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CADTH COMMON DRUG REVIEW

Clinical Review Report

abobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada Inc.)

Indication: For the symptomatic treatment of lower-limb spasticity in pediatric patients 2 years of age and older

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

aboBoNTA	abobotulinumtoxinA
AE	adverse event
APT	all patients treated
BoNT	botulinum toxin
BoNTA	botulinum toxin A
CI	confidence interval
CP	cerebral palsy
DB	double-blind
EOS	end of study
EW	early withdrawal
FMQ	Leeds Functional Mobility Questionnaire
FPS	Faces Pain Scale
GAS	goal attainment scaling
GMFCS	Gross Motor Function Classification System
GMFM	Gross Motor Function Measure
GMFM-88	88-item Gross Motor Function Measure
GSC	gastrocnemius-soleus complex
ICC	intraclass correlation coefficient
ITC	indirect treatment comparison
ITT	intention-to-treat (population)
LLS	lower-limb spasticity
LS	least squares
MAS	Modified Ashworth Scale
OGS	Observational Gait Scale
onaBoNTA	onabotulinumtoxinA
PedsQL	Pediatric Quality of Life Inventory
PGA	Physician's Global Assessment
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
TS	Tardieu Scale
U	units
ULS	upper-limb spasticity
VGA	Leeds Videographic Gait Assessment
WDAE	withdrawal due to adverse event

Drug	AbobotulinumtoxinA (Dysport Therapeutic)
Indication	For the symptomatic treatment of lower-limb spasticity in pediatric patients 2 years of age and older
Reimbursement Request	As per indication
Dosage Form	Sterile lyophilized powder for solution for injection, 300 U and 500 U per vial
NOC Date	December 21, 2017
Manufacturer	Ipsen Biopharmaceuticals Canada Inc.

Executive Summary

Introduction

Spasticity is a condition characterized by a velocity-dependent increase in muscle tone that results in tightness or stiffness of the muscles and can interfere with speech, gait, and normal movement.[1] The most common cause of spasticity in children is cerebral palsy (CP). "*Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems*."[2,3 4,5] Typical deformities arising from lower-limb spasticity (LLS) in children with CP include hip adduction and flexion, knee flexion, and equinus foot deformity.[6] Other causes of spasticity include stroke, brain injury, spinal cord injury.[1] In a study conducted in Quebec, spasticity affects up to 92.8% of children with CP. In this study, 31.6% were spastic hemiplegia, 35.2% were spastic quadriplegia, and 25.9% were spastic diplegia.[7] Another study estimated the prevalence rates of CP in Northern Alberta among five-year-old children to be 2.22 (95% confidence interval [CI], 2.12 to 2.32) per 1,000 five-year-old children.[5]

Usually, treatment is required only if the spasticity causes disruptive or painful symptoms, limits function, or contributes to the development of musculoskeletal complications such as contracture and/or bony malalignment. The management of LLS includes both pharmacological and non-pharmacologic treatments. Non-pharmacological treatments include physiotherapy and splinting. Pharmacological treatments include oral medications (such as benzodiazepines and imidazolines), intrathecal baclofen, or focal chemodenervation treatments (such as botulinum toxin A [BoNTA] intramuscular injections), and/or surgical interventions (such as selective dorsal rhizotomy and orthopedic surgeries).[8,9] Multiple therapies are often used concomitantly. Treatment goals in the management of LLS include increasing strength and voluntary motor control, improving and maintaining joint mobility, reducing spasticity, improving gait, increasing the ease of performing the basic activities of daily living, preventing skeletal deformity, and reducing and preventing pain. BoNTA injections are recommended treatment options for pediatric LLS to improve physical functioning through reduction of muscle tone.[10,11] Spasticity in children with CP is associated with reduced motor function, reduced muscle strength and a reduction in mobility, which impact quality of life and the ability to perform activities of daily

living.[12-15] In the American Academy of Neurology guidelines, BoNTA is recommended as an effective and generally safe treatment with level A evidence for the treatment of localized/segmental spasticity that warrants treatment in the pediatric population.[16] In Canada, there are currently two BoNTA products approved for the treatment of LLS in pediatric patients: abobotulinumtoxinA (aboBoNTA; trade name Dysport Therapeutic),[17] and onabotulinumtoxinA (onaBoNTA; trade name Botox).[18]

AboBoNTA has a Health Canada–approved indication for the symptomatic treatment of LLS in pediatric patients two years of age and older and for upper-limb spasticity (ULS) and cervical dystonia (spasmodic torticollis) in adults.[17] The CADTH Common Drug Review (CDR) previously reviewed aboBoNTA for the treatment of cervical dystonia and, in July 2017, the CADTH Canadian Drug Expert Committee (CDEC) recommended that aboBoNTA be reimbursed for reducing the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults with or without botulinum toxin (BoNT) treatment experience in a manner similar to the public plan listings for other BoNTA products and with a reduction in price. CDR previously reviewed aboBoNTA for the symptomatic treatment of focal spasticity affecting the upper limbs in adults and, in September 2017, CDEC recommended that aboBoNTA be reimbursed in a manner similar to other BoNTA products for the treatment of ULS and with a cost saving condition.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of aboBoNTA for the symptomatic treatment of LLS in pediatric patients two years of age and older.

Results and Interpretation

Included Studies

Two placebo-controlled randomized controlled trials (RCTs) (Study 141 and Study 701) met the inclusion criteria for this review. Study 141 was a pivotal trial. Study 141 (N = 241) was a phase III, multi-centre, double-blind, prospective, randomized, placebo-controlled, single treatment cycle study that assessed the efficacy of aboBoNTA compared with placebo in children with dynamic equinus foot deformity associated with CP. Patients were randomized into one of three treatment groups; aboBoNTA 10 U/kg, aboBoNTA 15 U/kg, or placebo in a ratio of 1:1:1, and stratified according to age range (two to nine years and 10 to 17 years) and BoNT-naive or non-naive status, as assessed at baseline. After randomization, aboBoNTA or placebo was administered by intramuscular injections into the gastrocnemius-soleus complex (GSC) of each affected lower limb. The dose of aboBoNTA administered was either 10 U/kg or 15 U/kg per affected GSC, so the total dose was either 10 U/kg or 15 U/kg for unilateral injections and 20 U/kg or 30 U/kg for bilateral injections. The primary outcome was the change from baseline in a Modified Ashworth Scale (MAS) score at week 4. Other outcomes included Physician's Global Assessment (PGA) score (first secondary outcome) measured at week 4, and goal attainment scaling (GAS) score (second secondary outcome) measured at week 4. MAS and PGA assessed at week 12, Tardieu Scale (TS), Observational Gait Scale (OGS), Faces Pain Scale (FPS), and health-related quality-of-life scales (Pediatric Quality of Life Inventory Version [PedsQL]) was assessed at weeks 4 and 12 as tertiary outcomes for exploratory purposes only.

Study 701 (N = 52) was a phase III, multi-centre, double-blind, prospective, randomized placebo-controlled study that compared the efficacy and safety of a single administration of aboBoNTA or placebo in the treatment of pediatric dynamic equinus spasticity associated

with diplegic CP. Eligible patients were randomized to receive a single treatment of either aboBoNTA (30 U/kg) or placebo. Study medication was distributed equally between both legs by injection of the gastrocnemius muscle of each limb. Two sites were injected in each muscle. The primary efficacy variable was functional change as assessed by the Gross Motor Function Measure (GMFM) score. Other outcomes assessed were Leeds Videographic Gait Assessment scores, Leeds Functional Mobility Questionnaire results, and subjective functional assessment of gait.

One of the main limitations of Study 141 was that clinically relevant outcomes such as passive and active function outcomes (e.g., TS) and the health-related quality-of-life outcomes (i.e., PedsQL) were analyzed as tertiary outcomes for exploratory purpose only and were not controlled for multiple statistical testing (i.e., increased risk of type I error). In addition, no Canadian sites were included in the study. The clinical expert consulted for this review indicated that patients included in the trial appeared to be limited to ambulatory patients with mild to moderately severe CP. In Study 701, the main limitations were that there was a substantial difference between groups in the baseline GMFM overall and goal-total scores, with aboBoNTA-treated patients being less functionally impaired than placebo-treated patients, which could introduce bias, and no adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error.

Efficacy

Modified Ashworth Scale

In Study 141 at week 4, the between-group mean difference in change from baseline was statistically significant (−0.49, 95% CI, −0.75 to −0.23, $P = 0.0002$) in the aboBoNTA 15 U/kg/leg group compared with the placebo group. Likewise, the between-group mean difference in change from baseline for the aboBoNTA 10 U/kg/leg group compared with placebo was statistically significant (−0.38, 95% CI, −0.64 to −0.13, $P = 0.0029$). One of the clinical experts consulted for this review indicated that a one-point difference in the MAS (in either direction) was clinically relevant, and that the decrease in MAS at week 4 within the aboBoNTA 10 U/kg treatment group of −0.86, and the −0.97 decrease within the aboBoNTA 15 U/kg treatment group are clinically significant. However, the between-group mean difference in change from baseline of −0.38 for the aboBoNTA 10 U/kg/leg group compared with the placebo group, and the between-group mean difference in change from baseline of −0.49 for the aboBoNTA 15 U/kg/leg group compared with the placebo group, while statistically significant, are not clinically significant in the expert's opinion, as this represents less than half of one gradation on the MAS scale. In contrast, the other clinical expert consulted for this review noted that while a clinically important change in a single patient must be at least a one-point change due to the nature of the MAS, a change between–treatment groups as low as 0.38 would be considered clinically significant when related to a group of patients receiving treatment. MAS scores assessed at week 12 were analyzed as a tertiary outcome for exploratory purposes only. The improvement in MAS score observed for both aboBoNTA groups at week 4 appeared to be maintained at week 12 to a lesser extent. The subgroup analysis for the MAS assessed by previous exposure to botulinum toxin (BoNT) treatment also showed an improvement in both aboBoNTA treatment groups compared with placebo, regardless of prior exposure to BoNT.

Goal Attainment Scaling

In Study 141, patients in both aboBoNTA treatment groups achieved a mean GAS score above 50.0, demonstrating that the overall response was better than expected. However, patients in the placebo group showed a mean GAS score below 50.0. This result was statistically significant in both aboBoNTA treatment groups compared with placebo. GAS scores assessed at week 12 were analyzed as a tertiary outcome for exploratory purposes only. The improvement in GAS score observed for both aboBoNTA groups at week 4 appeared to be maintained at week 12.

Physicians Global Assessment

In Study 141, at week 4, compared with placebo, the treatment-group difference (aboBoNTA minus placebo) of the PGA score was 0.82 (95% CI, 0.50 to 1.14) and 0.77 (95% CI, 0.45 to 1.10) in the aboBoNTA 10 U/kg and aboBoNTA 15 U/kg, respectively. The results of the PGA demonstrated that aboBoNTA (10 U/kg and 15 U/kg) was statistically significantly more effective than placebo ($P < 0.0001$). At week 12, the between–treatment group difference in change from baseline in the PGA score for aboBoNTA versus placebo (which was a tertiary, exploratory outcome) was numerically lower than what was observed at week 4.

Outcomes, including the TS, OGS, FPS, and PedsQL, were analyzed as tertiary outcomes for exploratory purposes only. The observed improvement in muscle tone at week 4 demonstrated in MAS score, was supported by the results of the TS, which is another efficacy measurement for spasticity. In the TS, the spasticity grade was reduced for both treatment groups at week 4. However, no conclusion could be derived from the TS because it was analyzed as a tertiary outcome end point and for exploratory purpose only, and no controls for multiple statistical testing were used to control for the risk of type I error. As for the FPS and PedsQL, the magnitude of reduction in all groups was negligible.

Study 701 was a relatively small trial that failed to demonstrate statistically significant between-group differences in the overall GMFM score without walking aids or orthoses at week 4. The clinical expert consulted for this review indicated the GMFM is a clinical tool designed to measure a child's ability to perform gross motor tasks such as sitting, crawling, standing, walking, and running. Treatment of focal or segmental spasticity (plus the small number of patients) is unlikely to improve the whole-body motions utilized for gross motor tasks, which is what the GMFM evaluates. Therefore, the lack of statistical significance with the GMFM score is possibly because it is not sensitive enough to identify differences in single muscle groups treated with aboBoNTA injections. Other functional outcomes were not controlled for multiplicity. The main limitations of Study 701 are that no adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error. Also, balance may not have been achieved across the baseline variables, suggesting randomization was not successful, which may substantially bias the study results.

In both trials, for all outcomes included in this review, no minimal clinically important differences (MCIDs) were established specific to a pediatric population with LLS and, thus, the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature.

The results from the open-label extension study (Study 147) demonstrating that the efficacy of repeated use of aboBoNTA in reducing the symptoms and signs of LLS appeared to be

maintained; however, very little can be concluded regarding the efficacy of aboBoNTA due to the limitations associated with this study, which are mainly its open-label nature (which can potentially bias the reporting of the outcome measures, especially the subjective measures), the lack of a control group, and the limited sample size of what is likely a highly select population. Therefore, no definitive conclusions can be made regarding the long-term efficacy of aboBoNTA (Appendix 6).

In the absence of direct evidence comparing aboBoNTA with other active treatments, the manufactured submitted an indirect treatment comparison (ITC). The results of this analysis suggest that the two BoNTAs (aboBoNTA and onaBoNTA) may have similar treatment effects in pediatric patients with LLS. These results, however, are limited by the small number of studies for some outcomes, the considerable amount of heterogeneity between studies, and the large number of assumptions required to pool the data for analysis. No evidence was available regarding the difference in the duration of effect between aboBoNTA and onaBoNTA.

Harms

[redacted] In Study 701, at least one treatment-emergent adverse event (TEAE) was reported in 39%, and 50% of patients in the aboBoNTA and placebo groups, respectively. The most common TEAEs were rhinitis (15% in the aboBoNTA and placebo treatment groups), bronchitis (15%, and 12% in the aboBoNTA and placebo groups, respectively). [redacted] The only notable harm reported in the placebo group was muscle weakness, which was reported by one patient (1.3%). While epilepsy was reported only by patients who were receiving aboBoNTA, these patients had a history of epilepsy. All five cases were in the aboBoNTA treatment groups and were assessed by the investigator as unrelated to study treatment. [redacted] In Study 701, two patients in the aboBoNTA group reported urinary incontinence. The open-label extension study (Study 174) results suggested there were no new safety signals identified, with the most common adverse events being nasopharyngitis, pharyngitis, and upper respiratory tract infection. The manufactured submitted an ITC that suggested there is no statistically significant difference in adverse events between aboBoNTA and onaBoNTA or placebo.

Potential Place in Therapy[a]

Spasticity management is typically classified within five general categories, including non-pharmacological techniques (e.g., conventional rehabilitation and bracing), focal chemodenervation (e.g., phenol/alcohol nerve blocks and BoNTA), intrathecal baclofen therapy, oral medications (e.g., baclofen, tizanidine, and dantrolene) and surgical interventions (e.g., selective dorsal rhizotomy).[19] Established practice parameters[16,20] and standard of care for management of pediatric spasticity would employ interventions from any or all of the general categories, depending on the severity and anatomical distribution of spasticity. Best available intervention evidence, which is dominated by pediatric spasticity-management studies in CP,[21] support various treatments in all intervention categories with the exception of non-pharmacological techniques. AboBoNTA resides within the focal chemodenervation category; this category possesses the most robust literature supporting its use in pediatric spasticity management. Focal chemodenervation utilizes treatment of selected spastic muscles to achieve functional and/or structural objectives. OnaBoNTA also resides within this category and has been used for years in Canada under the formal indication for treatment of dynamic equinus foot deformity in pediatric CP patients. Practically, onaBoNTA has also been used for focal spasticity management of ULS and LLS in pediatric patients. As such, aboBoNTA would join onaBoNTA as an additional focal chemodenervation treatment for LLS in pediatric patients two years of age and older.

Children aged two to 17 years of age with problematic LLS from a variety of underlying etiologies such as CP, stroke, brain injury, and spinal cord injury, and clearly identified functional (e.g., improve gait or activities of daily living or ease of care) or structural goals (e.g., delay or prevent contracture development) conducive to focal chemodenervation should receive this drug in practice. Anticipated barriers to consistently identifying appropriate patients who may benefit from this drug include the relative paucity of allied health and medical professionals appropriately trained to evaluate spasticity in children. Treatment availability may also be limited by the number of physicians adequately prepared to complete BoNTA injections in children, including access to injection-guidance technology (e.g., electromyography, electrical stimulation, or ultrasound) as well as suitable and safe procedural sedation for children unable to tolerate awake injections.

Conclusions

Two trials (Study 141 and Study 701) met the inclusion criteria for this review. Both trials were phase III, multi-centre, randomized, double-blind, controlled trials. Study 141 was a pivotal trial. While Study 141 demonstrated that both aboBoNTA doses (10 U/kg and 15 U/kg) were statistically significantly better than placebo for reducing muscle tone at week 4 (as assessed by MAS), there is some uncertainty around the clinical significance of the difference observed between groups, because each of the clinical experts consulted for this review provided different opinions regarding the difference seen in the MAS at week 4 between the aboBoNTA treatment groups and placebo groups. In addition, the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature. Study 701 did not meet its primary end point (change from baseline in overall GMFM core without walking aids or orthoses at week 4). In Study 141, the effect of aboBoNTA on other clinically meaningful outcomes such as health-related

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

quality of life (HRQoL) and patient-reported symptoms was uncertain, mainly because any observed effects were marginal and limited by methodological considerations. Overall adverse events were low, despite a numerically higher incidence of TEAEs in the aboBoNTA groups than in the placebo group. The open-label uncontrolled extension phase of the trial showed a similar efficacy and safety profile for aboBoNTA as reported in the double-blind phase; however, the study had a few limitations, including the open-label nature of the study, the lack of a control group, and the limited sample size. A network meta-analysis submitted by the manufacturer suggested that the two BoNTAs (aboBoNTA, and onaBoNTA) may have similar treatment effects in pediatric patients with LLS; however, the statistical analyses are limited by the large number of assumptions required to estimate the relative efficacy between toxins.

