table 37) and 0.78 (–0.13 to 1.70) in mITT analysis (Table 36). In the mITT population, the between-group differences at week 8 and 12 were –0.10 (–1.01 to 0.82) and 0.11 (–0.99 to 1.21), respectively. aboBoNTA was not noninferior to onaBoNTA based on the non-inferiority margin, which was defined as the upper limit of the one-sided 95% CI for the difference between treatments (aboBoNTA minus onaBoNTA) in changes from baseline as Tsui score ≤ 1.5 points in either mITT or PP analysis.

In the study by Rystedt et al., the Tsui scores in aboBoNTA and onaBoNTA groups appeared similar at week 4 and week 12, however, no statistical analysis was reported in the study.

In the study by Ranoux et al., the mean improvement of the Tsui score was 3.22 for onaBoNTA, 4.32 for aboBoNTA (3:1 ratio group), and 4.89 for aboBoNTA (4:1 ratio group). At week 4, in terms of Tsui score, compared with onaBoNTA, aboBoNTA was statistically significantly more effective in both aboBoNTA groups than onaBoNTA (P = 0.02 and 0.01, respectively). [20] (Table 36)

CGI-I, PGI-I and Investigator global assessment

Investigator's clinical global impression of illness (CGI-I) and patient's global impression of improvement (PGI-I) were only reported in the study by Yun et al. No significant differences were reported in the proportion of CGI-I or PGI-I over the four weeks and follow-up visits up to sixteen weeks.[18] (Table 38) Investigator global assessment was assessed in Study 24, where it showed a similar efficacy and safety profile between aboBoNTA and onaBoNTA treatment (See Table 39).

Duration of effect

The duration of the effect was assessed in Study 24 and in the study by Ranoux et al. In Study 24, a similar duration of effect between aboBoNTA and onaBoNTA was demonstrated. In the study by Ranoux et al., compared with onaBoNTA, the duration of effect was statistically longer in the aboBoNTA (4:1 dose ratio) group, but not statistically significantly different in the aboBoNTA (3:1 dose ratio) group. (See Table 40)

Harms

The incidence of TEAEs varied from study to study. But it was similar between aboBoNTA and onaBoNTA within each study except in the study by Ranoux et al., where the TEAE was reported higher in aboBoNTA group than that in placebo group (Table 41). The dysphagia and neck or/and should pain or weakness were reported in all studies. Especially, dysphagia was reported higher in aboBoNTA group than placebo group in study 24 and study by Ranoux et al. However, it was reported higher in onaBoNTA group than that in aboBoNTA group in study by Yun. (Table 41) One patient in onaBoNTA group reported SAE in study 24. No SAE was reported in remaining three studies. No patients withdrew due to adverse events (AEs) and no death was reported in any of the four RCTs. Antibody was not assessed in onaBoNTA-controlled RCTs.

Conclusion

The objective of the four onaBoNTA-controlled RCTs was to assess the clinical dose equivalence between aboBoNTA and onaBoNTA in the treatment of patients with CD who had been treated with, and had a stable response to, onaBoNTA or aboBoNTA previously. It was found that, compared with onaBoNTA treatment (mean dose range: 56 U to 142 U), aboBoNTA with 1.7 times, 2.5 times, 3 times, or 4 times the dose of onaBoNTA (mean dose range: 169 U to 477 U) showed an inconsistent dose ratio, but similar safety profiles. Two trials did not test for equivalency or non-inferiority. The trial by Ranoux et al. found statistical differences at a ratio of 3:1 and 4:1 in Tsui scores, but Study 24 did not find a statistical difference at a dose ratio of 3:1. Only one trial (Yun et al.)

concluded non-inferiority at a dose ratio of 2.5:1. No conclusion can be made for a dose ratio of 1.7:1 as statistical testing was not performed for equivalency or non-inferiority. Conflicting results are available for a dose ratio of 3:1, and at a dose ratio of 4:1, a statistical difference was found. Considering potential methodological limitations such as potential concomitant medication confounding, potential carry-over effect, limited statistical analysis to test for equivalency, study population limited to patients with stable response to onaBoNTA or aboBoNTA treatment, as well as the fact that none of the studies was conducted in North America, the findings from these trials should be interpreted with caution in Canadian settings.

Table 31: Details of OnaBoNTA-Controlled Studies

		Study 24	Study 227 by Yun et al.	Study by Rystedt et al.	Study by Ranoux et al.
Designs & Populations	**Study Design**	DB RCT	DB RCT, non-inferiority design	DB RCT	DB RCT, equivalence design
			(crossover design)		
	Locations	Sweden and Finland	Korea	Sweden	France
	Randomized (N)	73	102	46	54
	Inclusion Criteria	• Adult pts with CD • ≥ 4 onaBoNTA tx, with the latest being within 10 to 16 wks of study	• Pts with CD (regardless the history of onaBoNTA tx) • ≥ 20 yrs. • CD duration ≥ 18 mos.	• Pts with CD. • ≥ 18 yrs. • treated with aboBoNTA ≥ 1 year before the study and with a stabilized tx response to aboBoNTA	• Pts with CD • ≥18 yrs. • treated with two doses of onaBoNTA. • 16 weeks before the study with satisfying. • Improvement.
	Exclusion Criteria	• Other forms of CD • Pts required ≥ 250 U of onaBoNTA, or a dose of onaBoNTA 100 U more than a previous effective dose • Swallowing abnormalities	• Pts required dose ≥ 200 U onaBoNTA or ≥ 500 U aboBoNTA.	• Contraindications to onaBoNTA or aboBoNTA. • Other forms of CD.	• Contraindications to any of the investigational products.
Drugs	**Intervention**	aboBoNTA Dose: not fixed but based on the need of each pt. IM, single-dose tx			
		• aboBoNTA to onaBoNTA dose ratio: 3:1 • Average dose unit M ± SD (range) aboBoNTA: 477 ±131 (240 to 720)	• aboBoNTA to onaBoNTA dose ratio: 2.5:1 • Average dose unit M ± SD (range) aboBoNTA: 361.04 ± 57.91 (200 to 400)	• aboBoNTA to onaBoNTA dose ratio: 3:1 or 1.7:1 • Average dose unit: M ± SD (range) aboBoNTA (tr1) 169 ± 63 (50 to 400)	• aboBoNTA to onaBoNTA dose ratio: 3:1 or 4:1 • Average dose unit: M ± SD aboBoNTA: NR
	Comparator(s)	onaBoNTA Dose: M ± SD (range) 152 ± 45 (70 to 240)	onaBoNTA Dose: M ± SD (range) 144.41 ± 23.16 (80 to 160)	onaBoNTA (1:3 or 1:1.7 dose of aboBoNTA) Dose: M ± SD (range) NR	onaBoNTA Pre-tx average onaBoNTA: 104.44 ± 20.3 (70 to 180)
Duration	**Phase**	**3**	**4**	**3**	**3**
	Run-in	No	No	Yes (12 wks)	NR
	Double-blind	12 wks	16 wks (one period) plus washout: 4 wks	12 wks (one period) Washout: Not described	16 wks (one period to avoid carry-over effect)
	Follow-up	Followed up to Wk 16	Total: 36 wks	Total: 24 wks	Total: 32 wks

		Study 24	Study 227 by Yun et al.	Study by Rystedt et al.	Study by Ranoux et al.
Outcomes	**Primary End Point**	• Tsui score up to Wk 12 • Time to re-treatment	• Tsui score at Wk 4 (one month)	• TWSTRS at 4 wks	• Tsui score up to Wk 16
	Other End Points	• Pain • Investigator's global assessment • AEs	• TWSTRS at Wk 4 (one month); • % pts with CGI-I • % pts with PGI-I	• TWSTRS subscale s core • Tsui score • SF-36	• TWSTRS pain scale at Wk 16
Notes	**Publications**	Odergren et al.[17]	Yun et al.[18] Trial registry [51]	Rystedt et al.[19] Trial registry [52]	Ranoux et al.[20]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); AE = adverse event; BoNT = botulinum neurotoxin; BoNTA = botulinum neurotoxin A; BoNTB = botulinum neurotoxin B; CD = cervical dystonia; CGI-I = investigator clinical global impression of illness; CI = confidence interval; DB = double-blind; IM = intramuscular; NR = not reported; onaBoNTA = onabotulinumtoxinA (Botox); PGI-I = patient global impression of improvement; pts = patients; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; tx = treatment; wk = week