Table 1: Summary of Key Results in Study 141

Outcome	Study 141		
	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
MAS Score[a]			
MAS score at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
MAS score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change in MAS score from baseline to week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
PGA Score[b]			
PGA score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
GAS Score[b]			
GAS score at week 4			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

Adverse Events	AboBoNTA 10 U/kg/leg (N = 80)	AboBoNTA 15 U/kg/leg (N = 80)	Placebo (N = 79)
Patients with > 0 TEAE, N (%)	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]
Notable harms, 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]

aboBoNTA = abobotulinumtoxinA; ANCOVA = analysis of covariance; ANOVA = analysis of variance; BoNT = botulinum toxin; CI = confidence interval; GAS = goal attainment scaling; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; PGA = Physician's Global Assessment; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Introduction

Disease Prevalence and Incidence

Spasticity is a condition characterized by a velocity-dependent increase in muscle tone, resulting in tightness or stiffness of the muscles that can interfere with speech, gait, and normal movement.[1] The most common cause of spasticity in children is cerebral palsy (CP). "*Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.*"[2-5] Typical deformities arising from lower-limb spasticity (LLS) in children with CP include hip adduction and flexion, knee flexion, and equinus foot deformity.[6] Other causes of spasticity include stroke, brain injury, and spinal cord injury.[1]

In a systematic review and meta-analysis that included 49 population-based studies on the prevalence of CP in children born in 1985 or after, the pooled overall prevalence of CP was 2.11 per 1,000 live births (95% confidence interval [CI], 1.98 to 2.25). The prevalence of CP stratified by gestational age group showed the highest pooled prevalence to be in children weighing 1,000 g to 1,499 g at birth (59.18 per 1,000 live births; 95% CI, 53.06 to 66.01). The prevalence of CP expressed by gestational age was highest in children born before 28 weeks' gestation (111.80 per 1,000 live births; 95% CI, 69.53 to 179.78).[4] In another study conducted in Quebec, spasticity affects up to 92.8% of children with CP. In this study, 31.6% were spastic hemiplegia, 35.2% were spastic quadriplegia, and 25.9% were spastic diplegia.[7] Another study estimated the prevalence rates of CP in Northern Alberta among five-year-old children to be 2.22 (95% CI, 2.12 to 2.32) per 1,000 five-year-olds.[5]

Standards of Therapy

Usually, treatment is required only if the spasticity causes disruptive or painful symptoms, limits function, or contributes to the development of musculoskeletal complications such as contracture and/or bony malalignment. The management of LLS includes both pharmacological and non-pharmacologic treatments. Non-pharmacological treatments include physiotherapy and splinting. Pharmacological treatments include oral medications (such as benzodiazepines and imidazolines), intrathecal baclofen, or focal chemodenervation treatments (such as botulinum toxin A [BoNTA] intramuscular injections), and/or surgical interventions (such as selective dorsal rhizotomy and orthopedic surgeries).[8,9] Multiple therapies are often used concomitantly.[8,9]

Treatment goals in the management of LLS include increasing strength and voluntary motor control, improving and maintaining joint mobility, reducing spasticity, improving gait, and increasing the ease of performing the basic activities of daily living, preventing skeletal deformity, and reducing and preventing pain. BoNTA injections are a recommended treatment options for pediatric LLS to improve physical functioning through reduction of muscle tone.[10,11] Spasticity in children with CP is associated with reduced motor function, reduced muscle strength, and a reduction in mobility that impact quality of life and the ability to perform activities of daily living.[12-15] In the American Academy of Neurology guidelines, BoNTA is recommended as an effective and generally safe treatment with level A evidence

for the treatment of localized/segmental spasticity that warrants treatment in pediatric patients.[16]

In Canada, there are currently two BoNTA products approved for the treatment of LLS in pediatric patients: abobotulinumtoxinA (AboBoNTA; trade name Dysport Therapeutic),[17] and onabotulinumtoxinA (onaBoNTA; trade name Botox).[18] However, the wording of the indication is different between the two drugs, where aboBoNTA is indicated for the symptomatic treatment of LLS in pediatric patients two years of age and older.[17] OnaBoNTA is indicated for the treatment of dynamic equinus foot deformity due to spasticity in pediatric CP patients two years of age or older,[18] which is a more specific indication as per clinical expert.

Drug

AboBoNTA is a BoNTA that blocks neuromuscular transmission by preventing cellular acetylcholine release (chemodenervation) and remains the mainstay for the treatment of patients with LLS.[17] 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, a regulator protein, and the hemagglutinin proteins. These proteins and their derivatives, except for the regulator protein, form the components of the neurotoxin type A complex.[17] AboBoNTA is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps.[17] 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).[17] In Canada, aboBoNTA is indicated: for the symptomatic treatment of LLS in pediatric patients two years of age and older; for the symptomatic treatment of focal spasticity affecting the upper limbs in adults; and to reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults.[17]

The Health Canada–recommended dose of aboBoNTA (Dysport Therapeutic) for children with LLS is 10 U/kg to 15 U/kg for unilateral lower-limb injections or 20 U/kg to 30 U/kg for bilateral lower-limb injections per treatment session. With the maximum total dose administered per treatment session not exceeding 15 U/kg for unilateral lower-limb injections or 30 U/kg for bilateral lower-limb injections, or 1,000 units, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s). When possible, the dose should be distributed across more than one injection site in any single muscle (gastrocnemius and soleus muscles). No more than 0.5 mL of Dysport Therapeutic should be administered in any single injection site. It is also recommended that dosing in initial and sequential treatment sessions be tailored to the individual patient based on the size, number, and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins (BoNTs). AboBoNTA treatment should be repeated when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection.[17]

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

Table 2: Key Characteristics of Two Botulinum Neurotoxin A Formulations

	AboBoNTA (Ipsen)[17]	OnaBoNTA (Allergan)[18]
Molecular weight (kDa)	150	150
Complexing proteins	Hemagglutinin/non-hemagglutinin	Hemagglutinin/non-hemagglutinin
***Clostridium botulinum* strain**	Hall strain	Hall strain
Recommended re-treatment interval	≥ 12 weeks	≥ 12 weeks (3 months)
Mechanism of action	BoNTA inhibits release of the neurotransmitter acetylcholine from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves. Recovery of transmission occurs gradually as the neuromuscular junction recovers and as new nerve endings are formed.	
Indication[a]	For the symptomatic treatment of lower-limb spasticity in pediatric patients 2 years of age and older	In the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients, two years of age or older
Route of administration	For intramuscular injection only	
Recommended dose	• 10 U/kg to 15 U/kg for unilateral lower-limb injections or 20 U/kg to 30 U/kg for bilateral lower-limb injections. The maximum total dose administered per treatment session must not exceed 15 U/kg for unilateral lower-limb injections or 30 U/kg for bilateral lower-limb injections or 1,000 units, whichever is lower • Re-treatment interval, if needed: ≥ 12 weeks	• 4 U/kg administered by injecting into each of two sites in the medial and lateral heads of the gastrocnemius muscle of the affected lower limb(s). In diplegia, the initial recommended total dose is 6 U/kg body weight divided between the affected limbs • Re-treatment interval, if needed: ≥ 12 weeks (3 months)
Serious side effects / safety issues	• Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia, have been reported following treatment with BoNT A or B • Caution should be exercised when administering aboBoNTA to patients with inflammation at the injection site(s), deep dermal scarring, or thick sebaceous skin	• Progressive signs or symptoms of muscular weakness remote to the site of injection may include ptosis and diplopia, as well as other serious adverse effects including swallowing and speech disorders, generalized weakness, or respiratory failure • Certain adverse effects (e.g., dysphagia, aspiration pneumonia) have been rarely reported, some of which have been associated with a fatal outcome • Caution should be used when onaBoNTA 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; BoNT = botulinum toxin; BoNTA = botulinum toxin A; IM = intramuscular; onaBoNTA = onabotulinumtoxinA.

[a] Health Canada indication.[17,18]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of aboBoNTA (Dysport Therapeutic) for the symptomatic treatment of LLS in pediatric patients two years of age and older.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Pediatric (2 years of age and older) patients with LLS. **Subgroups:** • botulinum toxin experienced versus botulinum toxin–naive patients • baseline severity of spasticity
Intervention	AbobotulinumtoxinA 10 U/kg to 15 U/kg for unilateral lower-limb injections or 20 U/kg to 30 U/kg for bilateral lower-limb injections. The maximum total dose of abobotulinumtoxinA administered per treatment session must not exceed 15 U/kg for unilateral lower-limb injections or 30 U/kg for bilateral lower-limb injections or 1,000 units, whichever is lower
Comparators	OnabotulinumtoxinA (Botox) Placebo
Outcomes	**Key efficacy outcomes:** • functional/disability outcomes (e.g., MAS, TSS, AROM, GAS)[a] • HRQoL by a validated instrument (e.g., CP-QoL, PedsQL)[a] • patient-reported symptoms (e.g., pain, fatigue) [a] • PGA **Other efficacy outcomes:** • caregiver burden (measured by validated scales)[a] • duration of effect and re-treatment intervals[a] **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms/harms of special interest (generalized weakness, dysphagia, respiratory failure, seizure, incontinence, and death)
Study Design	Published and unpublished RCTs, phase III and higher

AE = adverse event; AROM = active range of motion; CP-QoL = Cerebral Palsy Quality of Life Questionnaire; GAS = goal attainment scaling; HRQoL = health-related quality of life; LLS = lower-limb spasticity; MAS = Modified Ashworth Scale; PedsQL = Pediatric Quality of Life Inventory; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SAE = serious adverse event; TSS = Tardieu Scale score; WDAE = withdrawal due to adverse event.

[a] Outcomes important to patients, as per the patient input received for this submission.

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 ALL (1946–); 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," "spasticity," and "lower limb."

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

The initial search was completed on March 8, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 18, 2018. Regular search updates were performed on databases that do not provide alert services.

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

Two 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; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in the Included Studies Section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

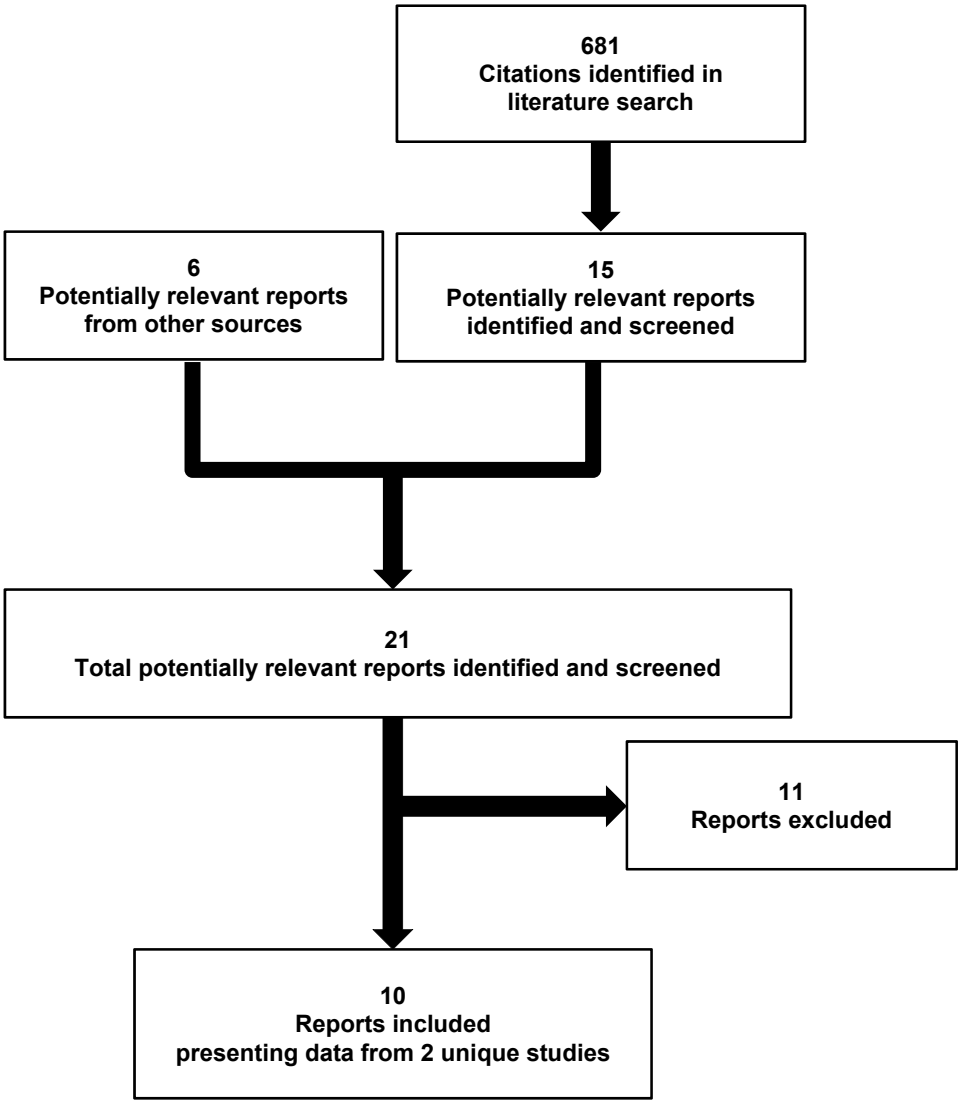

Table 4: Details of Included Studies

		Study 141	Study 701
Designs & Populations	**Study Design**	DB placebo-controlled, phase III RCT	DB placebo-controlled, phase III RCT
	Locations	35 centres in 6 countries: US, France, Mexico, Turkey, Poland, and Chile	5 centres (3 in the Czech Republic and 2 in the Slovak Republic)
	Randomized (N)	241	52
	Inclusion Criteria	• Children (aged 2–17 years) with a diagnosis of CP • Ambulatory with spastic hemiparesis, paraparesis, diparesis, or tetraparesis characterized by an equinus foot positioning during the stance phase of the gait • Able to walk (sufficient to complete a video analysis of 2-dimensional motion) with or without walking aids • Had a MAS score of ≥ 2 at the ankle joint of the (most) affected lower limb to be injected • Had a spasticity grade (Y) on the TS of 2, 3, or 4 assessed at the ankle joint of the most affected limb to be injected, with a spasticity angle (X) of 10 degrees or more • Had been classified as GMFCS level I, II, or III • Patients could be BoNT-naive or previously treated, but the last BoNT treatment of any type for any condition must have been more than 6 months prior to study entry • Previously established physiotherapy treatment was permitted up to at least the week 12 visit provided it had begun at least four weeks prior to study start and was to continue during the study at the same pre-study frequency and intensity (and provided the patient maintained their usual level of physical activity until the end of the study) • A previously established casting/orthoses regimen was permitted until the end of the week 12 visit provided it was used in the same way as before entry into the study	• Clinical diagnosis of diplegic cerebral palsy • Male or female aged between 2 and 7 years • Ambulatory (therapeutic ambulator as a minimum) • Considered by the investigator to have the potential to benefit from injection of aboBoNTA into the gastrocnemius muscles • Able to achieve passive ankle dorsiflexion of 10 degrees (in both limbs) with the knee straight
	Exclusion Criteria	• Evidence of non-ambulatory status • Major limitation in the passive range of motion at the ankle as defined by maximum ankle dorsiflexion measured by the slow-speed angle of arrest ($X_{V1)}$, of < 80 degrees (TS angle) in the most affected leg to be injected • Significant difference (> 2 cm) between the length of legs • Current need for surgery or previous surgery for spasticity of the GSC and/or hamstring muscles (and tendons) in the most affected leg to be injected • Serial casting in the past 12 weeks • Previous injection of alcohol and/or phenol into the GSC and/or hamstrings in the most affected leg to be injected • Severe athetoid or dystonic movements in the targeted lower limb(s) • Treatment with any drug that interferes either directly or indirectly with neuromuscular function (e.g., aminoglycoside antibiotics) or neuroblocking drugs used during surgery (e.g., curare) within the last 30 days prior to study treatment • Known resistant or sensitivity to BoNT or to any of the components in the formulation or allergy to cow's milk protein	• Perceived need for surgery to the affected limbs within six months • Requirement for multi-level injections of BoNT • Significant foot deformity defined as the inability to obtain a calcaneum-neutral position while measuring maximum passive dorsiflexion • Treatment with BoNT within nine months of entry into the study • Previous surgery on the affected muscles under investigation • Previous treatment with phenol for lower-limb spasticity • Known sensitivity to BoNT • Generalized disorder of muscle activity (e.g., myasthenia gravis) • Receiving aminoglycoside antibiotics or spectinomycin

		Study 141	Study 701
		• Ongoing treatment with intrathecal baclofen or previous/planned rhizotomy • Any medical condition, laboratory or diagnostic procedure finding that might preclude administration of BoNTA	
DRUGS	**Intervention**	AboBoNTA (10 U/kg or 15 U/kg per GSC injected into each affected leg) injected intramuscularly into six injection sites per affected lower limb (four sites in the gastrocnemius muscle and two sites in the soleus muscle).[a]	AboBoNTA 30 U/kg distributed equally between both legs by injecting the gastrocnemius muscle of each limb. Two sites were injected in each muscle. Target sites were at the junction of the proximal quarter and the distal three-quarters of the gastrocnemius.
	Comparator(s)	Placebo	Placebo
DURATION	**Phase**		
	Screening	Day −7 to day 1	
	Double-blind	12 weeks	16 weeks
	Follow-up	Discretionary follow-up at weeks 16, 22, and 28	If treatment effect was maintained at week 16, additional visits at weeks 24 and 36 could be scheduled.
	Open-label phase	Patients who required re-treatment at week 12, 16, 22, or 28 were considered to have completed the study and were offered entry into an open-label extension study (Study 147).	NA
OUTCOMES	**Primary End Point**	Change in MAS scores from baseline to week 4 in the GSC at the ankle joint of the (most) affected lower limb.	Change in the GMFM overall score, without walking aids/orthoses at week 4 compared with baseline.
	Other End Points	**Secondary Outcomes** • Mean PGA score at week 4 • Mean GAS score at week 4 **Tertiary Outcomes** • Mean change from baseline to week 12 (and to EOS/EW) in the MAS score in the GSC at the ankle joint of the (most) affected lower limb • Proportion of patients with at least one grade reduction in MAS score from baseline to week 4 (and to week 12 and EOS/EW) in the GSC at the ankle joint of the (most) affected lower limb • Mean PGA score at week 12 (and EOS/EW) • Mean GAS score at week 12 (and EOS/EW) • Mean change from baseline to week 4 (and to week 12 and EOS/EW) in the angle of arrest at slow speed (X_{V1}), angle of catch at fast speed (XV3), spasticity angle (X), and spasticity grade (Y) derived from the TS at the ankle joint of the (most) affected lower limb • Mean change from baseline to week 4 (and week 12 and EOS/EW) in the OGS total score • Proportion of patients with at least one grade improvement from baseline to week 4 (and to week 12 and EOS/EW) in the “initial foot contact” subsection of the OGS (OGS responders) • Mean change from baseline to week 4 (and week 12 and EOS/EW) in lower-limb pain (FPS score)	• GMFM overall score at weeks 8 and 16 • GMFM goal-total score at weeks 4, 8, and 16 • Leeds Videographic Gait Assessment at weeks 4 and 16 • Leeds Functional Mobility Questionnaire at weeks 4 and 16 • Subjective functional assessments of gait at weeks 4, 8, and 16 • Adverse events.