Source: CSRs 27 and publications.17-20

Table 32: Demographic and Baseline Characteristics (onaBoNTA-Controlled Studies)

	Study 24		Study 227 by Yun et al.			Study by Rystedt et al.		Study by Ranoux et al.
	aboBoNTA	onaBoNTA	Total	aboBoNTA – onaBoNTA	onaBoNTA – aboBoNTA	aboBoNTA – onaBoNTA	onaBoNTA – aboBoNTA	Total
No of patients	38	35	102 (94 completed)	49	53 (in total 102)	46 in total		In total 54
Age (yrs), M ± SD	51.3 ± 11.0	51.4 ± 10.4	53.30 ± 10.76	53.24 ± 11.44	53.35 ± 10.18	62 ± 11		56.1 (SD, NR)
range	31 to 78	26 to 70	NR	NR	NR	33–84		24–78
Female, n (%)	29 (76)	19 (54)	57 (55.9)	26 (50.1)	31(58.5)	NR		40 (74.1)
Height (cm) ± SD	169 ± 8	170 ± 8	60.03 ± 7.33	162.66 ± 7.08	162.00 ± 7.73			NR
range	155 to 187	154 to 187	NR	NR	NR			
Weight (kg) ± SD	71 ± 12	69 ± 10	162.66 ± 7.08	60.03 ± 7.33	60.25 ± 9.14			
range	(49 to 105)	(54 to 98)	NR	NR	NR			
Time since CD diagnosed (yrs), M ± SD	8.58 ± 8.67	11 ± 8.08	10.46 ± 8.62	11.36 ± 9.21	9.57 ± 8.00	17±10		13
range	2.5 to 47.6	1.25 to 34	NR	NR	NR	2 to 48		2 to 45
Patients with other dystonia, n (%))	2 (5)	4 (11)	NR	NR	NR	NR		NR
Family history of CD, n (%)	4 (11)	9 (26)	NR	NR	NR			
Pts with BoNTA or BoNTB tx before entry, n (%)	100%	100%	onaBoNTA 40 (42.6)	17 (37.0)	23 (47.9)	100%		100%
Pts with aboBoNTA tx before entry (%)	NR	NR	NR	NR	NR	100%		NR
Time since first onaBoNTA tx (yrs), M ± SD	3.5 ± 1.17	3.58 ± 1.5	NR	NR	NR	12 ± 5		
range	0.58 to 6.08	0.83 to 6.25	NR	NR	NR	2 to 21		
Total number of OnaBoNTA treatments, M ± SD	14.1 ± 5.7	15.9 ± 7.6	NR	NR	NR	NR		17.5 (SD: NR)
range	4 to 31	5 to 30	NR	NR	NR			(4 to 30)

	Study 24		Study 227 by Yun et al.			Study by Rystedt et al.	Study by Ranoux et al.
Total dose of onaBoNTA prior to entry (U), M ± SD	1,751 ± 884	2007 ± 1,110	NR	NR	NR		NR
range	345 to 4,980	370 to 4,115	NR	NR	NR		
Maximum single dose of onaBoNTA (U), M ± SD	168 ± 42	166 ± 44	NR	NR	NR		
range	90 to 250	90 to 275	NR	NR	NR		
Most recent onaBoNTA dose (U), M ± SD	152 ± 43	148 ± 43	NR	NR	NR		104.44 ± 20.6
range	60 to 240	50 to 240	NR	NR	NR		70 to 180
Time since most recent onaBoNTA treatment (mos.), M ± SD	3.2 ± 0.63	91 ± 22	19.59 ± 27.96	12.62 ± 9.56	24.37 ± 35.01		4.27
range	2.07 to 4.97	0.93 to 4.5	5 to 150	5 to 40	5 to 150		3.03 to 7.0
Tsui score at entry, M ± SD	7.4 ± 2.5	8.5 ± 2.4	NR	10.51 ± 4.66	10.73 ± 4.54		8.98 ± 3.3
range	3 to 14	4 to 14	NR				NR
TWSTRS total, M ± SD	NR	NR	NR	33.01 ± 13.90	32.49 ± 12.65	Median: 43.75	
Range	NR	NR	NR	NR	NR	16.00 to 62.75	
TWSTRS severity subscore, M ± SD	NR	NR	NR	16.63 ± 6.21	15.88 ± 5.85	NR	
TWSTRS disability subscore, M ± SD	NR	NR	NR	10.76 ± 5.52	10.62 ± 4.93		
TWSTRS pain subscore, M ± SD	NR	NR	NR	5.61 ± 4.84	6.12 ± 4.63		
Proportion of pain-free patients at entry, n (%)	12 (32)	11 (31)	NR				
N (%) scoring 1 or 2 or 3 in CGI (CGI-I)[a]	NR	NR	NR	25 (26.6)	24 (25.5)		

	Study 24		Study 227 by Yun et al.			Study by Rystedt et al.		Study by Ranoux et al.
The mean dose during the study (U), M ± SD	(3:1) 477 ± 131	152 ± 45	NR	(2.5:1) 361.04 ± 57.91	144.41 ± 23.16	169 ± 63	(1/3 or 1/1.7 of aboBoNTA) NR	NR, pre-baseline dose[a] 104.44 ± 20.6
range	240 to 720	70 to 240	NR	200 to 400	80 to 160	50 to 400	NR	70 to 180
Concomitant treatments (number of patients):								
Benzodiazepines	NR							22
Anticholinergics								29
Myorelaxants								30

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); BoNTA = botulinum neurotoxin A; BoNTB = botulinum neurotoxin B; CD = cervical dystonia; CGI = clinical global impression; CGI-I = CGI of illness; CI = confidence interval; DB = double-blind; M = mean; mos. = months; NR= not reported; onaBoNTA = onabotulinumtoxinA (Botox); pts = patients; SD = standard deviation; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; tx= treatment; U = units; yrs = years

[a] Pre-baseline dose in onaBoNTA minus aboBoNTA arm.

Source: CSRs [27] and publications.[17-20]

Table 33: Patient Disposition (onaBoNTA-Controlled RCTs)

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
	aboBoNTA	onaBoNTA	aboBoNTA – onaBoNTA	onaBoNTA – aboBoNTA	aboBoNTA – onaBoNTA	onaBoNTA – aboBoNTA	aboBoNTA – onaBoNTA	onaBoNTA – aboBoNTA
Screened, N	NR		103		123		NR	
Meet the inclusion criteria	NR		NR		73		NR	
Randomized, N (%)	38	35	49	53	46		54	
Dropout	NA	NA	4(8.2)	5(9.4)	NR		NR	
Protocol violation	NA	NA	4	4	NR		NR	
Assignment error	NA	NA	1	0	NR		NR	
ITT, N	38	35	mITT 48	mITT 46	NR		54	

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
PP, N	NR	NR	44	42	NR		NR	
Safety, N	38	35	48	46	44	45 in 1:3 43 in 1:1.7	52	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); ITT = intention-to-treat; mITT = modified intention-to-treat; NR= not reported; onaBoNTA = onabotulinumtoxinA (Botox); PP = per-protocol; pts = patients

Source: Consort tables in submission, [3] CSRs, [27] and publications.[17-20]

Table 34: Summary of Drug Exposure in onaBoNTA-Controlled RCTs

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
	aboBoNTA	**onaBoNTA**	**aboBoNTA – onaBoNTA**	**onaBoNTA – aboBoNTA**	**aboBoNTA – onaBoNTA**	**onaBoNTA – aboBoNTA**	**aboBoNTA – onaBoNTA**	**onaBoNTA – aboBoNTA**
Mean dose in the trial (U), M ± SD	(3:1) 477 ± 131	152 ± 45	(2.5:1) 361.04 ± 57.91	144.41 ± 23.16	169 ± 63	aboBoNTA : onaBoNTA (3:1 or 1.7:1) 56.33 ± 21 or 99.4 ± 3.71[a]	(3:1 or 4:1) 313 or 418[a]	NR pre-baseline dose: 104.44 ± 20.6.
Dose range	240 to 720	70 to 240	200 to 400	80 to 160	50 to 400	16.67 to 133.33 or 29.4 to 235.29[a]		70 to 180
# of tx	1		1		1		1	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; SD = standard deviation; onaBoNTA = onabotulinumtoxinA (Botox); tx = treatments; U = units

a Dose was calculated by CADTH.

Source: CSRs[27] and publications.[17-20]

Table 35: TWSTRS Scores (onaBoNTA-Controlled RCTs)

Scale	Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
	aboBoNTA	**onaBoNTA**	**aboBoNTA**	**onaBoNTA**	**aboBoNTA**	**onaBoNTA**
TWSTRS Total						
Baseline, M ± SD	33.01 ± 13.90	32.49 ± 12.65	Median: 43.75		NR	NR
Wk 4, M ± SD	NR	NR	33.86 ± 14.04	(1:3 arm) 35.75 ± 12.76; (1:1.7 arm) 34.60 ± 13.88	NR	NR
Mean changes of total TWSTRS from baseline at Wk 4, M ± SD	–9.76 ± 10.25	–8.78 ± 10.11	NR	NR	NR	NR

Scale	Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA
Btw-tx MD at wk 4 M (95% CI), *P* value	–0.97 (–3.39 to 1.45) *P* = 0.429		onaBoNTA vs. aboBoNTA (1:3) 1.86 (–0.88 to 4.60). *P* = 0.1812 onaBoNTA vs. aboBoNTA (1:1.7) 0.98 (–1.72 to 3.67), *P* = 0.4726 NR		NR	NR
Wk 12			36.88 ± 14.61	(1:3 arm): 39.81 ± 14.49; (1:1.17 arm): 38.11 ± 13.46	NR	NR
Mean changes of total TWSTRS from baseline at Wk 12	NR	NR	NR	NR	NR	NR
Between-tx MD at wk 12 M (95% CI), *P* value	–0.29 (–3.05 to 2.47) *P* = 0.837	NR	onaBoNTA vs. aboBoNTA (1:3) 3.07 (0.38 to 5.75), *P* = 0.0257 onaBoNTA vs. aboBoNTA (1:1.17) 1.54 (–1.15 to 4.22), *P* = 0.2576		NR	NR
TWSTRS Severity						
Baseline	16.63 ± 6.21	15.88 ± 5.85	NR	NR	NR	NR
Wk 4	NR	NR	NR	NR	NR	NR
Mean changes of TWSTRS severity subscore at Wk 4, M ± SD	–5.55 ± 4.99	–5.2 ± 64.79	NR	NR	NR	NR
Btw-tx MD at wk 4 Mean (95% CI) *P* value	–0.30 (–1.46, 0.86) *P* = 0.611		NR	NR	NR	NR
TWSTRS Disability			NR	NR	NR	NR
Baseline	10.76 ± 5.52	10.62 ± 4.93	NR	NR	NR	NR
Wk 4	NR	NR	NR	NR	NR	NR
Mean changes of TWSTRS disability subscore at Wk 4, M ± SD	–2.76 ± 3.64	–2.46 ± 3.60	NR	NR	NR	NR

Scale	Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA
Btw-tx MD at wk 4 M (95%) *P* value	–0.30 (–1.23 to 0.64) *P* = 0.529		NR	NR	NR	NR
TWSTRS Pain						
Baseline, M ± SD	5.61 ± 4.84	6.12 ± 4.63	NR	NR	(3:1 arm) 6.51 ± 5.29; (4:1 arm): 6.81 ± 6.01	5.65 ±5.27
Wk 4	NR	NR	NR	NR	NR	NR
Mean changes of TWSTRS pain subscore at Wk 4	–1.45 ± 4.05	–1.19 ± 4.16	NR	NR	(3:1) 4.41 ± 5.76 *P* = 0.04 (vs. onaBoNTA) (4:1): 5.37 ± 6.49 *P* = 0.02 (vs. onaBoNTA)	2.59 ± 5.43 (*P* value: NR)
Btw-tx MD at wk 4 M (95%), *P* value	–0.25 (–1.28 to 0.77) *P* = 0.623		NR	NR	NR	NR

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CI = confidence interval; M = mean; MD = mean difference; NR = not reported; onaBoNTA = onabotulinumtoxinA (Botox); SD = standard deviation; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; tx = treatment; wk = week;

Note: TWSTRS was not assessed in Study 24.

Source: Clinical Study Report, [27] publications.[17-20]

Table 36: Tsui Score (onaBoNTA-Controlled RCTs)

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
Scale	**aboBoNTA**	**onaBoNTA**	**aboBoNTA**	**onaBoNTA**	**aboBoNTA**	**onaBoNTA**	**aboBoNTA**	**onaBoNTA**
Tsui score								
Baseline	7.4 ± 2.5	8.5 ± 2.4	10.51 ± 4.66	10.73 ± 4.54	10.3 ± 4.8	10.3 ± 4.8	(3:1arm): 8.65 ± 3.39; (4:1 arm): 9.02 ± 3.32	8.65 ±3.34
Wk 4	3.8 ± 2.3	4.7 ± 2.7	NR	NR	7.5 ± 4.0	(3:1 arm): 8.1 ± 3.9; (1.7:1 arm) 7.6 ± 3.8	NR	NR
Btw-tx diff at wk 4 MD (95% CI) *P* value	NR	NR	0.78 (-0.13 to 1.70), P = 0.091 NS		NR	NR	NR	NR
Mean changes of from baseline at Wk 4	(%)↓ –49 ± 29	(%)↓ –37 ± 28	–3.98 ± 3.89 ↓	–4.77 ± 4.10 ↓	NR	NR	(3:1 arm): –4.29 ± 2.91 ↓ p = 0.02; (4:1 arm): –4.92 (2.86) ↓ *P* = 0.01	2.59 ±5.43↓
Wk 8	5.1 ± 3.1	5.9 ± 3.0	NR	NR	NR	NR	NR	NR
Mean changes of Tsui from baseline at Wk 8	(%) -32 ± 36	(%) -30 ± 30	NR	NR	NR	NR	NR	NR
Between-tx diff at wk 8 MD (95% CI) *P* value			–0.10 (–1.01 to 0.82), *P* = 0.836					
Wk 12	6.2 ± 2.9	7.2 ± 3.4	NR	NR	8.8 ± 4.6	(3:1 arm): 9.0 ± 4.2; (1.7:1 arm): 8.4 ± 3.8	NR	NR
Mean changes of Tsui from baseline at Wk 12	(%) –11 ± 40	(%) –14 ± 34	NR	NR	NR	NR	NR	NR
Btw-tx changes from baseline	NR	NR	NR	NR	NR	NR	NR	NR
Btw-tx diff at Wk 12, MD (95% CI),			0.11(–0.99 to 1.21)					

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.		Study by Ranoux et al.	
Scale	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA	aboBoNTA	onaBoNTA
P value			*P* = 0.837					

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); Btw = between; CI = confidence interval; diff = difference; M = mean; MD = mean difference; NR = not reported; onaBoNTA = onabotulinumtoxinA (Botox); SD = standard deviation; tx = treatment; Wk = week.