		Study 141	Study 701
		• Mean change from baseline to week 12 (and EOS/EW) in the PedsQL score.	
NOTES	**Publications**	Delgado et al.[23]	Kanovsky et al.[24]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); BoNT = botulinum toxin; BoNTA = botulinum toxin A; CP = cerebral palsy; DB = double-blind; EOS = end of study; EW = early withdrawal; FPS = Faces Pain Scale; GAS = goal attainment scaling; GMFCS = Gross Motor Function Classification System; GMFM = Gross Motor Function Measure; GSC = gastrocnemius-soleus complex; MAS = Score Modified Ashworth Scale; NA = not applicable; OGS = Observational Gait Scale; PedsQL = Pediatric Quality of Life Inventory; RCT = randomized controlled trial; TS = Tardieu Scale.
[a] The maximum dose injected in patients was not to exceed 1,000 U or 30 U/kg, whichever was the lower value.
Note: Four additional reports were included: CDR submission;[8] US Food and Drug Administration Statistical Review(s) and Medical Review(s) for aboBoNTA for the treatment of lower-limb spasticity in pediatric;[25,26] and Health Canada reviewer's report.[27]
Source: Delgado et al.,[23] Kanovsky et al.,[24] Tilton et al.,[28] Dabrowski et al.,[29] Study 141 Clinical Study Report,[22] Study 701 Clinical Study Report.[30]

Included Studies

Description of Studies

Two trials, Study 141 and Study 701, met the inclusion criteria for this review. Study 141 was a pivotal trial.

Study 141 (N = 241) was a phase III, multi-centre, double-blind, prospective, randomized, placebo-controlled, single treatment cycle study that assessed the efficacy of aboBoNTA compared with placebo in children with dynamic equinus foot deformity associated with CP. Study 141 consisted of a screening period (day −7 to day 1), and patients received treatment on day 1 and were followed up for a minimum of 12 weeks and a maximum of 28 weeks (double-blind treatment period). All patients who had had at least 12 weeks of follow-up were considered to have completed the study. Patients were randomized into one of three treatment groups; aboBoNTA 10 U/kg, aboBoNTA 15 U/kg, or placebo, in a ratio of 1:1:1, and stratified according to age range (2 to 9 years and 10 to 17 years) and botulinum toxin (BoNT)–naive or non-naive status, as assessed at baseline. After randomization, aboBoNTA or placebo was administered by intramuscular injections into the gastrocnemius-soleus complex (GSC) of each affected lower limb. The dose of aboBoNTA administered was either 10 U/kg or 15 U/kg per affected GSC, so the total dose was 10 U/kg or 15 U/kg for unilateral injections and 20 U/kg or 30 U/kg for bilateral injections. Patients who required re-treatment at week 12, 16, 22, or 28 were offered entry into an open-label extension study (Study 147).

Study 701 (N = 52) was a phase III, multi-centre, double-blind, prospective, randomized placebo-controlled study that compared the efficacy and safety of a single administration of aboBoNTA or placebo in the treatment of pediatric dynamic equinus spasticity associated with CP. Following initial assessment of their LLS, eligible patients were randomized to receive a single treatment of either aboBoNTA (30 U/kg) or placebo. Study medication was distributed equally between both legs by injection into each of the gastrocnemius muscles of each limb. Each muscle was injected at two sites. The effects of the treatment were monitored over a minimum 16-week period. Post-treatment assessments were made at weeks 4, 8, and 16. If an investigator believed that a treatment effect was maintained at week 16, additional visits at weeks 24 and 36 were scheduled.

Populations

Inclusion and Exclusion Criteria

Study 141 included ambulatory male or female patients with CP between two and 17 years of age who had spastic lower limbs characterized by an equinus foot positioning during the stance phase of the gait and the ability to walk with or without walking aids. These patients were BoNT-naive or had received their last BoNT treatment of any type more than six months prior to study entry. Additionally, patients had a spasticity grade of between 2 and 4, inclusive, on the Tardieu Scale (TS), assessed at the ankle joint of the (most) affected lower limb to be injected with a spasticity angle of 10 degrees or more, and classified as Gross Motor Function Classification System (GMFCS) level I to III inclusive (where level I indicates that patients can walk without limitations; level II indicates that patients can walk with limitations; level III indicates that patients can walk using a hand-held mobility device; level IV indicates that patients have self-mobility with limitations and may use powered mobility; and level V refers to patients who are transported in a manual wheelchair). All patients had signed informed consent obtained from the child's parent or guardian and signed consent from the child, when and where applicable. Patients were excluded if they had a current need for surgery or had previous surgery for spasticity of the GSC and/or hamstring muscles (and tendons) in the most affected leg to be injected. Furthermore, patients were excluded if there was evidence of non-ambulatory status, major limitation in the passive range of motion at the ankle, significant difference (> 2 cm) between the length of legs, serial casting in the past 12 weeks, previous injection of alcohol and/or phenol into the GSC and/or hamstrings in the most affected leg to be injected, severe athetoid or dystonic movements in the targeted lower limb(s), or known resistant or sensitivity to BoNT. Also excluded were patients who had received treatment with any drug that interferes either directly or indirectly with neuromuscular function or neuroblocking drugs used during surgery within the last 30 days prior to study treatment.

In Study 701, eligible patients aged between two and seven years were ambulatory, had a diagnosis of diplegic CP, had no evidence of fixed contracture (able to achieve 10 degrees passive ankle dorsiflexion in both legs), and had the potential to benefit from the injection of aboBoNTA to the gastrocnemius muscle. Patients were excluded if they had previously had surgery on the affected limbs or if there was a need for surgery within the next six months. Furthermore, patients were excluded if multi-level injections were required, if the patient had a significant foot deformity, if they had BoNT treatment within the previous nine months, had had previous phenol treatment for LLS, or had known hypersensitivity to BoNT. Also excluded were patients who had received an investigational new drug in the 30 days prior to entry, patients who were receiving aminoglycoside antibiotics or spectinomycin, patients with a generalized disorder of muscle activity (e.g., myasthenia gravis), and patients unwilling or unable to comply with the protocol. The parent/guardian of each patient gave written informed consent.

Baseline Characteristics

Patients enrolled in Study 141 were between two and 17 years of age (mean age 5.9 years). There were more male patients than female patients (60% versus 40%, respectively). The majority of patients were Caucasian (73.2%). More patients were treated in one leg than in both legs (59% versus 41%, respectively). Over half the patients (55.7%) were classified as GMFCS level I, and a third of the patients (33.2%) as level II. Approximately half of the patients (51.9%) were naive to treatment with any form of BoNT

before entering the study. The three treatment groups were well balanced with respect to disease characteristics. All patients had a diagnosis of CP as defined by Rosenbaum. Approximately half the patients (49.8%) had spastic hemiparesis and 43.4% had spastic diparesis. Of the 102 patients with diparesis, 83 patients (81.4%) were injected in both legs versus 19 patients (18.7%) injected in one leg. The right leg was the most affected leg in just over half of all patients (54.9%). Epilepsy was reported for a higher proportion of patients in the aboBoNTA 10 U/kg and aboBoNTA 15 U/kg groups (10.1% and 12.7%, respectively) than in the placebo group (6.5%). The majority of patients (88.5%) were receiving some sort of non-drug therapy, casting/orthoses, and/or formal physiotherapy when they entered the study, and the number of patients receiving therapy was similar between–treatment groups (Table 5).

In Study 701, the aboBoNTA-treated patients were approximately a year older with consequently greater weight and height. Also, almost two-thirds of the aboBoNTA group was males, compared with half of the placebo group. All patients were Caucasian. The aboBoNTA and placebo groups were well balanced with regard to baseline maximum passive ankle dorsiflexion and Leeds Videographic Gait Assessment (VGA) at baseline. There was a substantial difference between groups in the Gross Motor Function Measure (GMFM) overall and goal-total scores, with aboBoNTA-treated patients being less functionally impaired than placebo-treated patients (Table 6).

Table 5: Summary of Baseline Characteristics (ITT Population) for Study 141

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Age categories, n (%)			
2 to 9 years	[redacted]	[redacted]	[redacted]
10 to 17 years	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
Black/African-American	[redacted]	[redacted]	[redacted]
Caucasian/white	[redacted]	[redacted]	[redacted]
American Indian / Alaskan Native	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Height, cm			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
BMI kg/m^2			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
BMI categories, n (%)			
< 5th percentile (underweight)	[redacted]	[redacted]	[redacted]
5th percentile to < 95th percentile (healthy to overweight)	[redacted]	[redacted]	[redacted]
> 95th percentile (obese)	[redacted]	[redacted]	[redacted]
BoNTA status, n (%)			
Naive	[redacted]	[redacted]	[redacted]
Previous BoNTA	[redacted]	[redacted]	[redacted]
Number of legs being treated, n (%)			
One leg injected	[redacted]	[redacted]	[redacted]
Two legs injected	[redacted]	[redacted]	[redacted]
Geographical location, n (%)			
US	[redacted]	[redacted]	[redacted]
Non-US	[redacted]	[redacted]	[redacted]
GMFCS level, n (%)			
I	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
MAS score, n (%)			
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
Derived baseline MAS score			
Mean (SD)	[redacted]	[redacted]	[redacted]
Baseline OGS question 2 score,[a] n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Presence of epilepsy, n (%)	[redacted]	[redacted]	[redacted]
Patients with any prior and concomitant casting/orthoses, formal physiotherapy or selected non-drug therapies	[redacted]	[redacted]	[redacted]
Any concomitant medication for spasticity	[redacted]	[redacted]	[redacted]
Cyproheptadine hydrochloride	[redacted]	[redacted]	[redacted]
Baclofen	[redacted]	[redacted]	[redacted]
Other muscle relaxants, peripherally acting drugs	[redacted]	[redacted]	[redacted]
Patients with any prior and concomitant casting/orthoses, formal physiotherapy	[redacted]	[redacted]	[redacted]
Casting/orthoses	[redacted]	[redacted]	[redacted]
Formal physiotherapy[b]	[redacted]	[redacted]	[redacted]
History of cerebral palsy			
Paralysis, n (%)			
Hemiparesis	[redacted]	[redacted]	[redacted]
Paraparesis	[redacted]	[redacted]	[redacted]
Diparesis	[redacted]	[redacted]	[redacted]
Tetraparesis	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Most affected leg, n (%)	[redacted]	[redacted]	[redacted]
Left	[redacted]	[redacted]	[redacted]
Right	[redacted]	[redacted]	[redacted]
Cerebral palsy diagnosis, n (%)	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Fixed myocontracture with no dynamic component in the GSC, n (%)	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Presence of athetoid or dystonic movements, n (%)	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Intensity of athetoid or dystonic movements, n (%)	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Not applicable	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BMI = body mass index; BoNTA = botulinum toxin A; GMFCS = Gross Motor Function Classification System; GSC = gastrocnemius-soleus complex; ITT = intention-to-treat; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients with data; OGS = Observational Gait Scale; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 6: Summary of Baseline Characteristics for Study 701 (All-Patients-Treated Population)

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Gender, n (%)		
Male	[redacted]	[redacted]
Weight (kg)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Height (cm)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Baseline maximum passive dorsiflexion		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Baseline GMFM overall and goal-total scores		

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
Overall score		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Goal-total score		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Leeds Videographic Gait Assessment at baseline		
Initial foot contact,[a] n (%)		
Heel strike	[redacted]	[redacted]
Flat foot	[redacted]	[redacted]
Toe strike	[redacted]	[redacted]
Mild toe	[redacted]	[redacted]
Marked toe	[redacted]	[redacted]
Degree of knee flexion, n (%)		
Neutral/slightly flexed	[redacted]	[redacted]
Hyperextended	[redacted]	[redacted]
Marked knee flexion	[redacted]	[redacted]
Rocker-bottom foot, n (%)		
Not present	[redacted]	[redacted]
Present	[redacted]	[redacted]
Hindfoot deformity,[a] n (%)		
Neutral	[redacted]	[redacted]
Occasionally neutral	[redacted]	[redacted]
Valgus	[redacted]	[redacted]
Varus	[redacted]	[redacted]
Use of walking aids,[b] n (%)		
Not used	[redacted]	[redacted]
Used	[redacted]	[redacted]
Summary of concomitant therapy that started prior to the study and stopped or continued during the study		
Caregiver		
Therapy sessions per week		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Therapy session duration (hours)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
Median (range)	[redacted]	[redacted]
Physiotherapist		
Therapy sessions per week		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Therapy session duration (hours)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; GMFM = Gross Motor Function Measure; SD = standard deviation.
[redacted]
Source: Study 701 Clinical Study Report.[30]

Interventions

In Study 141, before administration, the powder was reconstituted at the investigational site with sterile, preservative-free saline (sodium chloride for injection 0.9%). Sterile saline was added to obtain a total volume to inject per patients of 2 mL per lower limb (i.e., 2 mL for unilateral and 4 mL for bilateral injections). Two aboBoNTA doses (10 U/kg or 15 U/kg per GSC injected into the affected leg (s)) were compared with placebo. The total dose was either 10 U/kg or 15 U/kg for unilateral injections, or 20 U/kg or 30 U/kg for bilateral injections. A total dose of either 10 U/kg or 15 U/kg of aboBoNTA was injected intramuscular into the gastrocnemius muscle and soleus muscle in four injection sites per affected lower limb. The 2 mL volume of injection per lower limb was split between gastrocnemius and soleus muscles according to a ratio of 3:2. The injection volume for each site is illustrated in Table 7 below. The maximum dose injected in patients was not to exceed 1,000 U or 30 U/kg, whichever was the lower value. The intramuscular injections were administered at the treatment visit into clinically indicated lower-limb muscles, using electrical stimulation or ultrasound (combined with complementary technique), in single dosing sessions. aboBoNTA was provided by the manufacturer as a white lyophilized powder in type I, 3 mL glass vials. Placebo was provided by the manufacturer in type I, 3.0 mL glass vials and was indistinguishable from aboBoNTA. The placebo contained only the excipients described for aboBoNTA. To maintain the blind, an independent reconstitutor prepared the study treatment in the syringes.

Concomitant use of anticholinergic drugs and concomitant treatment with dantrolene, tizanidine, or a gamma-aminobutyric acidergic (GABAergic) opioid or other anti-spasticity drug, including baclofen and benzodiazepines, were permitted during this study if the dosage had been stable for the four weeks prior to study treatment and was expected to remain at this stable dose throughout the study. Physiotherapy and the use of casts and orthoses were also permitted if they had been initiated prior to study entry (at least four weeks prior in the case of physiotherapy). In addition, both physiotherapy and the use of casts or orthoses had to continue at the same pre-study frequency and intensity until at least week 12. No new casts or orthoses were to be initiated until week 12, and no new

physiotherapy was to be initiated less than four weeks prior to study entry or during the course of study up to the week 12 visit. The following was not permitting during the study:

- the administration of BoNT into any site of the body other than the lower limb
- use of any investigational new drug or device or off-label use of any drug
- treatment with any drug that interfered either directly or indirectly with neuromuscular function (e.g., aminoglycoside antibiotics)
- use of neuroblocking drugs, such as those used during surgery (e.g., curare).

Table 7: Injection Volume in Gastrocnemius-Soleus Complex per Leg Without Hamstring Injections for Study 141

Muscle Injected	Upper Quadrant (Number of Sites)	Lower Quadrant (Number of Sites)	Total Volume
Gastrocnemius	0.4 mL (×2)	0.2 mL (×2)	1.2 mL
Soleus	NA	0.4 mL (×2)	0.8 mL
Per leg			2.0 mL

NA = not applicable.
Source: Study 141 Clinical Study Report.[22]

In Study 701, patients were randomized to one of two treatment groups, receiving either aboBoNTA (30 U/kg) or placebo. Study medication was prepared to a final volume of 2 mL and was administered equally into two sites in the gastrocnemius muscle in both legs (0.5 mL per site). aboBoNTA was presented as a freeze-dried white pellet containing 500 units of Clostridium BoNTA–hemagglutinin complex together with 125 mcg of human albumin and 2.5 mg of lactose in a clear glass vial. Matching placebo supplies were presented in identical clear glass vials containing 125 mcg of human albumin and 2.5 mg of lactose. Blinding was achieved by supplying the study medication for each patient in identical patient packs. The use of BoNT during the study or during the nine months preceding the study was prohibited. Any oral anti-spasticity medication being taken prior to the study was to be continued at the same dose throughout the study period. Other concomitant medications were allowed at the discretion of the investigator. Regular physiotherapy and the use of walking aids and orthoses were also permitted to continue during the study. If orthoses were changed at entry, it was recommended that the baseline assessments be delayed until the patient had stabilized. Nine patients (35%) in the placebo treatment group and seven patients (27%) in the aboBoNTA treatment group were taking concomitant medications at entry. Antiepileptics and psychoanaleptics were the most frequently used concomitant medications.

Outcomes

In Study 141, the primary outcome was the change from baseline to week 4 in the Modified Ashworth Scale (MAS) score in the GSC at the ankle joint of the (most) affected lower limb. The first secondary outcome was Physician's Global Assessment (PGA) at week 4. The second secondary outcome was goal attainment scaling (GAS) at week 4. Tertiary outcomes included:

- mean change from baseline to week 12 (and at end of study [EOS] or early withdrawal [EW]) in the MAS score in the GSC at the ankle joint of the (most) affected lower limb

- proportion of patients with at least one grade reduction in MAS score from baseline to week 4 (and to week 12 and EOS/EW) in the GSC at the ankle joint of the (most) affected lower limb
- mean PGA score at week 12 (and EOS/EW)
- mean GAS score at week 12 (and EOS/EW)

[redacted]

If relevant, the aforementioned tertiary efficacy end points were also assessed at week 16, week 22, and week 28.

In Study 141, effort was made in each centre to ensure that the same evaluating investigator assessed the same patients for the duration of the study. All investigators were trained in the use of the assessment scales prior to the start of the study in an attempt to minimize variability between centres. They were also given follow-up training during the study. The assessor who conducted the PGA of treatment response was different from the person who evaluated the MAS. When making their assessment, none of the assessors had knowledge of the scores obtained by the other assessor.

In Study 701, the primary efficacy variable was functional change, as assessed by the change from baseline in overall GMFM score without walking aids or orthoses at week 4 of the study. Secondary efficacy outcomes were: change in GMFM overall score at weeks 8 and 16 compared with baseline, change in GMFM total score at weeks 4, 8, and 16 compared with baseline, change in VGA scores at weeks 4 and 16 compared with baseline, change in Leeds Functional Mobility Questionnaire (FMQ) at weeks 4 and 16 compared with baseline, and subjective functional assessment of gait at weeks 4, 8, and 16.

Please refer to Appendix 5 for more information on the validity of the outcome measures described in this section.

Modified Ashworth Scale

The MAS is commonly used to measure increased muscle tone and spasticity due to different pathologies and neurologic conditions.[31] The MAS was derived from the original Ashworth Scale to measure muscle resistance while moving the affected joint through its full range of movement in order to passively stretch the muscle.[31] It provides a semi-

quantitative measure of this resistance to passive movement.[32,33] The MAS is easy to use as it requires no additional equipment; hence, it is one of the most commonly used tools to measure spasticity and muscle rigidity in patients with CP[34] or hypertonia.[35] It is administered by a physician or therapist during the patient visit and comprises a six-point scale used to measure the degree of spasticity (intensity of muscle tone) as follows: 0 = no increase in muscle tone; 1 = slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part(s) is moved in flexion or extension; 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement; 2 = more marked increase in muscle tone through most of the range of movement, but the affected part(s) is easily moved; 3 = considerable increase in muscle tone, passive movement is difficult; 4 = affected part(s) rigid in flexion or extension. [25,35,36] The MAS score is normally a categorical variable; however, for this review, it was treated as a continuous variable and, hence, needed to be transformed. The derived MAS scores that were used in this review were 0, 1, 2, 3, 4, and 5, which corresponded to the aforementioned original MAS scores of 0, 1, 1+, 2, 3, and 4 (as previously described), respectively.[25] A higher MAS score indicates increased muscle tone, rigidity, or spasticity. There is no evidence of the validity of the MAS in children with spasticity and there is conflicting evidence on reliability. In Study 141, all investigators were trained in the use of the assessment scales prior to the start of the study in an attempt to minimize variability between centres. They were also given follow-up training during the study. One of the clinical experts consulted for this review indicated that a one-point difference in the MAS (in either direction) was clinically relevant; however, no peer-reviewed evidence was identified regarding a minimal clinically important difference (MCID) for the MAS in pediatric patients with LLS. The other clinical expert consulted for this review indicated that defining an MCID is challenging for the MAS, but considers that a clinically important change in a single patient must be at least a one-point change due to the nature of the MAS. However, based upon his clinical experience, a change between–treatment groups as low as 0.38 would be considered clinically significant when related to a group of patients receiving treatment.

Physician's Global Assessment

In the pivotal study of this submission, the PGA of treatment response was conducted by the investigator by scoring responses to the question: "How would you rate the response to treatment in the patient's lower limb(s) since the last injection?" on a nine-point categorical scale where −4 = markedly worse, −3 = much worse, −2 = worse, −1 = slightly worse, 0 = no change, +1 = slightly improved, +2 = improved, +3 = much improved, and +4 = markedly improved. Assessment of the PGA was undertaken independently by an investigator who was different from the one who assessed the MAS.[22] No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the PGA for pediatric patients with LLS. In addition, no MCID for the PGA in this population has been identified.

Goal Attainment Scaling

GAS is a method of integrating the achievement of a number of individually set goals into a single goal attainment score.[37] It has been applied in various areas of complex interventions, including spasticity management.[38] Before the treatment, one or more individual goals are established by the patient (or their caregiver, if the patient is a child)[39] and one or more researchers or practitioners (or others agreed upon by the practitioner). The clinician/researcher requires sufficient knowledge and experience when supporting patients to set realistic goals. In addition, they must be able to respect the patient's ideology and

what is important to them when setting goals (and thus able to avoid projecting their own goals and what they perceive to be important onto the patient) and they must have good negotiating skills in order to manage potentially unrealistic goals set by the patient.[37] The number of goals can vary between patients in the same study and between patients in different studies. Numerical values ranging from −2 to +2 (a five-point scale) are used to describe the degree to which the goal(s) were or were not met.[37] The expected target of achievement is set by the patient and treating team and given a value of 0. Outcomes that are less than expected are given values of −1 or −2 (the most unfavourable outcome) and outcomes that are better than expected are given values of +1 or +2 (the most favourable outcome). The originators of the GAS score transformed it to a standard variable (the T score), with scores ranging from 0 to 100, a mean of 50, and a standard deviation of 10. A change in the GAS T score of more than 10 appeared clinically important in adult patients with upper-limb spasticity (ULS) who had suffered diffuse brain injury or stroke or who had been diagnosed with multiple sclerosis and had been classified as responders (positive clinical outcome associated with BoNT treatment as identified by the treating physician) and nonresponders (negative or non-significant clinical outcome associated with BoNT treatment as identified by the treating physician).[40] However, no validity or reliability studies have been conducted in children and, as a result, it is unclear if the psychometric properties observed in adults (particularly the responsiveness with GAS) apply to children. No MCID was identified for the GAS score in pediatric patients with LLS.

Tardieu Scale

The TS was developed by Tardieu et al. in 1954 to clinically measure spasticity by measuring the different angles of reaction when passing the muscle through stretches at different predefined velocities.[41,42] This outcome measure was developed to more closely align with the 1979 Lance definition of spasticity, specifically, a “motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone), with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome.”[41] Spasticity is thus rated by examining the reaction difference of the muscle in question between the slowest and fastest stretch speed, both of which are performed by the same practitioner at the same time of day with the muscle being in the same resting position.[41] The slow stretch assesses the passive range of motion and is slow enough to avoid producing a significant stretch reflex. The stretch at the fastest velocity is performed to maximize the involvement of the stretch reflex, thus producing a catch-and-release sensation (also termed clonus) that is dependent on the amount of spasticity present.[41] Two parameters are used to measure the muscle spasticity, namely the spasticity angle X (which is the difference between slow-speed angle of arrest [V_1] and the clonus or catch-and-release angle at the highest speed [V_3]) and the spasticity grade Y (the grading of the intensity of the muscle reaction to the fastest stretch [V_3] and is an ordinal variable). Larger spasticity angles correspond to more spasticity in the muscle. The spasticity is graded as follows: grade 0 = absence of spasticity as defined by a catch that is not followed by a release; grade 1 = passive movement is slowed down by mild resistance; grade 2 = passive movement (the catch and release) is transiently interrupted, grades 3 and 4 = severe spasticity; and non-ratable = a catch that is not followed by an obvious release occurring at inconsistent angles.[41] Training has been shown to enhance the reliability of the TS, particularly in the angle of catch at fast speed (X_{V3}), in all muscles except the knee flexors.[41] In Study 141, all investigators were trained in the use of the assessment scales prior to the start of the study in an attempt to minimize variability between centres. They were also given follow-up training during the study. No MCID was

identified in the literature with regard to pediatric patients with LLS. The TS at the ankle joint of the most affected lower limb was reported in Study 141.

Observational Gait Scale

The OGS is an objective outcome measure used to document gait changes (or impairments) of the upper motor syndrome in young children who have received injections of BoNT.[22,43] It was derived from the Physician Rating Scale by expanding the scale from six to eight sections, including putting more emphasis on the knee-to-foot relationship during the standing phase. The gait parameter sections that make up the OGS include knee position in mid stance, initial foot contact, foot contact mid stance, timing of heel rise, hindfoot at mid stance, base of support, gait assistive devices, and change. The maximum score is 22 for each leg, which denotes a normal gait. In older children, the standard of assessing gait includes instrumented three-dimensional gait analysis; however, this is not always appropriate for children due their potential to be uncooperative and their small size.[43] The child is recorded while walking and the investigator (e.g., someone with extensive knowledge of gait analysis) looks at the video in order to score each component.[43] The OGS is a validated and reliable instrument to assess response to treatment for pediatric patients with spasticity. No MCID was identified in the literature regarding pediatric patients with LLS. The OGS in the most affected leg was reported in Study 141.

Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales

The original Pediatric Quality of Life Inventory (PedsQL) was developed as a health-related quality-of-life (HRQoL) measure that addressed the paucity of appropriately validated and reliable instruments incorporating both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates generic and disease- and symptom-specific items that are appropriate for the assessment of pediatric chronic conditions.[44] The PedsQL 4.0 Generic Core Scales comprise 23 items under the following modules: Physical Functioning (eight items), Emotional Functioning (five items), Social Functioning (five items), and School Functioning (five items).[45] The Generic Core Scales comprise both a parent-proxy report and a child self-report that assess health perceptions. The child self-report format is specifically for three age groups: five to seven, eight to 12, and 13 to 18 years of age, while the corresponding parent-proxy reports are specifically for toddlers (ages two to four, for which there is no child self-assessment report), young children (ages five to seven), children (ages eight to 12), and adolescents (ages 13 to 18). The questions ask how much of a problem each item has been in the past month. A five-point Likert response scale is used across the child reports (from ages eight to 18) and the corresponding parent report and includes the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a three-point scale is used for simplification and ease of use for children aged five to seven years (0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem), with each of the response choices on the scale anchored to a happy, neutral, or sad face.[45] The scores, which are reversed scored, are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0, with higher scores indicative of a higher HRQoL. The PedsQL Generic Core Scales have been validated and determined to be reliable and responsive in pediatric patients with chronic conditions. However, whether validity and responsiveness of the PedsQL holds true in pediatric patients with LLS is unknown, as the PedsQL has never been evaluated in this population and currently no known MCID exists for the PedsQL in pediatric patients with LLS.

Faces Pain Scale — Revised

The Faces Pain Scale (FPS) and Faces Pain Scale — Revised (FPS-R) were developed to measure pain in pediatric patients.[46,47] Bieri et al.[46] developed the FPS using a five-phase approach, with each phase helping lead to the development of the seven-faces (seven items) scale construct. The final phase examined the test–retest reliability and subsequently showed that a rank correlation coefficient of 0.79 was obtained when six-year-old children rated a painful experience over a two-week time period.[46] Hicks et al.[47] undertook the revising of the original FPS, as the seven-point version was not easily rescaled to either a 0 to 5 or 0 to 10 metric. Instead, they adapted the FPS to a six-face scale, with corresponding scoring of 0, 2, 4, 6, 8, and 10 (or 0, 1, 2, 3, 4, 5); a higher score indicates more pain.[47] The clinical expert consulted for this review explained that pain is not normally associated with spasticity; therefore, the relevance of this outcome measure remains under question. No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the FPS for pediatric patients with LLS. In addition, no MCID for the FPS-R in this population has been identified.

Gross Motor Function Measure

The GMFM (and, subsequently, the 88-item GMFM [GMFM-88][48,49]) is an outcome measure used to evaluate change in gross motor function over time in children with varying degrees of CP.[50] The 85 items that made up the original GMFM (and the subsequent five additional items included in the GMFM-88[48,49]) were chosen because they were the items most likely to show change in patients with CP. Individuals items were combined into five separate areas of motor function to facilitate scoring. These dimensions include: A = lying and rolling; B = sitting; C = crawling and kneeling; D = standing; and E = walking, running, and jumping.[48,50] Each individual item is scored on a four-point Likert scale (0 to 3), with assignments as follows: 0 = cannot do; 1 = initiates (< 10% of the task is completed); 2 = partially completes (10% to < 100% of the task); and 3 = task completion (100% of the task). Each dimension contributes equal weight; therefore, dimension scores are calculated using the following formula: child's score ÷ maximum score × 100%. The total score is then obtained by adding up all of the dimension scores (per cent) and then dividing them by the total number of dimensions (five dimensions). To increase responsiveness, and if the therapist identifies specific goals, a goal-score total can also be calculated (using the same aforementioned algorithm for obtaining the total scores; however, this time, by dividing by the dimensions that were part of the goal setting).[48-50] It should be noted that the GMFM (and GMFM-88) only assesses how much of the task the child can perform (quantity) and does not measure how well the task is performed (quality).[49] The GMFM is a validated instrument to assess response to treatment for pediatric patients with spasticity. No MCID was identified in the literature for the GMFM-88 with regard to pediatric patients with LLS. In Study 701, the total score was named the overall score.

Leeds Functional Mobility Questionnaire

In Study 701,[51] the investigators used the Leeds FMQ, a 50-item questionnaire that was developed to identify and assess changes in the patient's ability to manage everyday activities that are typically impaired in patients with LLS. It is administered as a structured interview with the patient's parents and was administered at 0, 4, and 16 weeks post–aboBoNTA treatment. It is subdivided into three separate domains: sitting and standing, mobility, and other activities.[51] There is no overall score for this rating instrument and each question is summarized and analyzed separately. Categorical data are generated from each question and assess the degree of difficulty when performing certain activities. A

lower score indicates improved function. The Leeds FMQ was developed by the Regional Child Development Centre at St James's University Hospital in Leeds, UK; however, it is still in the process of development.[51] Hence, there has been no literature identified regarding its psychometric properties (validity, reliability, or responsiveness) for pediatric patients with LLS. In addition, no MCID for the Leeds FMQ in this population has been identified.

Leeds Videographic Gait Assessment

In Study 701,[51] the investigators used the Leeds VGA to observe patient gait, viewed in both the sagittal and coronal planes. It was developed by the Leeds Regional Child Development Centre at St James's University Hospital in Leeds, UK.[51] In the study, patients walked along a walkway both with and without their normal splints and footwear at weeks 0, 4, and 16. The video clips were blinded and randomized to be reviewed by a panel of clinicians and physiotherapists who had experience in the management of children with walking difficulties associated with muscle spasticity. A standard score sheet was used to rate the following parameters, with each leg scored separately: initial foot contact, degree of knee flexion, presence/absence of rocker-bottom foot, hindfoot deformity (presence of valgus or varus), and walking aids used.[51] No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the Leeds VGA for pediatric patients with LLS. In addition, no MCID for the Leeds VGA in this population has been identified.

Subjective Functional Assessment of Gait

This subjective functional assessment of gait was used by both the parent and investigator at each post-treatment visit to assess functional changes in response to treatment with aboBoNTA.[51] Specifically, there is the parent's and investigator's opinion (scored separately) on the child's functional changes, with the choices being presented as follows: good response; minimal response; no response; worse response; and not recorded.[51] No literature was identified regarding any psychometric properties (validity, reliability, or responsiveness) of the subjective functional assessment of gait for pediatric patients with LLS. In addition, no MCID for the outcome measure in this population has been identified.

Harms

Adverse events (i.e., treatment-emergent adverse events [TEAEs], serious adverse events [SAEs], withdrawal due to adverse events [WDAEs], and notable adverse events [i.e., adverse events of special interest in this review]) were reported in both randomized controlled trials (RCTs).

In Study 141, a TEAE was defined as any adverse event that occurs during the treatment phase of the study if it: was not present prior to receiving the first intake of study medication; was present prior to receiving the first intake of study medication but the intensity increased during the treatment phase of the study; or it was present prior to receiving the first intake of study medication and the intensity was the same as it was prior to the first intake of study medication, however, during the active phase of the study the adverse event was related to the medication intake. An SAE was defined as any adverse event that is life-threatening or resulted in death, patient hospitalization, or prolongation of an existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect in the offspring of a patient who received the study treatment. An SAE was also defined as an important medical event that, based on appropriate medical

judgment, may jeopardize the patient and may require medical and/or surgical intervention to prevent one of the outcomes listed previously.

In Study 701, an adverse event included any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of the clinical trial, whether associated with a drug or placebo and whether or not considered drug-related. An SAE was defined as any event that is fatal; life-threatening; permanently or temporarily disabling or incapacitating or results in hospitalization; or prolongs a hospital stay or is associated with congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, any event the investigator regards as serious, or which would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the drug, should be reported as a serious event.

Statistical Analysis

Study 141

In Study 141, the primary (MAS) and first secondary (PGA) efficacy end points were taken into account in the sample size calculation. The power used for the sample size calculations was equal to 85% for the primary efficacy end point and equal to 90% for the first secondary efficacy end point. The sample size needed per group was calculated for each end point separately, and then the larger one was retained. A total of 228 randomized patients (i.e., 76 randomized patients per treatment group) were necessary to demonstrate a statistically significant treatment effect on the primary efficacy end point with a type I error rate controlled at level 0.05 and a power of 85%, assuming: mean changes from baseline to week 4 in the MAS score of −1.3 and −0.9 in the aboBoNTA and placebo groups, respectively, a common standard deviation for the change from baseline to week 4 in the MAS score of 0.8, and a 3% dropout rate from baseline to week 4. A total of 165 randomized patients (i.e., 55 patients per treatment group) were necessary to demonstrate a statistically significant treatment effect on the mean PGA score with a two-sided comparison-wise type I error rate controlled at 0.05 and a power of 90%, assuming a between-group mean score difference of the PGA at week 4 of 0.7, a common standard deviation of the PGA score at week 4 of 1.1, and a 3% dropout rate at week 4. A targeted total sample size of 228 randomized patients (i.e., 76 randomized patients per treatment group) was considered sufficient to detect a treatment effect on both the primary and first secondary efficacy end points. Using a sample size of 228 as the larger of the two required figures meant the actual power for the PGA score comparison rose to 97%. The rationale for the above threshold for the MAS score was based on a previous clinical trial conducted in children with CP for lower extremity spasticity.[52] That study assessed three different doses of onaBoNTA (low-dose group [1 U/kg], middle-dose group [3 U/kg], and high-dose group [5 U/kg]). The rationale for the aforementioned threshold or PGA was based on a previous clinical trial for ULS conducted in adult patients after a stroke.[53]

Two different statistical methodologies for the efficacy analyses were applied for the registrations in the US and non-US countries. Only the non-US approach and data are presented for the purposes of this review.

In non-US countries, superiority was based on the primary efficacy end point only. In order to control the family-wise type I error rate, the following two-step hierarchical testing procedure was applied for the testing of the superiority of each of the two aboBoNTA doses to placebo, where the superiority of aboBoNTA 15 U/kg to placebo for MAS at four weeks

(primary efficacy outcome) was tested at a significance level of 0.05. If the *P* value associated with that testing was lower than 0.05, then the superiority of aboBoNTA 10 U/kg to placebo for MAS at four weeks (primary efficacy outcome) was tested at a significance level of 0.05. If the *P* value associated with that testing was lower than 0.05, it was then considered significant. In the event the hierarchical testing procedure was stopped at the end of step 1, the testing of the superiority of aboBoNTA 10 U/kg to placebo on the primary efficacy end point was performed to characterize the full clinical effect, but no formal statistical conclusion was drawn. Each of the two secondary efficacy end points was analyzed to compare each aboBoNTA dose with placebo at a 0.05 type I error rate.

Each tertiary efficacy end point was analyzed for exploratory purposes only to compare each aboBoNTA dose with placebo. No adjustment for multiplicity was completed for these analyses.

The primary efficacy analysis consisted of two contrast analyses within a single analysis of covariance (ANCOVA) model controlling for the baseline MAS score and the randomization stratification factors (age range and BoNT-naive or non-naive status as assessed at baseline) and the centre, all as fixed effects. The least squares (LS) means and the associated 95% CIs were calculated for the aboBoNTA and placebo groups, plus the differences in the LS means between these groups and the associated *P* values. The first secondary efficacy end point (mean PGA score at week 4) and the second secondary efficacy end point (mean GAS score at week 4) were analyzed using an analysis of variance (ANOVA) model, controlling for the randomization stratification factors (age range and BoNT treatment status) at baseline and at the centre, all as fixed effects. The LS means and the associated 95% CIs were calculated for the aboBoNTA and placebo groups, as were the differences in the LS means between these groups and the associated *P* values. For each of the tertiary end points, summary tables of raw values and change from baseline were provided at each visit. In ANOVA or analysis of covariance (ANCOVA) models, the LS means and the associated 95% CIs were calculated for the aboBoNTA and placebo groups, as were the differences in the LS means between these groups and the associated *P* values. The odds ratios and their 95% CIs were calculated from a logistic regression. To assess the impact of missing efficacy data at week 4, sensitivity analyses were performed with missing data imputed with baseline values (primary end point) or with the “markedly better” or “markedly worse” data (sensitivity analysis of the first secondary end point PGA data).