Source: CSRs[27] and publications.[17-20]

Table 37: Clinical Outcomes: Changes From Baseline at Week 4 (Per-Protocol Analysis)

Outcomes	aboBoNTA (N = 85)	onaBoNTA (N = 85)
Total Tsui Score		
Mean changes from baseline, M ± SD	–3.62 ± 3.76	–4.42 ± 4.05
Btw-group MD at end point, MD (95% CI)	0.80 (–0.20 to 1.80), *P* = 0.114	
TWSTRS Total		
Mean changes from baseline	–9.13 ± 10.03	–7.80 ±9.93
Btw-group MD at end point, MD (95% CI)	–1.32 (–3.39 to 1.45), *P* = 0.300	
TWSTRS Severity		
Mean changes from baseline, M ± SD	–5.18 ± 4.88	–4.81 ± 4.69
Btw-group MD at end point, MD (95% CI), *P* value.	–0.36 (–1.60 to 0.87), *P* = 0.558	
TWSTRS Disability		
Mean changes from baseline, M ± SD	–2.55 ± 3.56	–2.08 ± 3.48
Btw-group MD at end point, MD (95% CI), *P* value.	–0.47 (–1.43 to 0.48), *P* = 0.330	
TWSTRS Pain		
Mean changes from baseline, M ± SD	–1.40 ± 4.09	–1.01 ± 4.24
Btw-group MD at end point, MD (95% CI), *P* value.	–0.39 (–1.74 to 0.22), *P* = 0.487	
Patients Scoring 1 or 2 or 3 on CGI scale (CGI-I), n (%)	48/85 (56.5%)	50/85 (58.8%)
P value	0.839	
Patients Scoring 1, 2, or 3 on PGI Scale (PGI-I), n (%)	66/85 (77.6%)	70/85 (82.4%)
P value	0.481	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CGI = clinical global impression; CGI-I = clinical global impression of illness; onaBoNTA = onabotulinumtoxinA (Botox); M = mean; PGI = Patient's global impression; PGI-I = PGI of improvement; PP = per-protocol population; SD = standard deviation; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

Note: The proportions of patients with CGI of illness (CGI-I) of '1 = normal/not at all ill' or '2 = borderline mildly ill,' or '3 = mildly ill' and the proportions of patients with PGI of improvement (PGI-I) of '1 = very much improved,' '2 = much improved,' or '3 = mildly improved,' were compared for each month follow-up.

Source: Study by Yun et al.[18]

Table 38: CGI-I and PGI-I (onaBoNTA-Controlled RCTs)

Scale	Study 227 by Yun et al.	
	aboBoNTA (n = 94)	onaBoNTA (n = 94)
CGI-I, n (%) Number of patients (%) scoring 1 or 2 or 3 on CGI scale (CGI-I)[a]		
Baseline	25 (26.6)	24 (25.5)
Week 4	54 (57.4)	57 (60.6)
Between-treatment difference at Week 4 M (95% CI) *P* value	NR *P* = 0.648	
PGI-I, n (%) Number of patients (%) scoring 1 or 2 or 3 on PGI scale (PGI-I)[a]		
Baseline	NR	NR
Week 4	75 (79.8)	78 (83.0)
Between-treatment difference at Week 4 M (95% CI) *P* value	NR *P* = 0.690	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CGI = clinical global impression; CGI-I = CGI of illness; CI = confidence interval; M = mean; MD = mean difference; NR = not reported; onaBoNTA = onabotulinumtoxinA (Botox); PGI = patient's global impression; PGI-I = PGI of improvement.

a The proportion of patients with CGI of illness (CGI-I) of '1 = normal/not at all ill,' '2 = borderline mildly ill,' or '3 = mildly ill' and the proportion of patients with PGI of improvement (PGI-I) of '1 = very much improved,' '2 = much improved,' or '3 = mildly improved,' were compared for each month follow-up.

Source: Study by Yun.et al.[18]

Table 39: Investigator Global Assessment of Efficacy and Safety (onaBoNTA-Controlled RCTs)

Week 12	Study 24	
	aboBoNTA (N = 38)	onaBoNTA (N = 35)
Investigator global assessment - *efficacy* n (%)		
Much better	[redacted]	[redacted]
Better		
No change from baseline	[redacted]	[redacted]
Worse	[redacted]	[redacted]
Much worse	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]
Investigator global assessment - *safety* n (%)		
None	[redacted]	[redacted]
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Extreme	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); onaBoNTA = onabotulinumtoxinA (Botox);

a Reported as "excellent," "good," "moderate" and "slight" (improvement)

Source: Study 24 Clinical Study Report.[27]

Table 40: Duration of Action in Study 24 and Study by Ranoux et al.

	Study 24		Study by Ranoux et al.		
	aboBoNTA	onaBoNTA	aboBoNTA (3:1)	aboBoNTA (4:1)	onaBoNTA
N			51	52	51
Duration of action (wks) M ± SD	12 ± 2	11.6 ± 2	13.8 ± 5.61	16.29 ± 9.9	12.76 ± 5.7
Median	12	12	NR	NR	NR
Range	8 to 17.4	7 to 15.9	0 to 24.6	6.91 to 70.1	0 to 33.6
P value (aboBoNTA vs. onaBoNTA)	0.85		0.58	0.02	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); M = mean; NR = not reported; onaBoNTA =onabotulinumtoxinA (Botox); SD = standard deviation; wks = weeks

Source: Study 24 Clinical Study Report [27] and study by Ranoux et al.[20]

Table 41: Adverse Events (onaBoNTA-Controlled RCTs)

	Study 24		Study 227 by Yun et al.		Study by Rystedt et al.			Study by Ranoux et al.		
	aboBoNTA (n = 38)	onaBoNTA (n = 35)	aboBoNTA (n = 94)	onaBoNTA (n = 94)	aboBoNTA (n = 44)	onaBoNTA (3:1) (n = 45)	onaBoNTA (1.7:1) (n = 43)	aboBoNTA (3:1) (N = 51)	aboBoNTA (4:1) (N = 52)	onaBoNTA (N = 51)
Pts with ≥ one AE, n (%)	22 (58)	24 (69)	14 (14.9)	19 (20.2)	27 (61.4)	29 (64.4)	30 (69.8)	17 (33)	19 (36)	9 (17.6)
Dysphagia	6 (16)	4 (11)	6 (6.4)	12 (12.8)	7 (15.9)	7 (15.6)	9 (20.9)	8 (15.6)	9 (17.3)	2 (3.9)
Pharyngitis	4 (11)	6 (11)			NR	NR	NR	NR	NR	NR
Headache	3 (8)	6 (17)	1 (1.1)	0 (0.0)	NR	NR	NR	NR	NR	NR
Fatigue	3 (8)	4 (11)	0 (0.0)	1 (1.1)	NR	NR	NR	NR	NR	NR
URT infection	4 (8)	3 (9)			NR	NR	NR	NR	NR	NR
Neck/shoulder pain or weakness	3 (8)	1 (3)	11 (11.7)	20 (21.2)	12 (27.3)	11 (24.4)	15 (34.9)	3 (5.9)	2 (3.8)	2 (3.9)
Dry mouth	0 (0)	3 (9)	NR	NR	4 (9.1)	12 (26.7)	6 (14.0)	2 (3.9)	1 (1.9)	0
Muscle weakness	3 (8)	0 (0)	NR	NR	NR	NR	NR	NR	NR	NR
Diarrhea	1 (3)	2 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Coughing	0 (0)	2 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Dysphonia	0 (0)	2 (6)	NR	NR	NR	NR	NR	3 (5.9)	3 (5.8)	0
Epistaxis	2 (5)	0 (0)	NR	NR	NR	NR	NR	NR	NR	NR
Urinary tract infection	0 (0)	2 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Local pain (at injection)	NR	NR	2 (2.1)	1 (1.1)	NR	NR	NR	3 (5.9)	3 (5.8)	2 (3.9)
Neck rigidity	NR	NR	1 (1.1)	1 (1.1)	NR	NR	NR	NR	NR	NR
Hoarseness	NR	NR	1 (1.1)	1 (1.1)	NR	NR	NR	NR	NR	NR
Dyspnea	NR	NR	0 (0.0)	1 (1.1)	NR	NR	NR	NR	NR	NR
Paresthesia	NR	NR	0 (0.0)	1 (1.1)	NR	NR	NR	NR	NR	NR
Dysarthria	NR	NR	0 (0.0)	1 (1.1)	NR	NR	NR	NR	NR	NR
Asthenia	NR	NR	NR	NR	NR	NR	NR	2 (3.9)	7 (13.5)	2 (3.9)
Others*	7 (16)	21 (40)	NR	NR	NR	NR	NR	1 (2.0)	2 (3.8)	2 (3.9)

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); NR = not reported; onaBoNTA = onabotulinumtoxinA (Botox); pts = patients; URT = upper respiratory tract

Source: Clinical Study Report[27] and publications.[17-20]

Appendix 8: Summary of Indirect Treatment Comparisons

Background

The aim of this section is to review and critically appraise any indirect treatment comparisons (ITCs) that compare abobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) 500 U to any appropriate comparison in the management of patients with cervical dystonia (CD).

Dysport Therapeutic 500 U has been previously compared with placebo in two clinical trials. However, no head-to-head evidence of Dysport Therapeutic 500 U compared against other forms of botulinum toxin exist. Therefore, ITCs that include Dysport Therapeutic 500 U can provide information on the comparative effectiveness and safety of this drug to existing therapies, and would be relevant to this CADTH Common Drug Review (CDR).

Methods

The manufacturer submitted one published ITC and one commissioned ITC, both were reviewed and critically appraised. Also, a comprehensive literature search was performed by an information specialist to identify published ITCs. Any potentially identified ITCs from the literature were summarized and contrasted against the manufacturer's ITC.

Description of Indirect Treatment Comparisons Identified

We were able to identify one published, manufacturer-submitted ITC.[23] Han et al. 2016 was a systematic review, and a Bayesian-based mixed treatment comparison of the efficacy of all available botulinum toxin serotypes A and B for the treatment of patients with CD measured through the Toronto Western Spasmodic Torticollis Rating Score (TWSTRS) score.

Also, the manufacturer commissioned and submitted an ITC as part of their economic evaluation.[24] The manufacturer's ITC was a structured review and a Bayesian-based mixed treatment comparison to assess the efficacy, as measured by the TWSTRS score, of Dysport Therapeutic compared with incobotulinumtoxinA (incoBoNTA, Xeomin) through onabotulinumtoxinA (onaBoNTA, Botox) in patients with CD.

Review and Appraisal of ITCs

Review of Han et al. 2016

The objective of Han et al. 2016 was to perform an analysis on the comparative efficacy all available botulinum toxin serotypes A and B for the treatment of patients with CD measured through the TWSTRS score. Specifically, the ITC aimed to assess the comparative effectiveness of five botulinum toxin products: Dysport Therapeutic (aboBoNTA, abobotulinumtoxinA), Botox (onaBoNTA, onabotulinumtoxinA), Xeomin (incoBoNTA, incobotulinumtoxinA), Prosigne (Chinese botulinum toxin serotype A), and Myobloc (rimabotulinumtoxinB).[23]

The lack of appropriate head-to-head comparison and the unlikely aspect of such evidence existing shortly, coupled with the considerable prevalence of the condition at neurology clinics was used as a rationale for conducting this ITC. The authors also reported that no other ITC that compared these interventions exists in the literature.

Methods for Han et al. 2016

Study eligibility and selection process

Inclusion criteria for Han et al. 2016 ITC were randomized controlled trials (RCTs) of patients diagnosed with CD who underwent therapy with Dysport Therapeutic (dose unspecified but only studies with a reported 500 U were included), or any dosage of Botox, Xeomin, Prosigne, or Myobloc, and the outcome was reported using the TWSTRS tool. Specific exclusion criteria included studies comparing other interventions than the ones mentioned previously.

Regarding the literature search, a systematic search was conducted over the following bibliographical databases: Embase, MEDLINE, and MEDLINE(R) In-Process. The search covered articles from the database inception up to February 2014 and had no language restrictions.

The published article did not specify on the method in which retrieved citations were screened and selected.

Data extraction

The published article did not specify on the method in which relevant data were extracted from included studies.

Comparators

All relevant comparators were included in Han et al. 2016, including Dysport Therapeutic, Botox, Xeomin, Prosigne, and Myobloc.

Outcomes

Han et al. 2016 focused on reporting on the TWSTRS efficacy outcome. TWSTRS pain and dysphagia subcategory, as well as injection site pain, were synthesized as safety-related outcomes.

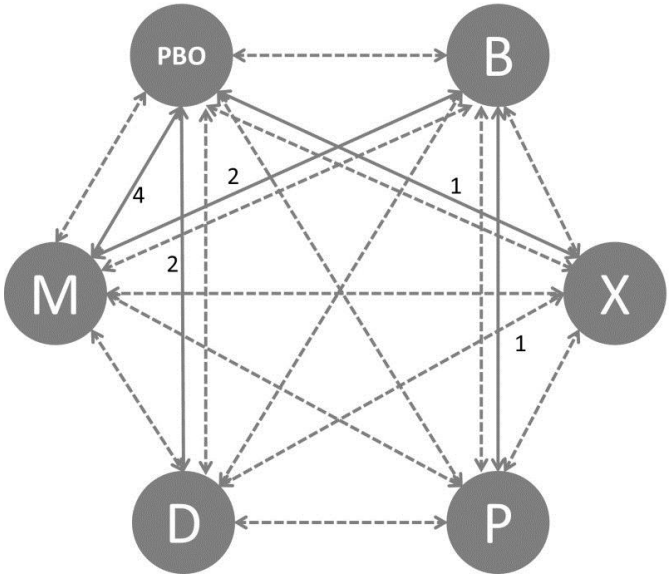
Quality assessment of included studies

The published article did not specify on the method in which included studies were assessed for quality and potential sources of bias.

Evidence network

Han et al. 2016 provided three network diagrams: one based on the efficacy as measured by TWSTRS total, disability and severity, one based on the TWSTRS pain subscale and dysphagia, and one based on the injection site pain. Graphical representation of the networks, as presented in Han et al. 2016, is provided below.

Figure 2: TWSTRS Total, Disability, and Severity Network



PBO = placebo; B = Botox; X = Xeomin; P = Prosigne; M = Myobloc.

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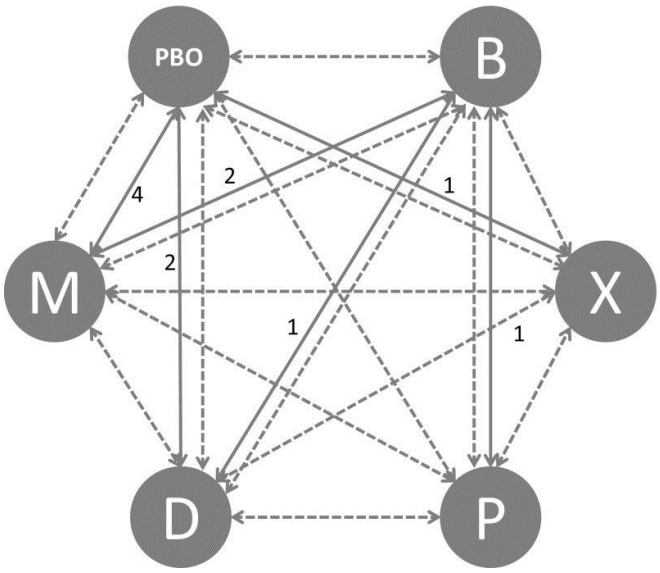
Figure 3: TWSTRS Pain and Dysphagia Network



PBO = placebo; B = Botox; X = Xeomin; P = Prosigne; M = Myobloc.

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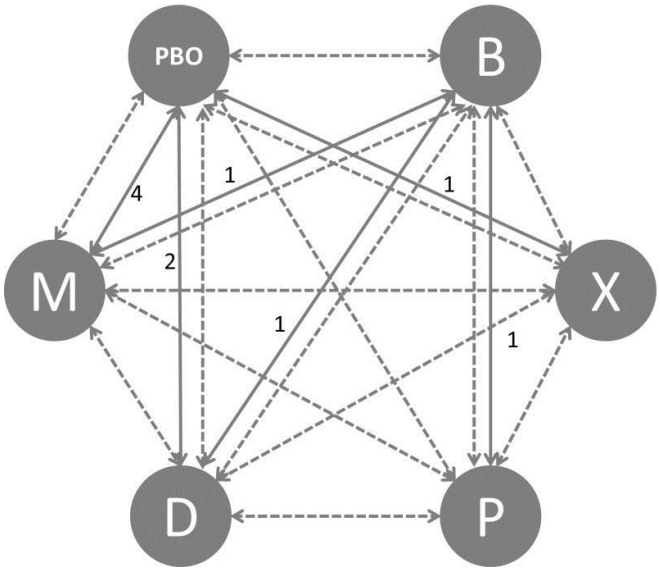
Figure 4: Injection Site Pain Network



PBO = placebo; B = Botox; X = Xeomin; P = Prosigne; M = Myobloc.