Subgroup analyses were performed on the primary and secondary efficacy end points in the intention-to-treat (ITT) population by BoNT status (naive or non-naive) at baseline. In the protocol for this review, a subgroup analysis by baseline severity of spasticity was identified; however, such analyses were not conducted.

Study 701

In Study 701, a sample size of 50 patients (25 patients per treatment group) was planned to provide 90% power to detect a clinically significant between-group difference of 10% in the overall GMFM score at the 0.05 significance level, allowing for a dropout rate of 5% to 10%. No rationale was provided on how the clinically significant between-group difference of 10% was selected. The primary efficacy end points in GMFM scores were analyzed using ANCOVA. For all other efficacy variables, analysis was performed using logistic regression. Centre, strata, and baseline scores were included in the model, as appropriate. No adjustments for multiplicity were performed. Missing data were imputed using the last observation carried forward (LOCF). No subgroup analysis was conducted in Study 701.

Analysis Populations

In Study 141, efficacy analyses were performed using the ITT population, which included all randomized patients who received at least one injection of study treatment and who had a MAS score in the GSC assessed both at baseline and at week 4. The per-protocol (PP) population was defined as all patients in the ITT population who did not have major protocol violations between baseline and week 4, inclusive. The safety population was defined as all randomized patients who received at least one injection of study treatment. The ITT population should be considered modified ITT given that appropriate ITT population would include all randomized patients regardless if they received treatment or had assessment after receiving treatments.

In Study 701, all safety and efficacy analyses were performed using the all-patients-treated (APT) population, which comprised all patients randomized to the study who received some study medication. The PP population comprised all patients in the APT population who did not have major protocol violations.

Patient Disposition

In Study 141, a total of 253 patients were screened, of whom 241 were enrolled into the study and were randomized. Of the randomized patients, a total of 239 patients received study treatment and 230 patients had at least 12 weeks of follow-up: 75 in the placebo group, 78 in the aboBoNTA 10 U/kg treatment group, and 77 in the aboBoNTA 15 U/kg treatment group (Table 8). Overall, 15 patients (6.2%) discontinued the study prematurely; 13 patients discontinued prior to or at week 12 (eight in the placebo group, two in the aboBoNTA 10 U/kg treatment group, and three in the aboBoNTA 15 U/kg treatment group); and two patients discontinued after week 12, both of whom were in the aboBoNTA 15 U/kg treatment group. The most common reason for discontinuation was consent withdrawal (seven patients). Two patients who were screening failures were randomized to the placebo group in error. The reasons given for these two patients withdrawing from the study were “does not meet entry criteria” and “other” (patient refused to enrol in the study). This was noted at the time and both patients were withdrawn from the study before receiving study treatment.

In Study 701, a total of 52 patients were randomized. There were no withdrawals and all patients completed the study up to week 16 (Table 9). A total of 16 patients were considered to have ongoing benefit and continued to week 24. Of these, 14 patients continued to week 36.

Table 8: Patient Disposition for Study 141

	AboBoNTA 10 U/kg/leg	AboBoNTA 15 U/kg/leg	Placebo
Screened, N			
Randomized, N			
Discontinued, N (%)			
Completed, N (%)			
ITT, N (%)			
PP, N (%)			
Safety, N (%)			

aboBoNTA = abobotulinumtoxinA; GSC = gastrocnemius-soleus complex; MAS = Modified Ashworth Scale; ITT = intention-to-treat; PP = per-protocol.

Source: Study 141 Clinical Study Report.[22]

Table 9: Patient Disposition for Study 701

	AboBoNTA 30 U/kg	Placebo
Screened, N	NR	
Randomized, N	26	26
Discontinued, N (%)	0	0
APT, N (%)	26 (100)	26 (100)
PP, N (%)	15 (58)	18 (69)
Safety, N (%)	26 (100)	26 (100)

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; NR = not reported; PP = per-protocol.
Source: Study 701 Clinical Study Report.[30]

Exposure to Study Treatments

In Study 701, with the exception of one placebo-treated patient and two aboBoNTA-treated patients who had only one leg treated, all other patients received the appropriate study medication specified by the randomization list.

Table 10: Exposure (Dose per Leg) for Study 141 — Safety Population

Length of Exposure (Weeks)	AboBoNTA 10 U/kg/leg (N = 80)	AboBoNTA 15 U/kg/leg (N = 80)	Placebo (N = 79)
All patients			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
All completed patients[a]			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; SD = standard deviation.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 11: Number of Legs Treated (Dose per Leg) for Study 141 — Safety Population

Number of Legs Treated, n (%)	AboBoNTA 10 U/kg/leg (N = 80)	AboBoNTA 15 U/kg/leg (N = 80)	Placebo (N = 79)
One leg injected	[redacted]	[redacted]	[redacted]
Two legs injected	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA.
Source: Study 141 Clinical Study Report.[22]

Critical Appraisal

Internal Validity

The objectives of Study 141 were well defined. Randomization was stratified by patient age and previous exposure to BoNT treatment. Allocation concealment was sufficiently described. The randomization manager, who was a statistician independent from the study, prepared and kept the master randomization list for this study. The treatment arm allocations, as well as the treatment numbers supplied, were managed by an interactive voice response system (IVRS). The IVRS also managed all the logistical aspects for the study treatments. The sample size was determined based on the power (≥ 85%) to detect a difference of change from baseline (mean ± SD: 1.3 ± 0.8 and 0.9 ± 0.8 in the aboBoNTA and placebo groups, respectively) for MAS score at week 4 ($P < 0.05$) and based on the power (≥ 90%) to detect a between-group mean difference (mean ± SD: 0.7 ± 1.1) for the PGA score at week 4. The rationale for the aforementioned threshold for MAS was based on a previous clinical trial conducted in children with CP for lower extremity spasticity.[52] That study assessed three different doses of onaBoNTA (1 U/kg, 3 U/kg, and 5 U/kg) and there was no placebo treatment group included, so it is not clear what the rationale was for using 0.9 for the change from baseline in the placebo group. The rationale for the aforementioned threshold for PGA was based on a previous clinical trial for ULS conducted in adult patients after a stroke, which is a different population than pediatric patients with LLS.[53] Key patient baseline characteristics were balanced across treatment groups. The relevant concomitant medications (for spasticity) and the physiotherapy treatments were well described and balanced between the aboBoNTA and placebo groups. The outcome

measurements (especially for the primary outcome and the secondary outcome) were well described. The overall dropout rate was low, but it was slightly higher in the placebo group (9.9%) than in the aboBoNTA treatment groups (2.5% in the aboBoNTA 10 U/kg treatment group and 6.3% in the aboBoNTA 15 U/kg treatment group). However, for the assessment of the primary outcome (MAS at 4 weeks), 99% of the patients randomized to the aboBoNTA treatment groups and 95% of those randomized to the placebo treatment group were included in this analysis. Hence the dropout rate does not seem to be a big limitation for the primary outcome.

In Study 141, effort was made in each centre to ensure the same evaluating investigator assessed the same patients for the duration of the study. All investigators were trained in the use of the assessment scales prior to the start of the study in an attempt to minimize variability between centres. They were also given follow-up training during the study. The assessor who conducted the PGA of treatment response was different from the person who evaluated the MAS. When making their assessment, none of the assessors had knowledge of the scores obtained by the other assessor. Providing training in the use of the assessment scales prior to the start of the study, and having the same evaluating investigator assessing the same patients for the duration of the study, would help in improving inter-rater reliability.

While, overall, Study 141 was generally well designed, as mentioned previously, some methodological limitations of the RCT need to be discussed in the interpretation of the results. Although the master randomization list was prepared independently and the allocation concealment was sufficient, how the randomization list was generated was not clearly described in the Clinical Study Report. While identical active and placebo vials were provided to maintain blinding for patients and investigators, there was a risk of unblinding in this trial as, overall, 48% of patients had previous exposure to BoNT treatment and were therefore likely to expect a reduction in symptoms after the injection. Placebo-treated patients would not experience this reduction in symptoms and, therefore, the patient and investigators might be able to identify treatment based on response, potentially impacting subjective outcomes, adverse effect reporting, and study dropout rates. Further, the criteria for re-treatment were not clearly defined. In addition, the analysis set for the primary analysis was identified as the ITT population; however, this is not a true ITT because the ITT population used in Study 141 was defined as all randomized patients who received at least one injection of study treatment and who had an MAS score in the GSC assessed both at baseline and at week 4, whereas the appropriate ITT population would include all randomized patients and, hence, the ITT population used in Study 141 should have been identified as a modified ITT population. Except for the primary outcome (MAS at week 4) which was analyzed based on a two-step statistical testing hierarchy to control type I error, the secondary outcomes (PGA and GAS at week 4), subgroup analyses, and all tertiary outcomes (such as MAS, PGA assessed at week 12, TS, OGS, FPS, and PedsQL) were analyzed for exploratory purpose only and no control for multiplicity of testing was employed, thus increasing the risk of type I error for all end points assessed, other than the primary end point; thus, all end points beyond the primary should be interpreted cautiously. In addition, subgroups were not analyzed appropriately, as no-test for interaction by previous BoNT experience was conducted to determine if there was an interaction between the treatment effect and previous exposure to BoNT. Also, the interpretation of data beyond week 12 in Study 141 should be interpreted with extreme caution due to the large number of dropouts. Furthermore, no MCIDs were established specific to a pediatric population with LLS, and the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature.

The objectives of Study 701 were well defined. Eligible patients were randomly allocated to one of the two treatment groups following the randomization schedule, generated in blocks of four prior to the study. Each centre was supplied with blocks of four patient numbers, as required. Production of the randomization list and the blinding of study medication were performed by Penn Pharmaceuticals Ltd. Blinding was achieved by supplying the study medication for each patient in identical patient packs. Given the small number of patients included and that blocks of four were used, which potentially could make the allocation of participants predictable, selection bias might have been introduced. Also, balance may not have been achieved across the baseline variables, suggesting randomization was not successful, which may substantially bias the study results. In addition, it is not clearly described in the Clinical Study Report how the randomization list was generated. The sample size was determined based on the power (90%) to detect a clinically significant between-group difference of 10% in the overall GMFM score at the 0.05 significance level. However, no rationale was provided on how that clinically significant between-group difference of 10% was calculated. Study 701 did not show statistical significance between groups; this could be due to wrong assumptions made in the sample size calculation. The aboBoNTA and placebo groups were well balanced with regard to baseline maximum passive ankle dorsiflexion and Leeds VGA at baseline; however, there was a substantial difference between groups in the GMFM overall and goal-total scores with aboBoNTA-treated patients being less functionally impaired than placebo-treated patients. No patient discontinued the study. Also, the potential implications of conducting multiple statistical tests were not considered, and no adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error; thus, all end points beyond the primary should be interpreted cautiously. Furthermore, no MCIDs were established specific to a pediatric population with LLS, and the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature.

External Validity

There were no Canadian sites enrolled in both studies. According to the clinical expert consulted for this review, the population enrolled in both trials was generally representative of Canadian pediatric patients with LLS. The expert did note, however, that based on the baseline characteristics, the patient population appeared to be limited to ambulatory patients with mild to moderately severe spasticity. Only patients with LLS with a diagnosis of CP were included in both trials. No patients with LLS from other causes such as stroke, brain injury, or spinal cord injury were included in both trials; therefore, it is unclear whether the reported efficacy and safety of aboBoNTA could be generalized to pediatric patients who have LLS due to other causes or higher levels of functional impairment. (GMFCS levels IV and V). However, the clinical expert consulted for this review indicated that the underlying cause of the LLS would not impact the treatment strategy applied.

In Study 701, only the gastrocnemius was injected and not the GSC muscles, hence, the soleus was not injected as recommended in the Health Canada product monograph. The clinical expert consulted for this review indicated this might be an issue or a limitation and the response might differ from what would be seen when the muscles of the GSC are injected.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently (Objective and Methods Section and Table 3). See Appendix 4 for detailed efficacy data.

Modified Ashworth Scale

MAS scores were assessed only in Study 141. The MAS was used to measure the intensity of muscle tone in the GSC at the ankle joint by measuring the resistance of the muscle to passive lengthening or stretching. The muscle tone of the affected leg was assessed in patients with unilateral lower-limb impairment, and of the most affected leg in patients with bilateral lower-limb impairment. The muscle tone was graded on a six-point scale, from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).

In Study 141, the MAS scores at baseline (mean ± SD) were 3.1 ± 0.3, 3.1 ± 0.3, and 3.2 ± 0.4 in the aboBoNTA 10 U/kg/leg, aboBoNTA 15 U/kg/leg, and placebo groups, respectively. At week 4, the between-group mean difference in change from baseline was statistically significant (−0.49, 95% CI, −0.75 to −0.23, *P* = 0.0002) in the aboBoNTA 15 U/kg/leg group compared with the placebo group. Likewise, the between-group mean difference in change from baseline for the aboBoNTA 10 U/kg/leg group compared with placebo was statistically significant (−0.38, 95% CI, −0.64 to −0.13, *P* = 0.0029) (Table 12). MAS scores assessed at week 12 were analyzed as a tertiary outcome for exploratory purposes only. The improvement in MAS score observed for both aboBoNTA groups at week 4 appeared to be maintained at week 12 to a lesser extent. The MAS score results after week 4 and up to week 28 (for those who continued in the study) are presented in Table 18.

The sensitivity analysis of the primary efficacy end point, performed on all randomized patients who received study treatment by imputing missing data with baseline values, appeared to be in the same direction as the primary analysis, [redacted]

The subgroup analysis for the MAS assessed by previous exposure to BoNT treatment also showed an improvement in aboBoNTA 15 U/kg group compared with placebo, regardless of prior exposure to BoNT. An improvement was also seen in aboBoNTA 10 U/kg group compared with placebo regardless of prior exposure to BoNT (Table 19). No test for interaction by previous BoNT experience was conducted in order to determine if there was an interaction between the treatment effect and previous exposure to BoNT.

Table 12: Modified Ashworth Scale Score in the (Most) Affected Leg, Change From Baseline at Week 4 (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
MAS score at baseline			
Mean (SD)	3.1 (0.3)	3.1 (0.3)	3.2 (0.4)
MAS score at week 4			
Mean (SD)	2.3 (0.9)	2.2 (0.8)	2.6 (0.9)
Change in MAS score from baseline to week 4			
Mean (SD)	−0.9 (0.9)	−1.0 (0.9)	−0.6 (0.8)
LS mean (95% CI)	−0.86 (−1.07 to −0.65)	−0.97 (−1.18 to −0.76)	−0.48 (−0.69 to −0.27)
Comparison with placebo			
Difference in LS mean (95% CI)	−0.38 (−0.64 to −0.13)	−0.49 (−0.75 to −0.23)	NA
P value	0.0029	0.0002	NA

aboBoNTA = abobotulinumtoxinA; ANCOVA = analysis of covariance; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; NA = not applicable; SD = standard deviation; U = unit.
Note: MAS is displayed on a derived scale. LS means for each treatment group and treatment comparisons as well as the *P* values are obtained from an ANCOVA on the change from baseline with treatment, baseline MAS score, age range at baseline, BoNT status at baseline, and centre as covariates.
Source: Study 141 Clinical Study Report.[22]

Responders Based on Modified Ashworth Scale

[redacted]

Tardieu Scale Score

The TS score was analyzed in Study 141 for exploratory purposes only to compare each aboBoNTA dose with placebo. The spasticity angle (which is the difference between slow-speed angle of arrest and the clonus or catch-and-release angle at the highest speed, with larger spasticity angles corresponding to more spasticity in the muscle) and the spasticity grade Y (which is the grading of the intensity of the muscle reaction to the fastest stretch and is an ordinal variable ranging from 0 [defined as absence of spasticity as defined by a catch that is not followed by a release] to 4 [indicating severe spasticity]) are presented in Table 22.

[redacted]

Goal Attainment Scaling

GAS at week 4 was analyzed as the second secondary outcome in Study 141. However, this outcome was not included in the statistical testing hierarchy and, hence, was not controlled for type I error and the level of significance may be inflated; therefore, statistical significance should be interpreted with caution for this outcome.

GAS was used to measure progress toward individual therapy goals. Between one and three individual goals (from a list of pre-selected goals) were defined for each patient by the physician, and the child's parents (caregiver) where applicable, prior to treatment. The goal outcome scores were incorporated into a single aggregated overall GAS T score for each patient. If all goals were achieved as expected, the overall GAS score was 50.0. If the overall response was better than expected, the value was > 50.0 and, conversely, if the overall response was less than expected, the overall GAS score was < 50.0. Table 23 summarizes the goals selected at baseline for each treatment group. The five main goals chosen were "improved walking pattern," "improved balance," "decreased frequency of falling," "decreased frequency of tripping," and "improved endurance." The most commonly chosen goal for each treatment group was "improved walking pattern."

Patients in both aboBoNTA treatment groups achieved a mean GAS score above 50.0, demonstrating that the overall response was better than expected. However, patients in the placebo group showed a less-than-expected response with a mean GAS score below 50.0. This result was statistically significant in both aboBoNTA treatment groups compared with placebo (Table 13). The outcome measure GAS at 4 weeks was not part of the hierarchical analysis plan and therefore was not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution. GAS scores assessed at week 12 were analyzed as a tertiary outcome for exploratory purposes only. The improvement in GAS score observed for both aboBoNTA groups at week 4 appeared to be maintained at week 12. The GAS score results after week 4 and up to week 28 are presented in Table 24.

The three most commonly chosen goals in the study were "improved walking pattern," "improved balance," and "decreased frequency of falling." For "improved walking pattern" and "decreased frequency of falling," there was a higher mean score in the aboBoNTA 10 U/kg treatment group and aboBoNTA 15 U/kg treatment group compared with the placebo group, and for the "improved balance" there was a similar mean score in all three treatment groups (Table 25).

The subgroup analysis for GAS assessed by previous exposure to BoNT treatment also showed an improvement in both aboBoNTA treatment groups compared with placebo, regardless of prior exposure to BoNT (Table 26). No test for interaction by previous BoNT experience was conducted to determine if there was an interaction between the treatment effect and previous exposure to BoNT.