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Indirect treatment comparison methods of Han et al. 2016

Han et al. 2016 reported using a Bayesian hierarchical mixed treatment comparison model. The authors used a random effect model to account for potential heterogeneity in included trials. The authors did not report on the type of prior use, testing for convergence, the number of iterations and burn-ins, diagnostics for model fit and residual heterogeneity, testing for inconsistency, whether any sensitivity analysis was conducted, or if any subgroup analysis was planned. The authors described that in cases where the standard deviation was not reported in the trial, they imputed it with the largest deviation measure that is reported either at baseline or week 4. Similar doses of the same ingredient were pooled together. The continuous outcome was modelled from a normal distribution centred on the pairwise mean differences; dichotomous outcomes were modelled as a binomial distribution with a logit transformation.

Results of Han et al. 2016

A total of 11 RCTs were included in the ITC. These trials included Myobloc versus placebo (four trials), Dysport Therapeutic versus placebo (two trials), Xeomin versus placebo (one trial), Dysport Therapeutic versus Botox (one trial), Prosigne versus Botox (one trial), and Myobloc versus Botox (two trials). All trials were of a double-blind (DB), randomized controlled design, one was specified as a crossover trial, and all but two trials specified the outcomes measure at four weeks. The dose of interventions varied between trials. The authors did not report any further characteristics regarding the study and patient characteristics. Even for Dysport Therapeutic, for which the authors seemed to have intended to use only a dose of 500 U, they included one study that did not use a fixed 500 U dose.

Clinical efficacy outcomes using the TWSTRS total and subscale scores showed that all interventions, except Prosigne, are statistically significantly superior when compared with placebo (Table 42). The authors did not publish the exact results of head-to-head comparisons between different toxins. However, they reported that, with the exception of Prosigne, all other interventions did not show a statistically significant difference. Safety outcomes were focused on the incidence of dysphagia and injection site pain; the authors reported the relative log odds ratio of dysphagia compared with placebo. The results showed that Dysport Therapeutic, Xeomin, and Myobloc had statistically significantly higher odds of being associated with dysphagia when compared with placebo. All other comparisons showed no statistically significant differences with placebo. The authors did not publish any direct or indirect head-to-head safety outcomes.

Table 42: Efficacy Results Compared With Placebo From Han et al. 2016 Indirect Treatment Comparison

Change at 4 weeks	TWSTRS total		TWSTRS severity		TWSTRS disability		TWSTRS pain	
BoNT	Median	95 % CrI	Median	95 % CrI	Median	95 % CrI	Median	95 % CrI
Botox	−5.779	−9.222, −2.399	−2.007	−3.726, −0.2261	−1.784	−3.293, −0.3679	−1.164	−2.419, 0.0401
Dysport Therapeutic	−7.761	−11.43, −4.195	−3.439	−4.938, −1.687	−2.161	−3.536, −0.5743	−2.554	−3.777, −1.392
Xeomin	−8.215	−10.97, −5.352	−2.645	−4.133, −1.219	−3.146	−4.318, −2.029	−2.222	−3.36, −1.084
Myobloc	−7.221	−9.535, −4.91	−2.383	−3.451, −1.138	−2.007	−2.962, −1.119	−2.276	−3.184, −1.408
Prosigne	−3.645	−17.31, 9.059	−1.972	−7.483, 3.23	−0.6752	−5.357, 3.448	−0.6075	−4.761, 3.393

CrI = credible interval; BoNT = botulinum neurotoxin; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

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Table 43: Safety Results Compared With Placebo From Han Et Al. 2016 Indirect Treatment Comparison

Log odds ratio (LOR)	Dysphagia			Injection site pain		
	Median	95 % CrI low	95 % CrI high	Median	95 % CrI low	95 % CrI high
Botox	1.012	−0.3997	2.855	1.076	−0.6695	3.065
Dysport Therapeutic	2.212	0.8621	4.108	0.9522	−0.01974	2.016
Xeomin	2.086	0.347	4.349	0.1427	−1.123	1.611
Myobloc	2.144	1.116	3.818	0.2664	−0.5163	1.027
Prosigne	1.293	−1.264	4.366	−2.238	−5.726	1.417

CrI = credible interval; LOR = log odds ratio.

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The authors provided no assessment of consistency, model fit, convergence, residual heterogeneity, or sensitivity analysis.

Critical appraisal of Han et al. 2016

Han et al. 2016 provided research questions that incorporated relevant population, interventions, comparators, and outcomes. The inclusion of patients with CD and the specific assessment of Dysport Therapeutic 500 U make this a relevant ITC. In addition, the outcome (synthesized TWSTRS) is the same primary efficacy outcome used in this Formulary Review. The authors conducted a wide search strategy that is likely to capture all relevant studies over two major bibliographic databases. The authors' method of imputing missing deviation information was conservative and would have substituted the missing data with a "worst case scenario" data point.

However, the study lacks reporting on essential items that would allow us to assess the credibility and quality of the results and the conduct of the studies. These items include:

- It is unclear whether the screening and data extraction processes were conducted in duplicate. Systematic reviews minimize human error in screening and data extraction through employing a screening and extraction process that includes at least two independent reviewers with a third reviewer to adjudicate disagreements. As the authors did not inform on this item, we are unable to judge if proper standards were conducted in the review process. Potential drawbacks of using a single reviewer would include missing relevant articles and extracting wrong data which can affect both the internal and external validity of the ITC.
- The characteristics of the enrolled patients in each of the included studies were not described in detail. While the authors provided sufficient information regarding the characteristics of the studies included, not enough information was provided regarding the population in each of these studies. These include: treatment experience, disease duration, disease severity, and any potential co-interventions. Such information is important to assess potential methodological and clinical heterogeneity in the included studies.
- The priors that were used in the Bayesian analysis were not described. This is an important piece of information, as informative priors can affect the result in either direction. The authors did not report if they used an informative or a non-informative (vague) prior.
- It is unclear whether the statistical model achieved convergence. A Bayesian statistical model that does not achieve convergence cannot produce reliable and replicable results. The authors did not provide any diagnostic measure to assess convergence.
- The number of burn-ins and iterations were conducted were not reported. Should the authors have conducted a Bayesian model using a simulation method then the number of the simulations conducted should have been reported to provide an indication on the homogeneity of the data and the reliability of the results.
- It is unclear whether there is a good statistical fit for the model. Diagnostics for the statistical fit of the model indicate the extent at which the model is appropriate for answering the research question using the data at hand. The authors did not report any diagnostic to allow such assessment to be made.

Further to the lack of reporting of key information, the authors included one study of Dysport Therapeutic versus Botox, Ranoux et al., which did not administer Dysport Therapeutic at 500 U. This affects the internal validity of the analysis as well as its applicability to this CDR. Also, the authors pooled together different doses of same interventions and included some outcomes beyond week 4 in the analysis, these points increase the heterogeneity in the ITC. While the authors recognize that the trial that compared Prosigne to Botox was exerting a large influence over the network, the authors do not expand on the reasons behind this and do not perform a sensitivity analysis to estimate the exact influence this trial has on the network. Also, the evidence network included no closed loops. Thus, an assessment of consistency between direct and indirect evidence cannot be made.

Finally, the authors only provided results of the interventions compared with placebo. Arguably, ITC is valuable in provided head-to-head evidence between two active interventions, as evidence with comparisons against placebo is already available. Also, only outcomes at week 4 were analyzed, limiting the usability of the results. The authors, narratively, report that there were no differences between the interventions, without providing exact numbers. As such, it is exceedingly difficult to draw any conclusions. In addition, the authors did not discuss whether they had sufficient statistical power to detect differences between active interventions. As such, a finding of lack of statistically significant difference does not necessary indicate similarity in effect.

Review of Manufacturer-Submitted Indirect Treatment Comparison

Objectives and rationale for ITC B

Due to the increasing evidence of similarity in clinical efficacy and safety features of Dysport Therapeutic and Xeomin in comparison to the conventional Botox therapy for the treatment of CD, the authors thought it necessary to conduct a comparative analysis of the two alternatives to inform the economic evaluation of Dysport Therapeutic. It is through available published evidence of direct comparison between Botox and Dysport Therapeutic and Xeomin each, that an ITC is feasible using a common reference group.

Study eligibility and selection process

A structured literature search was conducted by the manufacturer using clinical trial registries and the following electronic medical databases: MEDLINE including epub ahead of print, in-process and non-indexed citations, Embase, and Cochrane Library on Wiley. A number of vocabulary and keywords were used to screen relevant articles, and a modified Cochrane highly-sensitive search strategy was used to filter for RCTs. There is no information on duplicate reviewers for study selection process.

Inclusion criteria for the structured literature search included RCTs conducted in adults ≥ 18 years with CD and where an active comparator of botulinum toxin A (BoNTA) therapies was included. Studies involving animals only and opinion pieces were excluded, as were studies published in a language other than English. No publication period was specified.

In total, five direct, DB RCTs were identified, four of which compared Dysport Therapeutic to Botox and one compared Xeomin to Botox directly. Only two head-to-head RCTs, one comparing Dysport Therapeutic to Botox and the other comparing Xeomin and Botox were included in the ITC by the manufacturer as only these two had the relevant outcome measured (TWSTRS severity subscale score).

Data extraction

From the available information, the authors did report if data extraction process involved independent reviewers.

Comparators

The comparator in all included studies in the structured literature review and the ITC was Botox.

Outcomes

In this ITC, the primary efficacy outcome was based on the TWSTRS severity subscale score. A secondary ITC analysis using the TWSTRS pain subscale score was also conducted. Any occurrence of adverse event (AE) and dysphagia were considered measurements of safety.

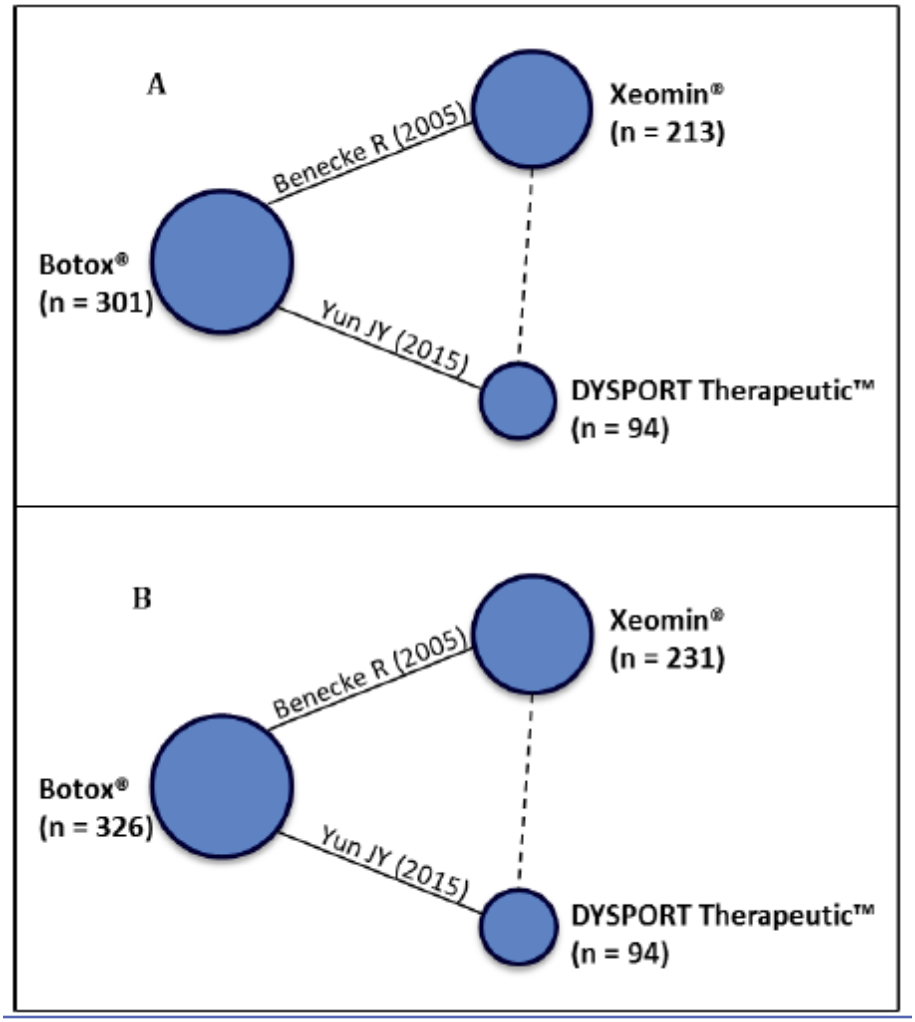
Quality assessment of included studies

The authors did not provide any information on quality assessment of studies for inclusion/exclusion, or any source of biases.

Evidence network

Two network diagrams were presented in the ITC, the first one depicting available evidence for the TWSTRS severity and TWSTRS pain subscale scores analysis and the second one depicting available evidence for the safety outcomes. Within the diagrams, treatment is represented by a node, and the link between the nodes reflects randomized comparisons between each treatment. The size of each node and the width of each link are proportional to the sample size and number of studies, respectively.

Figure 5: Network Diagrams of Included Studies Showing Available Evidence for (A) TWSTRS Severity and TWSTRS Pain Subscale Scores Analysis, and (B) Any AE and Dysphagia



Source: Manufacturer-submitted pharmacoevaluation report.[24]

Indirect Treatment Comparison Methods of Manufacturer-Submitted Indirect Treatment Comparisons

For this ITC analysis, a Bayesian ITC as described in the National Institute for Health and Care Excellence (NICE) Technical Support Document Series was performed for each outcome.

To compare the measure of effect following intervention, a continuous ITC model was used for outcomes of interest (i.e., TWSTRS severity subscale score and TWSTRS pain subscale score) and a binary ITC model was used for safety-related outcomes (i.e., any AEs and dysphagia). For continuous end points, the comparisons were reported as mean difference (MD) along with 95% credible intervals (CrI), with an MD value < 0 indicating beneficial effect. For binary end points, odds ratios (ORs) were generated along with 95% CrI.

The authors performed both fixed and random effect model to account for summary effect across studies and potential heterogeneity between studies, respectively. Vague prior distribution was used; however, there is no information on checking for sensitivity to the prior assumptions. Burn-in and sample iterations of 40,000 were conducted for both analyses. Model convergence was assessed by Trace plots and Gelman–Rubin plots. Adequacy of model fit was tested using the deviance information criterion (DIC) and by comparing the posterior residual deviance with the number of unconstrained data points (i.e., the number of intervention groups). Tests for homogeneity between studies, similarity across studies, and consistency between direct and ITC as well as sensitivity/subgroups analyses were not reported.

Results for Manufacturer-Submitted Indirect Treatment Comparison

The two RCTs in this ITC involved a comparison of Dysport Therapeutic (given at a dose below 500 U) to Botox and Xeomin to Botox. The patient and study characteristics were similar in nature and are outlined in Table 44. Briefly, both trials were randomized, DB, and crossover in design. The commonly measured end point in both studies was mean change in TWSTRS severity from baseline to week four following each injection. There were differences in sample size, follow-up period, and patient inclusion criteria between the two studies.

Table 44: Overview of Study and Patient Baseline Characteristics in RCTs Included in the ITC

Comparing Factors	Yun et al.	Benecke et al.
Intervention	aboBoNTA (below 500 U)	incoBoNTA
Comparator	onaBoNTA	onaBoNTA
Study size (N)	102	463
Primary end point	Mean change in Tsui scale from baseline to 4 weeks post injection	Mean change in TWSTRS severity subscale score from baseline to 4 weeks post injection
Secondary end point	Mean change in TWSTRS total score and TWSTRS severity, disability, and pain subscale scores from baseline to week 4 post injection	Mean change in TWSTRS severity and pain subscale score scores from baseline to week 4 post injection
Follow-up	36 weeks	16 weeks
Patient inclusion criteria	Diagnosed with cervical dystonia Age > 20 years Disease duration ≥ 18 months	Diagnosed with cervical dystonia Stable response to previous Botox therapy TWSTRS severity subscale score ≥ 10, rotational score ≥ 2, and rotational score higher than laterocollis and retrocollis
TWSTRS severity (mean score)	16.73	18[a]
Previous BoNTA use (%)	40	100

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); onaBoNTA = onabotulinumtoxinA (Botox); RCT = randomized controlled trial

Note: A number of primary and secondary efficacy outcomes and patient characteristics are not provided in this table, as these were not consistently reported across the two trials.