Table 13: Goal Attainment Scaling Total Score at Week 4 (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
GAS score at week 4			
n (%)	78 (99)	79 (100)	76 (99)
Mean (SD)	50.4 (10.1)	49.8 (11.1)	45.5 (10.4)
LS mean (95% CI)	51.53 (49.05 to 54.01)	50.86 (48.36 to 53.36)	46.21 (43.70 to 48.72)
Comparison with placebo			
Difference in LS mean (95% CI)	5.32 (2.31 to 8.32)	4.65 (1.59 to 7.71)	NA
P value	0.0006	0.0031	NA

aboBoNTA = abobotulinumtoxinA; ANOVA = analysis of variance; BoNT = botulinum toxin; CI = confidence interval; GAS = goal attainment scaling; ITT = intention-to-treat; LS = least squares; N = number of patients in group; n = number of patients with data; NA = not applicable; SD = standard deviation; U = unit.
Note: LS means for each treatment group and treatment comparisons, as well as the *P* values, are obtained from an ANOVA on the visit value with treatment, age range at baseline, and BoNT status at baseline and at centre as covariates.
Source: Study 141 Clinical Study Report.[22]

Health-Related Quality of Life (Pediatric Quality of Life Inventory)

Pediatric Quality of Life Inventory Generic Core Scales

Physician's Global Assessment

The PGA of treatment response at week 4 was analyzed as the first secondary outcome in Study 141. The LS means of the PGA at week 4 were 1.54 (95% CI, 1.28 to 1.81) in the aboBoNTA 10 U/kg group, 1.50 (95% CI, 1.23 to 1.77) in the aboBoNTA 15 U/kg group, and 0.73 (95% CI, 0.46 to 0.99) in the placebo group, respectively (Table 14). The results of the PGA show that aboBoNTA (10 U/kg and 15 U/kg) were statistically significantly more effective than placebo (0.82 [95% CI, 0.50 to 1.14, $P < 0.0001$] and 0.77 [95% CI, 0.45 to 1.10, $P < 0.0001$], respectively). The PGA was not part of the hierarchical analysis plan and therefore was not adjusted for multiple comparisons, hence, the level of significance is inflated and results should be interpreted with caution. The PGA assessed at week 12 was analyzed as a tertiary outcome for exploratory purposes only. The improvement in PGA score observed for both aboBoNTA groups at week 4 was maintained at week 12 to a lesser extent. PGA findings assessed at weeks 12, 16, 20, and 24 are presented in Table 30.

The subgroup analysis for the PGA assessed by previous exposure to BoNT treatment also showed that, in both treatment groups, aboBoNTA was statistically significantly more effective than placebo, regardless of prior exposure to BoNT (Table 31). No test for interaction by previous BoNT experience was conducted to determine if there was an interaction between the treatment effect and previous exposure to BoNT.

Table 14: Physician's Global Assessment of Treatment Response at Week 4 (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
PGA score at week 4			
Mean (SD)	1.6 (1.1)	1.4 (1.1)	0.7 (0.9)
LS mean (95% CI)	1.54 (1.28 to 1.81)	1.50 (1.23 to 1.77)	0.73 (0.46 to 0.99)
Comparison with placebo			
Difference in LS mean (95% CI)	0.82 (0.50 to 1.14)	0.77 (0.45 to 1.10)	NA
P value	< 0.0001	< 0.0001	NA

aboBoNTA = abobotulinumtoxinA; ANOVA = analysis of variance; CI = confidence interval; ITT = intention-to-treat; LS = least squares; N = number of patients in group; NA = not applicable; PGA = Physician's Global Assessment; SD = standard deviation; U = unit.
Note: LS means for each treatment group and treatment comparisons as well as the *P* values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BoNT status at baseline, and centre as covariates.
Source: Study 141 Clinical Study Report.[22]

Observational Gait Scale

[redacted]

[redacted]

Gross Motor Function Measure

In Study 701, the primary efficacy variable was functional change, as assessed by the change from baseline in overall GMFM score without walking aids or orthoses at week 4 of the study. There were no statistically significant between-group differences in the overall GMFM score at week 4 (Table 34).

In Study 701, change from baseline in overall GMFM score at weeks 8 and 16, and change from baseline in GMFM goal-total score at weeks 4, 8, and 16, were secondary efficacy variables. Table 35 summarizes the data for all patients treated and demonstrates there were no statistically significant between-group differences for both outcomes at all time points assessed.

Leeds Videographic Gait Assessment

In Study 701, change in VGA scores at weeks 4 and 16 compared with baseline was a secondary efficacy variable. The results for the APT population demonstrated statistically significant between-group differences at week 16, but not at week 4. Significantly more treated legs in the aboBoNTA group demonstrated a valgus or varus deformity of the hindfoot at week 16 (Table 36). Finally, fewer patients in the Dysport Therapeutic group used walking aids. In Study 701, all outcomes were not controlled for type I error and the level of significance may be inflated; therefore, any statistically significant results should be interpreted with caution.

Subjective Functional Assessment of Gait

In Study 701, subjective functional assessment at weeks 4, 8, and 16 was a secondary efficacy variable. Although at weeks 4 and 8 more patients in the aboBoNTA group demonstrated a good response (defined as an observable change that was also of functional benefit), no statistically significant between-group differences were reported at either time point (Table 37).

Leeds Functional Mobility Questionnaire

[redacted]

Caregiver Burden Scale

Caregiver burden was an outcome identified as important to patients, according to the patient group input received for this review. This outcome was not assessed in either included trial.

Duration of Effect (Re-Treatment Intervals)

[redacted]

Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol).

Adverse Events

[redacted]

The incidence of TEAEs by dose per leg in Study 701 is presented in Table 17. At least one TEAE was reported in 39% and 50% of patients in the aboBoNTA and placebo groups, respectively. The most common TEAEs were rhinitis (15% in the aboBoNTA and placebo treatment groups), bronchitis (15% and 12% in the aboBoNTA and placebo groups, respectively), pharyngitis (12% in the aboBoNTA and placebo treatment groups), and viral infection (8% and 15% in the aboBoNTA and placebo groups, respectively).

Serious Adverse Events

In Study 141, one SAE was reported in the aboBoNTA 10 U/kg treatment group, no SAEs were reported in the aboBoNTA 15 U/kg treatment group, and five SAEs were reported in four patients in the placebo group (Table 15). In the aboBoNTA 10 U/kg treatment group, the SAE was adenoidal hypertrophy while, in the placebo group, the SAEs were gastroenteritis, pneumonia, rotavirus infection, head injury, and upper-limb fracture. Pneumonia and rotavirus infection SAEs occurred in one patient in the placebo group.

In Study 701, one SAE was reported in the aboBoNTA group, where the patient suffered an episode of acute bronchitis. The event lasted for two days, during which he was hospitalized for monitoring. The patient recovered without sequelae. No SAEs were reported in the placebo group (Table 16).

Withdrawal Due to Adverse Events

In Study 141, one patient in the placebo group was withdrawn from the study because of an adverse event. This patient had Pelizaeus–Merzbacher disease. The investigator considered this event to be unrelated to study treatment. No other WDAE was reported in Study 141 (Table 15).

In Study 701, there were no WDAEs in either treatment arm.

Mortality

No death was reported in either study.

Notable Harms

Generalized weakness, dysphagia, respiratory failure, seizure, and incontinence were identified as the notable harms of interest based on the review protocol. In Study 141, the number of patients experiencing muscular weakness were 2 (2.5%), 0 (0%), and 1 (1.3%) in the aboBoNTA 10 U/kg, aboBoNTA 15 U/kg, and placebo groups, respectively, and the number of patients experiencing epilepsy was 2 (2.5%), 3 (3.5%), and 0 (0%) in the aboBoNTA 10 U/kg, aboBoNTA 15 U/kg, and placebo groups, respectively. All of the patients who reported epilepsy had a history of epilepsy. All five cases were in the aboBoNTA treatment groups and were assessed by the investigator as unrelated to study treatment. One patient in the aboBoNTA 15 U/kg group experienced dysphagia, while fecal incontinence and incontinence were each experienced by one patient in the aboBoNTA 10 U/kg group. There were no reports of patients experiencing respiratory failure (Table 15).

In Study 701, two patients in the aboBoNTA treatment group experienced urinary incontinence; no other notable harms of interest were reported (Table 16).

Table 15: Harms (Dose per Leg) for Study 141 — Safety Population

	AboBoNTA 10 U/kg/leg (N = 80)	AboBoNTA 15 U/kg/leg (N = 80)	Placebo (N = 79)
Patients with > 0 TEAE, N (%)	[redacted]	[redacted]	[redacted]
Most common TEAEs,[a] 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]

	AboBoNTA 10 U/kg/leg (N = 80)	AboBoNTA 15 U/kg/leg (N = 80)	Placebo (N = 79)
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]
Most common SAEs, 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]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]
Notable harms, 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]

aboBoNTA = abobotulinumtoxinA; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 16: Harms by Total Dose Received for Study 141 — Safety Population

	One Leg Injected		Two Legs Injected		Placebo (N = 79)
	AboBoNTA 10 U/kg (N = 43)	AboBoNTA 15 U/kg (N = 50)	AboBoNTA 20 U/kg (N = 37)	AboBoNTA 30 U/kg (N = 30)	
Patients with > 0 TEAE, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common TEAEs,[a] 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]	[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]
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	One Leg Injected		Two Legs Injected		Placebo (N = 79)
	AboBoNTA 10 U/kg (N = 43)	AboBoNTA 15 U/kg (N = 50)	AboBoNTA 20 U/kg (N = 37)	AboBoNTA 30 U/kg (N = 30)	
Notable harms, N (%)					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

aboBoNTA = abobotulinumtoxinA; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
[redacted]
Source: Study 141 Clinical Study Report.[22]

Table 17: Harms for Study 701 — APT Population

	AboBoNTA (N = 26)	Placebo (N = 26)
Patients with > 0 TEAE, N (%)	10 (39)	13 (50)
Most common TEAEs,[a] N (%)		
Rhinitis	4 (15)	4 (15)
Bronchitis	4 (15)	3 (12)
Pharyngitis	3 (12)	3 (12)
Viral infection	2 (8)	4 (15)
Pain	2 (8)	2 (8)
Urinary incontinence	2 (8)	0 (0)
Otitis media	1 (4)	3 (12)
Number of deaths, N (%)	0	0
Patients with > 0 SAEs, N (%)	1 (4)	0

aboBoNTA = abobotulinumtoxinA; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Frequency > 5%.
Source: Study 701 Clinical Study Report.[30]

Discussion

Summary of Available Evidence

Two placebo-controlled RCTs (Study 141 and Study 701) met the inclusion criteria for this review. Study 141 was a pivotal trial. Study 141 included ambulatory patients with CP between two and 17 years of age who had spastic lower limbs. These patients had an MAS score of 2 or higher; were classified at GMFCS level I to III; had a spasticity grade of between 2 and 4; and had a spasticity angle of at least 10 degrees. Study 141 assessed the efficacy and safety of a single treatment episode of aboBoNTA injections (10 U/kg or 15 U/kg for unilateral injections, or 20 U/kg or 30 U/kg for bilateral injections) versus placebo in the treatment of children with dynamic equinus foot deformity associated with CP. The primary outcome was the change from baseline MAS score at week 4. Other outcomes measured at week 4 included PGA score (first secondary outcome) and GAS score (second secondary outcome). MAS, PGA, and GAS scores were assessed at week 12; TS, OGS, FPS, and scores for HRQoL scales (PedsQL) were assessed as tertiary outcomes for exploratory purposes only. Except for the primary outcome (MAS at week 4), no control for multiplicity of testing was employed, increasing the risk of type I error for all end points assessed other than the primary end point; thus, all end points beyond the primary should be interpreted cautiously. TEAEs, SAEs, and WDAEs were also reported.

Study 701 included patients aged between 2 and 7 years who were ambulatory, had a diagnosis of diplegic CP, and had no evidence of fixed contracture (able to achieve 10 degrees of passive ankle dorsiflexion in both legs). Study 701 assessed the efficacy and safety of a single treatment episode of aboBoNTA injections (30 U/kg) versus placebo in the treatment of pediatric dynamic equinus spasticity associated with CP. The primary efficacy variable was functional change, as assessed by GMFM score. Other outcomes assessed were VGA scores, Leeds FMQ, and subjective functional assessment. No adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error.

In addition to the main trials reviewed, the long-term efficacy and safety of aboBoNTA treatment of LLS in pediatric patients was also assessed in Study 147, an open-label extension of Study 141 (Appendix 6). No RCTs were identified that directly compared aboBoNTA with onaBoNTA in this review. However, the manufactured submitted an indirect treatment comparison (ITC), which is summarized in Appendix 7.

Interpretation of Results

Efficacy

The primary efficacy outcome for the pivotal RCT (Study 141) was the change from baseline in MAS score in the GSC at the ankle joint of the (most) affected lower limb. Families and patients with CP who are experiencing LLS indicated they would like longer-lasting treatments that reduce muscle spasticity and tone. Efficacy results from Study 141 indicated an effect for aboBoNTA in the treatment of LLS consistently across the primary and the first secondary outcome (PGA). It demonstrated that both aboBoNTA doses (10 U/kg and 15 U/kg) were more effective than placebo for reducing muscle tone (as assessed by MAS) at week 4. The between-group mean difference of changes from baseline (AboBoNTA minus placebo) for MAS score was statistically significant. No peer-reviewed evidence was identified regarding an MCID for the MAS in the pediatric population

with LLS. One of the clinical experts consulted for this review indicated that a one-point difference in the MAS (in either direction) was clinically relevant, and that the decrease in MAS at week 4 within the aboBoNTA 10 U/kg treatment group of −0.86, and the decrease of −0.97 within the aboBoNTA 15 U/kg treatment group are clinically significant. However, the between-group mean difference in change from baseline of −0.38 for the aboBoNTA 10 U/kg/leg group compared with the placebo group, and −0.49 for the aboBoNTA 15 U/kg/leg group compared with the placebo group, while statistically significant, are not clinically significant in that expert's opinion, as this represents less than half of one gradation on the MAS scale. In contrast, the other clinical expert consulted for this review noted that while a clinically important change in a single patient must be at least a one-point change due to the nature of the MAS, a change between–treatment groups of as low as 0.38 would be considered clinically significant when related to a group of patients receiving treatment. The improvements in muscle tone for both aboBoNTA doses at week 4 were associated with a statistically significant improvement, based on the PGA. The between-group mean difference (AboBoNTA minus placebo) for PGA score was statistically significant (0.82 in the aboBoNTA 10 U/kg/leg group and 0.77 in the aboBoNTA 15 U/kg/leg group). No validity information or MCID were identified for PGA. The PGA was used to evaluate the investigator's impression or perception of improvement. This assessment was performed by an investigator who was different from the one who assessed the MAS scores. The observed improvement in muscle tone at week 4 was not only demonstrated in MAS, it was supported by the results of the TS, another efficacy measurement for spasticity. In the TS, the spasticity grade was reduced for both treatment groups at week 4. However, no conclusion could be derived from the TS because it was analyzed as a tertiary end point and for exploratory purposes only, and no controls for multiple statistical testing were used to control for the risk of type I error.

In Study 141, GAS and OGS were used to evaluate functional improvements. The GAS score at week 4 was a second secondary end point, while OGS was a tertiary (i.e., exploratory) outcome. In GAS, parents were asked to select goals that were relevant to them and their child. The achievement of these goals was then measured and a score was calculated from the achievements. The baseline goal selection showed that most parents wanted their child's gait to improve and so they selected "improved walking pattern." The second and third most selected goals were improved functions such as "improved balance" and "decreased frequency of falling," respectively. All three of these are active functional goals. The results of this scale at week 4 showed a significant improvement in both aboBoNTA groups against placebo. The other functional assessment in this study was the OGS. Both aboBoNTA doses produced improvements in OGS score between baseline and week 4, which were maintained at week 12 in the aboBoNTA 10 U/kg group. This result was supported by a higher number of OGS responders in the aboBoNTA 10 U/kg treatment group and aboBoNTA 15 U/kg treatment group compared with placebo at both visits. However, no conclusion could be derived from the OGS because it was analyzed as a tertiary outcome and for exploratory purposes only, and no controls for multiple statistical testing were used to control for the risk of type I error.

The between-group mean difference in change from baseline for the aboBoNTA 15 U/kg/leg group compared with the placebo group was slightly larger than the between-group mean difference in change from baseline for the aboBoNTA 10 U/kg/leg group compared with placebo for the MAS and TS outcomes at week 4. This was not the case for the GAS and PGA outcomes at week 4. However, no conclusion can be drawn about the dose–response relationship, given that no appropriate statistical test was conducted.

From the patient group input received by CDR on this submission, it is clear that patients consider improved quality of life and reduction in pain to be important outcomes of treatment. In Study 141, the level of pain was low at baseline in all three treatment groups (range 0.4 to 0.8) and the magnitude of reduction in all groups was negligible. Two quality-of-life questionnaires, the PedsQL Generic Core Scales and the PedsQL Cerebral Palsy Module were used in Study 141. No difference was observed in changes in the Total Scale score, the Psychosocial Health Summary, or the Physical Health Summary of the PedsQL Generic Core Scales between both aboBoNTA treatment groups and placebo group. In the PedsQL Cerebral Palsy Module, the only parameter showing improvement from baseline was the fatigue dimension at week 12 in both aboBoNTA treatment groups, with deterioration in the placebo group. However, at the end of the study, both aboBoNTA treatment groups and the placebo group had improvement in fatigue. No difference was observed in the other dimensions of the PedsQL Cerebral Palsy Module. No conclusion could be derived from the quality-of-life and pain assessments because they were analyzed as tertiary outcomes and for exploratory purposes only, and no controls for multiple statistical testing were used to control for the risk of type I error.

The following methodological limitations of the design of Study 141 should be considered when interpreting the results reported in the RCT. Except for the primary outcome (MAS at week 4), which was analyzed based on a two-step statistical testing hierarchy to control type I error, the secondary outcomes (PGA and GAS at week 4), subgroup analyses, and all tertiary outcomes (such as MAS, PGA assessed at week 12, and the TS, OGS, FPS, and PedsQL) were analyzed for exploratory purpose only and no control for multiplicity of testing was employed, increasing the risk of type I errors. Furthermore, no MCIDs were established specific to a pediatric population with LLS, and the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature. In addition, while the analysis set for the primary analysis was identified as the ITT population, this is not a true ITT because the ITT population used in Study 141 was defined as all randomized patients who received at least one injection of study treatment and who had an MAS score in the GSC assessed both at baseline and at week 4, whereas the appropriate ITT population would include all randomized patients and, hence, the ITT population used in Study 141 should have been identified as a modified ITT.