[a] Represents median score

Source: Manufacturer-submitted pharmacoevaluation report.[24]

ITC results for efficacy outcomes

With regards to the outcomes, both Dysport Therapeutic and Xeomin had similar mean improvement of TWSTRS severity and TWSTRS pain subscale scores and the occurrence of safety-related outcomes had similar rates in these interventions. Using these date, ITC models were generated to compare Dysport Therapeutic and Xeomin, fixed and random effect ITCs were performed and adequacy of model fit was tested.

Findings from the efficacy results of the ITCs show that in both FE and RE models, there were no statistically significant improvements in TWSTRS severity or TWSTRS pain subscale scores between Dysport Therapeutic and Xeomin. These results were mostly replicated when the two treatments were compared individually with Botox, with the exception of TWSTRS pain subscale scores, which showed an improvement by Xeomin compared with Botox only in the FE model.

Table 45: Results for Primary Measure of Efficacy for the ITC and Individual RCTs

ITC Groups	Primary Efficacy Outcome			
	Fixed-Effects Model MD Change From Baseline to Week 4, (95% CrI)		Random-Effects Model MD Change From Baseline to Week 4, (95% CrI)	
	TWSTRS – Severity	TWSTRS – Pain	TWSTRS –Severity	TWSTRS – Pain
aboBoNTA vs. incoBoNTA	–0.09 (–1.68 to 1.50)	–0.46 (–1.65 to 0.72)	–0.09 (–9.15 to 8.91)	–0.45 (–9.36 to 8.37)
aboBoNTA vs. onaBoNTA	–0.29 (–1.69 to 1.11)	–0.26 (–1.43 to 0.91)	–0.28 (–6.70 to 6.17)	–0.24 (–6.63 to 6.12)
incoBoNTA vs. onaBoNTA	–0.20 (–0.96 to 0.57)	0.20 (0.03 to 0.37)	–0.20 (–6.54 to 6.16)	0.20 (–6.06 to 6.47)

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CrI = credible interval; incoBoNTA = incobotulinumtoxinA (Xeomin); ITC = indirect treatment comparison onaBoNTA = onabotulinumtoxinA (Botox); RCT = randomized controlled trial; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

Source: Manufacturer-submitted pharmacoevaluation report.[24]

Results of model fit statistics indicated that both FE and RE model achieved an adequate fit for the efficacy end points, as demonstrated by the posterior residual deviance values of 1.993 and 2.006 for the primary efficacy end point, respectively for FE and RE models; both of which were close to the number of unconstrained data points of 2. Further, DIC values were similar in the two models, 5.111 and 5.138 for FE and RE, respectively.

ITC results for safety-related outcomes

The pattern of ITC results for safety-related outcomes was similar to the efficacy end points in both FE and RE models. Both the comparator groups, Dysport Therapeutic and Xeomin, showed no significant difference in the occurrence of any AEs or dysphagia when modelled for ITC using the FE and RE models. This pattern remained consistent across the individual trials when each of the comparators was analyzed against Botox.

Table 46: Safety results for the ITC and individual RCTs

ITC Groups	Primary Safety Outcome			
	Fixed-effects Model OR (95% CrI)		Random-effects Model OR (95% CrI)	
	Any Adverse Event	Dysphagia	Any Adverse Event	Dysphagia
aboBoNTA vs. incoBoNTA	0.56 (0.23 to 1.33)	0.33 (0.09 to 1.09)	0.55 (0.01 to 21.45)	0.33 (0.01 to 13.10)
aboBoNTA vs. onaBoNTA	0.69 (0.31 to 1.47)	0.45 (0.15 to 1.24)	0.68 (0.05 to 9.44)	0.45 (0.03 to 6.36)
incoBoNTA vs. onaBoNTA	1.23 (0.81 to 1.87)	1.37 (0.73 to 2.60)	1.24 (0.10 to 16.21)	1.36 (0.10 to 17.81)

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CrI = credible interval; incoBoNTA = incobotulinumtoxinA (Xeomin); ITC = indirect treatment comparison onaBoNTA = onabotulinumtoxinA (Botox); OR = odds ratio; RCT = randomized controlled trial

Source: Manufacturer-submitted pharmacoevaluation report.[24]

Similar to ITC models for efficacy outcomes, model fit statistics for both safety end points showed adequate model fit. The posterior residual deviance values for any AE were 4.025 and 4.012, respectively, for FE and RE models; close to the number of unconstrained data points of 4. DIC values for both FE and RE models were similar, 28.199 and 28.171, respectively.

Critical appraisal of manufacturer-submitted ITC

The authors provided a clear research question, were transparent with the methods that were taken in the study, provided sufficient information regarding the characteristics of included studies, and provided a comprehensive report of the statistical analysis.

Several major limitations are associated with the manufacturer-submitted ITC. They include:

- Lack of systematic review approach: Although the authors performed a comprehensive search over several key databases, the approach was not systematic in nature and lacked the appropriate steps of screening articles, extracting relevant data, and assessing the quality of included studies. This leaves a room for missing relevant literature that would inform the results, increase the possibility of human error in screening and data extraction, and leaves the quality of the ITC unknown — thus, threatening both internal and external validity of the ITC.
- Dysport Therapeutic dose not the approved dose: The dose included in this ITC was below 500 U. The Health Canada approval as well as the focus of this CDR is for Dysport Therapeutic at a dose of 500 U. This threatens the applicability of the ITC.
- Missing Patient Population Data: There was a considerable amount of information missing regarding the characteristics of enrolled patients in each of the included studies. While the authors provided sufficient information regarding the characteristics of the studies included, not enough information was provided regarding the population in each of these studies. These include, treatment experience, disease duration, diseases severity, and any potential co-interventions. Such information is important to assessing potential methodological and clinical heterogeneity in the included studies.
- The authors used the lack of statistically significant differences as an indicator of similarity. This is not necessary the case, especially in the small network like this one and where the authors provided us no calculation of power analysis.

Discussion and Conclusion

Both ITCs followed a similar analysis approach using Bayesian mixed treatment comparison, and both have reported results that lack statistical significance when comparing Dysport Therapeutic to other treatments. However, this is the extent of their similarities; as both have different inclusion criteria with regard to the dose of Dysport Therapeutic and the type of studies to be included, and one was a systematic review while the other was a structured review.

Han et al. 2016 included 11 trials in the ITC and had reported clinical efficacy outcomes using the TWSTRS total and subscale scores that demonstrated that all interventions, with the exception of Prosigne, were statistically significantly superior when compared with placebo. The authors also reported narratively that, with the exception of Prosigne, all other interventions did not show a statistically significant difference, despite not providing any numerical evidence to support this claim. The authors omitted several key pieces of information that would have allowed us to assess the reliability and robustness of the results. Also, the authors included one study that did not administer Dysport Therapeutic at the approved dose. In addition, the authors limited the overall value of the results by restricting the outcome reporting to comparisons with placebo. As such, we cannot determine the overall conclusion that Dysport Therapeutic has a similar effect to Botox, Xeomin, or Myobloc.

The manufacturer's ITC was not a systematic review and thus is potentially missing vital information. Efficacy was reported between Dysport Therapeutic and Xeomin and Botox as lacking statistical significance on the TWSTRS severity subscale, TWSTRS pain subscale, AEs, and dysphagia. Despite good statistical analysis and similar results with Han et al. 2016, the lack of a systematic review approach and the inclusion of a Dysport Therapeutic dose that is not the approved by Health Canada, makes the results of the analysis highly uncertain.

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