Study 701 was a relatively small trial that failed to demonstrate statistically significant between-group differences in the overall GMFM score without walking aids or orthoses at week 4. The clinical expert consulted for this review indicated the GMFM is a clinical tool designed to measure a child's ability to perform gross motor tasks, such as sitting, crawling, standing, walking, and running. Treatment of focal/segmental spasticity (plus the small number of patients) is unlikely to improve the whole-body motions utilized for gross motor tasks, which is what the GMFM evaluates. Therefore, the lack of statistical significance with the GMFM score is possibly due to the fact that it is not sensitive enough to identify differences in single muscle groups treated with aboBoNTA injections. Other functional outcomes were not controlled for multiplicity. The main limitation for Study 701 is that no adjustment was made for multiple testing despite secondary end points analyses, which would increase the risk of type I (false-positive) error. Also, balance may not have been achieved across the baseline variables, suggesting randomization was not successful, which may substantially bias the study results.

In both trials, for all outcomes included in this review, no MCIDs were established specific to a pediatric population with LLS, and the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature.

While the results from the open-label extension study (Study 147) demonstrated that the efficacy of repeated use of aboBoNTA in reducing the symptoms and signs of LLS in patients appeared to be maintained; however, very little can be concluded regarding the efficacy of aboBoNTA due to the limitations associated with this study, which are mainly its open-label nature (which can potentially bias the reporting of the outcome measures, especially the subjective measures), the lack of a control group, and the limited sample size of what is likely a highly select population. Therefore, no definitive conclusions can be made regarding the long-term efficacy of aboBoNTA (Appendix 6).

The manufactured submitted an ITC that suggested there is no statistical difference between aboBoNTA and onaBoNTA at weeks 4 and 12 and that aboBoNTA is more efficacious than placebo in treating pediatric patients with LLS. These results, however, are limited by the small number of studies available for some outcomes, with small sample sizes (seven RCTs had fewer than 30 patients per arm), the considerable amount of heterogeneity between studies, and the large number of assumptions required to pool data for analysis (Appendix 7). No evidence was available regarding the difference in the duration of effect between aboBoNTA and onaBoNTA.

Harms

In general, there were no clinically important safety concerns identified for aboBoNTA in the treatment of children with LLS. [redacted] The only notable harm reported in the placebo group was muscle weakness, which was reported by one patient (1.3%). While epilepsy was reported only by patients who were receiving aboBoNTA, these patients had a history of epilepsy. All five cases were in the aboBoNTA treatment groups and were assessed by the investigator as unrelated to study treatment. [redacted]

The open-label extension study (Study 147) results suggested there were no new safety signals identified, with the most common adverse events being nasopharyngitis, pharyngitis, and upper respiratory tract infection. The manufactured submitted an ITC that suggested there is no statistically significant difference in adverse events between aboBoNTA and onaBoNTA or placebo.

Potential Place in Therapy[b]

Spasticity management is typically classified within five general categories including non-pharmacological techniques (e.g., conventional rehabilitation and bracing), focal chemodenervation (e.g., phenol/alcohol nerve blocks and BoNTA), intrathecal baclofen therapy, oral medications (e.g., baclofen, tizanidine, and dantrolene) and surgical interventions (e.g., selective dorsal rhizotomy).[19] Established practice parameters[16,20] and standard of care for management of pediatric spasticity would employ interventions from any or all of the general categories, depending on the severity and anatomical distribution of spasticity. Best available intervention evidence, dominated by pediatric spasticity-management studies in CP,[21] support various treatments in all intervention categories with the exception of non-pharmacological techniques. AboBoNTA resides within the focal chemodenervation category; this category possesses the most robust literature supporting its use in pediatric spasticity management. Focal chemodenervation utilizes treatment of selected spastic muscles to achieve functional and/or structural objectives. OnabotulinumtoxinA also resides within this category, and has been used for years in Canada under the formal indication for treatment of dynamic equinus foot deformity in pediatric CP patients. Practically, onaBoNTA has also been used for focal spasticity management of ULS and LLS in pediatric patients. As such, aboBoNTA would join onaBoNTA as an additional focal chemodenervation treatment for LLS in pediatric patients two years of age and older.

Children aged two to 17 years of age with problematic LLS from a variety of underlying etiologies such as CP, stroke, brain injury, and spinal cord injury, and clearly identified functional (e.g., improve gait or activities of daily living or ease of care) or structural goals (e.g., delay or prevent contracture development) conducive to focal chemodenervation should receive this drug in practice. Anticipated barriers to consistently identifying appropriate patients who may benefit from this drug include the relative paucity of allied health and medical professionals appropriately trained to evaluate spasticity in children. Treatment availability may also be limited by the number of physicians adequately prepared to complete BoNTA injections in children, including access to injection-guidance technology (e.g., electromyography, electrical stimulation or ultrasound) as well as suitable and safe procedural sedation for children unable to tolerate awake injections.

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

Conclusions

Two trials (Study 141 and Study 701) met the inclusion criteria for this review. Both trials were phase III, multi-centre, randomized, double-blind, controlled trials. Study 141 was a pivotal trial. While Study 141 demonstrated that both aboBoNTA doses (10 U/kg and 15 U/kg) were statistically significantly better than placebo for reducing muscle tone (as assessed by MAS) at week 4, there is some uncertainty around the clinical significance of the difference observed between groups because each of the clinical experts consulted for this review provided different opinions regarding the difference seen in the MAS at week 4 between the aboBoNTA treatment groups and placebo groups. In addition, the clinical significance of the benefit of aboBoNTA compared with placebo for all outcomes assessed was not clear from the literature. Study 701 did not meet its primary end point (change from baseline in overall GMFM score without walking aids or orthoses at week 4). In Study 141, the effect of aboBoNTA on other clinically meaningful outcomes such as HRQoL and patient-reported symptoms was uncertain, mainly because any observed effects were marginal and limited by methodological considerations. Overall adverse events were low despite a numerically higher incidence of TEAEs in the aboBoNTA groups than that in the placebo group. The open-label uncontrolled extension phase of the trial showed an efficacy and safety profile for aboBoNTA that was similar to the profile reported in the double-blind phase; however, the study had a few limitations, including the open-label nature of the study, the lack of a control group, and the limited sample size. A network meta-analysis submitted by the manufacturer suggested that the two BoNTAs (aboBoNTA and onaBoNTA) may have similar treatment effects in pediatric patients with LLS; however, the statistical analyses are limited by the large number of assumptions required to estimate the relative efficacy between toxins.

Appendix 1: Patient Input Summary

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

1. Brief Description of Patient Groups Supplying Input

There were two patient groups who submitted input; namely the Cerebral Palsy Association in Alberta (CPAA) and the Multiple Sclerosis (MS) Society of Canada.

The CPAA is a registered charity that aims to enrich and support the lives of people with CP and their families. In collaboration with other CP organizations and their members (which includes researchers, physicians, and community stakeholders), the CPAA promotes awareness, acceptance, and understanding for people with disabilities in order for them to live, learn, and work in their communities. CPAA has received funding in the last two years from Allergan International Foundation (Allergan Botox) and Ipsen Pharmaceutical.

The MS Society of Canada provides services to patients with MS and their families and caregivers and aims to be a leader in finding a cure for MS and enhancing the quality of life of its members. In the last two years, the MS Society of Canada has received funding from Allergan, Bayer, Biogen, EMD Serono, Novartis, Roche, Pfizer, Sanofi Genzyme, and Teva Neuroscience.

Neither of the aforementioned patient groups had any conflicts of interest to declare with regard to their patient input submissions.

2. Condition Related Information

The CPAA acquired information using a survey that was distributed to its own client group and to the CP Canada Network and Facebook Special Needs groups using social media channels. Twenty-four responses were received. The MS Society of Canada launched both an English and French online survey on their national website's www.mssociety.ca main page and Facebook page on January 22, 2018, which closed on February 19, 2018. Eight survey responses were received from parents with children between the ages of six and 19 suffering from MS; however, it should be noted that none of the surveys were fully completed.

CP is a neurodevelopmental disorder that can severely affect the patient and their family's life. In terms of physical and emotional functioning, patients can have delays in reaching motor skill milestones; they often have difficulties with or are unable to walk or talk. They experience pain and have variations in muscle tone that can lead to significant stiffness. Physical symptoms are typically characterized by muscle spasticity; problems maintaining an appropriate posture; improper gait patterns; fatigue; and stiff, contracted, overactive, and spastic muscles. The stress associated with having these issues or being a caregiver taking care of patients with these issues is often overwhelming and all-consuming. Leisure activities, socializing, and work are all often negatively affected, as the demands on personal time for both patients and caregivers are significant. Since a lot of the treatments are not pharmacologically based, both the patient and caregiver have to manage their time in order to attend physiotherapy or occupational therapy sessions.

MS is an unpredictable and often disabling disease that affects the central nervous system and is caused by an interruption or loss of the usual flow of nerve impulses along the axons that result in a wide variety of symptoms. Common MS symptoms include fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. Other less common symptoms include issues with balance, sexual dysfunction, spasticity,

tremor, weakness, and difficulty speaking and swallowing. Of the three survey respondents (parents) whose children experienced lower-limb spasticity (LLS), children were negatively impacted in terms of their ability to attend school, participate in extracurricular activities (such as sports or clubs), sleep, socialize (e.g., going out with friends, attending parties), be mobile, independently perform age-appropriate activities, drive a car, take care of themselves (e.g., dressing, eating, and personal/toilet care), provide care to younger siblings, maintain family relationships, and participate in recreational and/or physical activities (e.g., active play, riding a bicycle, etc.).

3. Current Therapy Related Information

The majority of patients with CP who are experiencing the aforementioned physical symptoms are actively being treated with physiotherapy and occupational therapy. Other therapies that have been tried by a smaller proportion of the surveyed population include hippotherapy, conductive education, and the Anat Baniel Method. The requirement for regular stretching and exercise is a hallmark of the physical therapies.

Pharmacological therapies that had been used by the CP survey respondents include onabotulinumtoxinA (Botox), baclofen, trihexyphenidyl (Artane), and carbidopa-levodopa (Sinemet). In terms of dealing specifically with LLS, the use of Botox is associated with easier stretching; reductions in spasticity; improvements in positioning, range of motion, and gait patterns; decreases in stiff muscle pain and improved tolerance of leg braces; greater independence; and improved patient ability to personally care for themselves. Upon receiving these drugs, patients still require intensive physiotherapy post-injection. Some adverse events reported with the use of the pharmacologic treatments include muscle weakness, bruising, and pain near the injection site. In addition, patients and caregivers also experienced difficulties in receiving these treatments due to travel and access issues and due to the financial challenges experienced by some families.

None of the respondents' children in the MS survey were being treated for their LLS.

4. Expectations About the Drug Being Reviewed

No patient from the CP survey or the MS Society had any experience with Dysport Therapeutic and many were not even aware of its existence.

While not specifically pertaining to this drug in particular, families and patients with CP who are experiencing LLS would like longer-lasting treatments with longer-lasting effects, easier access to specialists and local therapists, more intensive and frequent interventions, reduced muscle spasticity and tone, financial accommodation for travel- and specialist-related expenses, and access for First Nations groups. If the aforementioned were addressed, families hope the patients would be able to participate in more social and recreational activities, that the time for hospital and treatment trips and the costs associated with treatment would be reduced, that patients would have an increased amount of independence, and that life stress would be lessened.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note**: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 8 2018
Alerts:	Weekly search updates until July 18 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.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#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt .po	Publication type Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. exp Botulinum Toxins, Type A/
2. (Abobotulinum* or bobotulinum* or abo botulinum* or Dysport* or Azzalure* or Reloxin* or CNT52120 or CNT 52120 or aboA or abo A or ABO or AboBTXA or aboBoNT A or aboBoNTA or "953397358" or 95339735 8 or 953397 358).ti,ab,kf,ot,hw,rn,nm.
3. (BoNT or BoNTA* or BTA or BTXA or BTX A or BTX).ti,ab,kf,ot,hw,rn,nm.
4. (botulin* adj3 (typeA or type A)).ti,ab,kf,ot,hw,rn,nm.
5. (botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kf,ot,hw,rn,nm.
6. 1 or 2 or 3 or 4 or 5
7. exp Lower extremity/
8. (lower adj2 (limb* or extremit* or bod*)).ti,ab,kf.
9. Membrum inferius.ti,ab,kf.
10. (leg* or hip* or knee* or buttock* or toe* or foot or feet or thigh* or calf or calves or hamstring* or quadricep* or adductor* or soleus or gastrocnem* or equin* or gait).ti,ab,kf.
11. 7 or 8 or 9 or 10
12. exp muscle spasticity/
13. (spas* or rigidity* or hyperton*).ti,ab,kf.
14. exp paraparesis, spastic/
15. 12 or 13 or 14
16. 6 and 11 and 15
17. 16 use medall
18. *botulinum toxin a/
19. (Abobotulinum* or bobotulinum* or abo botulinum* or Dysport* or Azzalure* or Reloxin* or CNT52120 or CNT 52120 or aboA or abo A or ABO or AboBTXA or aboBoNT A or aboBoNTA or "953397358" or 95339735 8 or 953397 358).ti,ab,kw.
20. (BoNT or BoNTA* or BTA or BTXA or BTX A or BTX).ti,ab,kw.
21. (botulin* adj3 (typeA or type A)).ti,ab,kw.
22. (botulinumtoxintypeA or botulinumtoxinA or botulin A or botulin toxin A or BoNT?A or botulinum neurotoxin* or botulinum neuro toxin*).ti,ab,kw.
23. 18 or 19 or 20 or 21 or 22
24. lower limb/
25. (lower adj2 (limb* or extremit* or bod*)).ti,ab,kw.
26. Membrum inferius.ti,ab,kw.
27. (leg* or hip* or knee* or buttock* or toe* or foot or feet or thigh* or calf or calves or hamstring* or quadricep* or adductor* or soleus or gastrocnem* or equin* or gait).ti,ab,kw.
28. 24 or 25 or 26 or 27
29. muscle spasm/
30. spasticity/
31. (spas* or rigidity* or hyperton*).ti,ab,kw.
32. 29 or 30 or 31
33. 23 and 28 and 32
34. 33 use oemezd
35. 17 or 34

MULTI-DATABASE STRATEGY
36. conference abstract.pt. 37. 35 NOT 36 38. Remove duplicates

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

Grey Literature

Dates for Search:	March 2018
Keywords:	Dysport AND Spasticity
Limits:	No date or language limits used

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

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

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Delgado MR, Bonikowski M, Carranza J, et al. Safety and Efficacy of Repeat Open-Label AbobotulinumtoxinA Treatment in Pediatric Cerebral Palsy. J Child Neurol. 2017;32(13):1058-1064.	No comparator
Gracies JM, Esquenazi A, Brashear A, et al. Efficacy and safety of abobotulinumtoxinA in spastic lower limb: Randomized trial and extension. Neurology. 2017;89(22):2245-2253.	Inappropriate population
Colovic H, Dimitrijevic L, Stankovic I, Nikolic D, Radovic-Janosevic D. Estimation of botulinum toxin type A efficacy on spasticity and functional outcome in children with spastic cerebral palsy. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic. 2012;156(1):41-47.	No comparator
Kanovsky P, Bares M, Severa S, Richardson A, Dysport Paediatric Limb Spasticity Study G. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. Dev Med Child Neurol. 2009;51(6):436-445.	Inappropriate comparator
Hu GC, Chuang YC, Liu JP, Chien KL, Chen YM, Chen YF. Botulinum toxin (Dysport) treatment of the spastic gastrocnemius muscle in children with cerebral palsy: a randomized trial comparing two injection volumes. Clin Rehabil. 2009;23(1):64-71.	Inappropriate comparator
Pittock SJ, Moore AP, Hardiman O, et al. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis. 2003;15(4):289-300.	Inappropriate population
Dursun N, Dursun E, Alican D. The role of botulinum toxin a in the management of lower limb spasticity in patients with cerebral palsy. Int J Clin Pract. 2002;56(8):564-567.	Inappropriate dosage
Baker R, Jasinski M, Maciag-Tymecka I, et al. Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study. Dev Med Child Neurol. 2002;44(10):666-675.	Phase II non-pivotal trial
Polak F, Morton R, Ward C, Wallace WA, Doderlein L, Siebel A. Double-blind comparison study of two doses of botulinum toxin A injected into calf muscles in children with hemiplegic cerebral palsy. Dev Med Child Neurol. 2002;44(8):551-555.	Inappropriate comparator
Pieper C. Botulinum toxin type a neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. Pediatr Phys Ther. 2001;13(2):92-94.	Inappropriate dosage
Moore AP, Ade-Hall RA, Smith CT, et al. Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy. Neurology. 2008;71(2):122-128.	Inappropriate dosage

Appendix 4: Detailed Outcome Data

Table 18: Modified Ashworth Scale Score in the (Most) Affected Leg, Change From Baseline at all Time Points (Except Week 4) (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
MAS score at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 12			
N (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
N (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
N (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 28[a]			
N (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANCOVA = analysis of covariance; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 19: Modified Ashworth Scale Score in the (Most) Affected Leg, Change From Baseline at Week 4, by Botulinum Toxin Status and Treatment Group (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA10 U/kg/leg (N = 79)	AboBoNTA15 U/kg/leg (N = 79)	Placebo (N = 77)
Botulinum toxin status = naive			
N (%)	[redacted]	[redacted]	[redacted]
MAS score at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
MAS score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change in MAS score from baseline to week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Botulinum toxin status = experienced			
N (%)	[redacted]	[redacted]	[redacted]
MAS score at baseline			
Mean (SD)	[redacted]	[redacted]	[redacted]
MAS score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
Change in MAS score from baseline to week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; SD = standard deviation; U = unit.

[redacted].

Source: Study 141 Clinical Study Report.[22]

Table 20: Modified Ashworth Scale Score Responders in the (Most) Affected Leg (One Grade Improvement) (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 4			
n	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
n	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 28			
n	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients with data; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 21: Tardieu Scale: Angle of Arrest and Angle of Catch in the (Most) Affected Leg, Change From Baseline at all Time Points (Dose per Leg) — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Angle of arrest (X_{V1}) in degrees			
Baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Angle of catch (X_{V3}) in degrees			
Baseline			
N (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANCOVA = analysis of covariance; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients with data; NA = not applicable; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 22: Tardieu Scale: Spasticity Angle and Spasticity Grade in the (Most) Affected Leg, Change From Baseline at all Time Points (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Spasticity angle (X) in degrees			
Baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Spasticity grade (Y)			
Baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change versus placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; MAS = Modified Ashworth Scale; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 23: Goal Attainment Scaling: Summary of Goals Selected at Baseline for Study 141, (ITT Population)

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Improved walking pattern	48 (60.8)	63 (79.7)	54 (70.1)
Improved balance	31 (39.2)	26 (32.9)	19 (24.7)
Decreased frequency of falling	22 (27.8)	26 (32.9)	25 (32.5)
Decreased frequency of tripping	16 (20.3)	17 (21.5)	13 (16.9)
Improved endurance	18 (22.8)	11 (13.9)	11 (14.3)
Other	10 (12.7)	12 (15.2)	18 (23.4)
Decreased foot pain	6 (7.6)	5 (6.3)	10 (13.0)
Increased walking speed	6 (7.6)	9 (11.4)	3 (3.9)
Improved tolerance of the AFO	7 (8.9)	4 (5.1)	5 (6.5)
Looks better	2 (2.5)	5 (6.3)	7 (9.1)
Longer shoe wear	1 (1.3)	2 (2.5)	1 (1.3)
Improved ease in putting on the AFO	0	1 (1.3)	2 (2.6)

aboBoNTA = abobotulinumtoxinA; AFO = ankle-foot orthoses; ITT = intention-to-treat; N = number of patients in group; n = number of patients with data; U = unit.
Source: Study 141 Clinical Study Report.[22]

Table 24: Goal Attainment Scaling Total Score at all Time Points (Except Week 4) (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 28[a]			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANOVA = analysis of variance; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit; vs. = versus.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 25: Goal Attainment Scaling — Top Three Most Commonly Selected Individual Goals (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Improved walking pattern			
n (%)	[redacted]	[redacted]	[redacted]
Mean total score (SD)	[redacted]	[redacted]	[redacted]
Improved balance			
n (%)	[redacted]	[redacted]	[redacted]
Mean total score (SD)	[redacted]	[redacted]	[redacted]
Decreased frequency of falling			
n (%)	[redacted]	[redacted]	[redacted]
Mean total score (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ITT = intention-to-treat; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 26: Goal Attainment Scaling Total Score at Week 4 by Botulinum Toxin Status and Group (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
BoNT Status = Naive			
GAS score at week 4			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
BoNT Status = Experienced			
GAS score at week 4			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

BoNT = botulinum toxin; CI = confidence interval; GAS = goal attainment scaling; ITT = intention-to-treat; LS = least squares; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 27: Pediatric Quality of Life Inventory Generic Core Scores, Change From Baseline (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Score = Physical Health Summary			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Score = Psychosocial Health Summary			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Total Scale			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; SD = standard deviation.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 28: Pediatric Quality of Life Inventory Cerebral Palsy Module Scores, Change From Baseline (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Score = Daily Activities			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Eating Activities			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Fatigue			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Movement and Balance			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Pain and Hurt			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = School Activities			
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Score = Speech and Communication			

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; LS = least squares; SD = standard deviation.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 29: Lower-Limb Pain — Faces Pain Scale, Change From Baseline (Dose per Leg) for Study 141 (ITT Population)

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
At baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
At Week 4			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 4			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
At Week 12			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
P value	[redacted]	[redacted]	[redacted]
At Week 16			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 16			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
At Week 22			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to end of study			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
At end of study			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 22			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval LS = least squares; SD = standard deviation.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 30: Physician's Global Assessment of Treatment Response at All Time Points (Except Week 4) (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 28[a]			
n (%)	[redacted]	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; ANOVA = analysis of variance; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit; vs. = versus.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 31: Physician's Global Assessment of Treatment Response at Week 4, by Botulinum Toxin Status and Treatment Group (Dose per Leg) for Study 141− ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Botulinum Toxin Status = Naive			
n (%)	[redacted]	[redacted]	[redacted]
PGA score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Botulinum Toxin Status = Experienced			
n (%)	[redacted]	[redacted]	[redacted]
PGA score at week 4			
Mean (SD)	[redacted]	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Difference in LS mean (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; N = number of patients in group; PGA = Physician's Global Assessment; SD = standard deviation; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 32: Observational Gait Scale in the (Most) Affected Leg, Change From Baseline at All Time Points (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Baseline			
n (%)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
LS mean change (95% CI)	[redacted]	[redacted]	[redacted]
LS mean change vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; LS = least squares; N = number of patients in group; n = number of patients with data; SD = standard deviation; U = unit; vs.= versus.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 33: Observational Gait Scale Responders (One Grade Improvement in the "Initial Foot Contact" Subsection of the OGS in the [Most] Affected Leg) (Dose per Leg) for Study 141 — ITT Population

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 4			
n (%)	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]
Week 12			
n (%)	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Week 16			
n (%)	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 22			
n (%)	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]
Odds ratio vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]
Week 28			
n (%)	[redacted]	[redacted]	[redacted]
Responders (%)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; BoNT = botulinum toxin; CI = confidence interval; ITT = intention-to-treat; N = number of patients in group; n = number of patients with data; vs.= versus; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Table 34: GMFM overall score at Week 4 for Study 701 — APT Population

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
GMFM overall score at baseline		
Mean (SD)	87 (10)	76 (18)
GMFM overall score at week 4		
Mean (SD)	89 (10)	79 (16)
Change from baseline		
Mean (SD)	2.0 (1.8)	2.9 (4.3)
Comparison with placebo		
Difference in mean (95% CI)	0.49 (−1.21 to 2.18)	
P value	0.566	

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; GMFM = Gross Motor Function Measure; SD = standard deviation.
Source: Study 701 Clinical Study Report.[30]

Table 35: Change in GMFM Overall and Goal-Total Scores Post-Treatment for Study 701 — APT Population

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
Overall Score		
Week 8		
Mean (SD)	2.4 (2.7)	3.8 (4.9)
P value	0.980	
Week 16		
Mean (SD)	3.4 (4.0)	4.5 (4.5)
P value	0.765	
Goal-Total Score		

	AboBoNTA 30 U/kg (N = 26)	Placebo (N = 26)
Week 4		
Mean (SD)	2.9 (2.9)	3.9 (6.3)
P value	0.945	
Week 8		
Mean (SD)	3.8 (4.6)	4.8 (7.5)
P value	0.878	
Week 16		
Mean (SD)	5.9 (5.6)	6.6 (6.6)
P value	0.925	

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; GMFM = Gross Motor Function Measure; SD = standard deviation.
Source: Study 701 Clinical Study Report.[30]

Table 36: Leeds Videographic Gait Assessment for Study 701 — APT Population

	AboBoNTA (N = 52)	Placebo (N = 52)
Initial Foot Contact		
Week 4, N (%)		
Heel strike	[redacted]	[redacted]
Flat foot	[redacted]	[redacted]
Toe strike	[redacted]	[redacted]
Mild toe	[redacted]	[redacted]
Marked toe	[redacted]	[redacted]
P value	[redacted]	
Week 16, N (%)		
Heel strike	[redacted]	[redacted]
Flat foot	[redacted]	[redacted]
Toe strike	[redacted]	[redacted]
Mild toe	[redacted]	[redacted]
Marked toe	[redacted]	[redacted]
P value	[redacted]	
Leeds Videographic Assessment		
At week 4		
Degree of knee flexion,[a] N (%)		
Neutral/slightly flexed	[redacted]	[redacted]
Hyperextended	[redacted]	[redacted]
Marked knee flexion	[redacted]	[redacted]
P value	[redacted]	
Rocker-bottom foot,[a] N (%)		
Not present	[redacted]	[redacted]
Present	[redacted]	[redacted]
P value	[redacted]	
Hindfoot deformity,[a] N (%)		
Neutral	[redacted]	[redacted]
Occasionally neutral	[redacted]	[redacted]
Valgus	[redacted]	[redacted]

	AboBoNTA (N = 52)	Placebo (N = 52)
Varus	[redacted]	[redacted]
P value	[redacted]	
Use of walking aids,[b] N (%)	[redacted]	[redacted]
At week 16		
Degree of knee flexion,[a] N (%)		
Neutral/slightly flexed	[redacted]	[redacted]
Hyperextended	[redacted]	[redacted]
Marked knee flexion	[redacted]	[redacted]
P value	[redacted]	
Rocker-bottom foot,[a] N (%)	[redacted]	[redacted]
Not present	[redacted]	[redacted]
Present	[redacted]	[redacted]
P value	[redacted]	
Hindfoot deformity,[a] N (%)	[redacted]	[redacted]
Neutral	[redacted]	[redacted]
Occasionally neutral	[redacted]	[redacted]
Valgus	[redacted]	[redacted]
Varus	[redacted]	[redacted]
P value	[redacted]	
Use of walking aids,[b] N (%)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; GMFM = Gross Motor Function Measure.

[redacted]

Source: Study 701 Clinical Study Report.[30]

Table 37: Subjective Functional Assessment of Gait for Study 701 — APT Population

	AboBoNTA (N = 26)	Placebo (N = 26)
At Week 4		
Parent assessment, N (%)		
Good response	13 (50)	12 (46)
Minimal response	9 (35)	6 (23)
No response	4 (15)	8 (31)
P value	0.478	
Investigator assessment, N (%)		
Good response	15 (58)	11 (42)
Minimal response	6 (23)	5 (19)
No response	5 (19)	10 (39)
P value	0.171	
At Week 8		
Parent assessment, N (%)		
Good response	15 (58)	10 (39)
Minimal response	5 (19)	8 (31)
No response	6 (23)	8 (31)

	AboBoNTA (N = 26)	Placebo (N = 26)
P value	0.238	
Investigator assessment, N (%)		
Good response	14 (54)	7 (27)
Minimal response	5 (19)	9 (35)
No response	7 (27)	10 (39)
P value	0.099	
At Week 16		
Parent assessment, N (%)		
Good response	8 (31)	7 (27)
Minimal response	8 (31)	6 (23)
No response	10 (39)	13 (50)
P value	0.457	
Investigator assessment, N (%)		
Good response	8 (31)	8 (31)
Minimal response	6 (23)	4 (15)
No response	12 (46)	14 (54)
P value	0.673	

aboBoNTA = abobotulinumtoxinA; APT = all patients treated.
Source: Study 701 Clinical Study Report.[30]

Table 38: Analysis of Number of Patients in Each Category of Change in Leeds Functional Mobility Questionnaire — Sitting and Standing Treatment Comparisons at Weeks 4 and 16, APT Population

	Treatment Comparison[a] AboBoNTA Versus Placebo	
	Odds Ratio (95% CI)	*P* Value
At Week 4		
How difficult is it for your son/daughter to get up from the floor to standing?	[redacted]	[redacted]
How difficult is it for your son/daughter to sit on a normal chair without falling?	[redacted]	[redacted]
How difficult is it for your son/daughter to balance when bending forward?	[redacted]	[redacted]
How difficult is it for your son/daughter to balance when standing on one affected leg?	[redacted]	[redacted]
How difficult is it for your son/daughter to stand unaided without splints?	[redacted]	[redacted]
How difficult is it for you to relax your son/daughter's leg muscles with stretching exercises?	[redacted]	[redacted]
At Week 16		
How difficult is it for your son/daughter to get up from the floor to standing?	[redacted]	[redacted]
How difficult is it for your son/daughter to sit on a normal chair without falling?	[redacted]	[redacted]
How difficult is it for your son/daughter to balance when bending forward?	[redacted]	[redacted]
How difficult is it for your son/daughter to balance when standing on one affected leg?	[redacted]	[redacted]
How difficult is it for your son/daughter to stand unaided without splints?	[redacted]	[redacted]

	Treatment Comparison[a] AboBoNTA Versus Placebo	
	Odds Ratio (95% CI)	*P* Value
How difficult is it for you to relax your son/daughter's leg muscles with stretching exercises?	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; APT = all patients treated; CI = confidence interval; LOCF = last observation carried forward.
[redacted]
Source: Study 701 Clinical Study Report.[30]

Table 39: Analysis of Number of Patients in Each Category of Change in Leeds Functional Mobility Questionnaire — Mobility, Treatment Comparisons at Weeks 4 and 16 (APT Population)

	Treatment Comparison[a] AboBoNTA Versus Placebo	
	Odds Ratio (95% CI)	*P* Value
At Week 4		
How difficult is it for your son/daughter to walk while carrying something?	[redacted]	[redacted]
How difficult is it for your son/daughter to get up stairs?	[redacted]	[redacted]
How difficult is it for your son/daughter to get down stairs?	[redacted]	[redacted]
How tired does your son/daughter become during walking?	[redacted]	[redacted]
How frequently does your son/daughter's left foot turn in during walking?	[redacted]	[redacted]
At Week 16		
How difficult is it for your son/daughter to walk unaided without splints?	[redacted]	[redacted]
How difficult is it for your son/daughter to walk while carrying something?	[redacted]	[redacted]
How difficult is it for your son/daughter to get up stairs?	[redacted]	[redacted]
How difficult is it for your son/daughter to get down stairs?	[redacted]	[redacted]
How tired does your son/daughter become during walking?	[redacted]	[redacted]
How frequently does your son/daughter's left foot turn in during walking?	[redacted]	[redacted]
How frequently does your son/daughter's right foot turn in during walking?	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; APT = all patients treated.
[redacted]
Source: Study 701 Clinical Study Report.[30]

Table 40: Analysis of Number of Patients in Each Category of Change in Leeds Functional Mobility Questionnaire — Other Activities, Treatment Comparisons at Weeks 4 and 16 (APT Population)

	Treatment Comparison[a] AboBoNTA Versus Placebo	
	Odds Ratio (95% CI)	*P* Value
At Week 4		
How much help does your son/daughter need to use the toilet?	[redacted]	[redacted]
How much help does your son/daughter need to get dressed?	[redacted]	[redacted]
How much help does your son/daughter need to get undressed?	[redacted]	[redacted]
How much help does your son/daughter need to get in the bath?	[redacted]	[redacted]
How much help does your son/daughter need to get out of the bath?	[redacted]	[redacted]
How difficult is it for your son/daughter to play while sitting on the floor with legs straight out in front?	[redacted]	[redacted]
How difficult is it for your son/daughter to play while sitting on the floor with legs in any position?	[redacted]	[redacted]
How difficult is it for your son/daughter to ride a tricycle or bicycle?	[redacted]	[redacted]
How difficult is it for your son/daughter to jump?	[redacted]	[redacted]
How difficult is it for your son/daughter to kick a ball?	[redacted]	[redacted]
How difficult is it for your son/daughter to walk to the side of the swimming pool?	[redacted]	[redacted]
How difficult is it for your son/daughter to swim a width of the swimming pool?	[redacted]	[redacted]
How difficult is it for your son/daughter to get on the school bus?	[redacted]	[redacted]
At Week 16		
How much help does your son/daughter need to use the toilet?	[redacted]	[redacted]
How much help does your son/daughter need to get dressed?	[redacted]	[redacted]
How much help does your son/daughter need to get undressed?	[redacted]	[redacted]
How much help does your son/daughter need to get in the bath?	[redacted]	[redacted]
How much help does your son/daughter need to get out of the bath?	[redacted]	[redacted]
How difficult is it for your son/daughter to play while sitting on the floor with legs straight out in front?	[redacted]	[redacted]
How difficult is it for your son/daughter to play while sitting on the floor with legs in any position?	[redacted]	[redacted]
How difficult is it for your son/daughter to jump?	[redacted]	[redacted]
How difficult is it for your son/daughter to walk to the side of the swimming pool?	[redacted]	[redacted]
How difficult is it for your son/daughter to swim a width of the swimming pool?	[redacted]	[redacted]
How difficult is it for your son/daughter to get on the school bus?	[redacted]	[redacted]
How difficult is it for your son/daughter to get off the school bus?	[redacted]	[redacted]
How confident is your son/daughter while walking?	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; CI = confidence interval; APT = all patients treated.

[redacted]

Source: Study 701 Clinical Study Report.[30]

Table 41: Proportion of Patients Eligible for Re-Treatment (Dose per Leg) for Study 141 — ITT Population

Eligible for Re-Treatment at Visit, n (%)	AboBoNTA 10 U/kg/leg (N = 79)	AboBoNTA 15 U/kg/leg (N = 79)	Placebo (N = 77)
Total eligible for re-treatment	[redacted]	[redacted]	[redacted]
At week 12	[redacted]	[redacted]	[redacted]
At week 16	[redacted]	[redacted]	[redacted]
At week 22	[redacted]	[redacted]	[redacted]
At week 28	[redacted]	[redacted]	[redacted]
After week 28[a]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; N = number of patients in group; U = unit.

[redacted]

Source: Study 141 Clinical Study Report.[22]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures (placed in alphabetical order):

- Faces Pain Scale (FPS)
- goal attainment scaling (GAS)
- Gross Motor Function Measure (GMFM)
- Leeds Functional Mobility Questionnaire (FMQ)
- Leeds Videographic Gait Assessment (VGA)
- Modified Ashworth Scale (MAS)
- Observational Gait Scale (OGS)
- Pediatric Quality of Life Inventory (PedsQL)
- Physician's Global Assessment (PGA) of treatment response
- subjective functional assessment of gait
- Tardieu Scale (TS).

Findings

A focused literature search was conducted to identify the psychometric properties and minimum clinically important difference (MCID) of each of the stated outcome measures. Table 42 summarizes the findings.

Table 42: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
FPS-R	A generic instrument used to measure the intensity of pain in children It is a pictorial presentation of faces that are associated with different levels of pain	Yes	Not identified	Bieri 1990[46] Hicks 2001[47]
GAS	Generic instrument used to evaluate whether the goals have been achieved Goals set by patients/parents and their practitioners	Yes	Score of > 10 is clinically important in adults with ULS due to brain injury; however, no MCID was identified in the pediatric population with LLS	Cusick et al. 2006[39] Turner-Stokes et al. 2010[38]
GMFM	Standardized, evaluative instrument used to measure change in motor function over time in children with CP It contains 88 items that are grouped into five dimensions: lying/rolling, sitting, crawling/kneeling, standing, and walk/run/jump	Yes	Not identified	Russell et al. 1989[50] Bjornson et al. 1998[49] Lundkvist et al. 2009[48]

Instrument	Type	Evidence of Validity	MCID	References
Leeds FMQ	5-item questionnaire used to assess the patient's ability to assess everyday activities that would be affected by LLS Administered as a structure interview with the patient's parents	No	Not identified	Study 701 CSR[51]
Leeds VGA	Video clips used to assess the patient's gait at different time points by clinicians and physiotherapists experienced in the management of children with walking difficulties Using a standardized score sheet to assess different gait parameters	No	Not identified	Study 701 CSR[51]
MAS score	Most common clinical instrument used to measure spasticity 6-point scale, with higher scores indicating increased muscle tone and spasticity	No/ Uncertain Conflicting evidence on reliability	1-point change was considered clinically meaningful;[a] however, no MCID identified in the literature	Meseguer-Henarejos et al. 2017[31] Numanoglu and Gunel 2012[54] Mutlu et al. 2008[34] Biering-Sorensen et al. 2006[32] Yam and Leung 2006[55] Clopton et al. 2005[35] Fosang et al. 2003[36] Bohannon and Smith 1987
OGS	Used to measure gait using video analysis Looks at various components of gait, with a maximum of 22 points (meaning normal gait)	Yes	Not identified	Mackey et al. 2003[43] Study 141 CSR[22]
PedsQL 4.0 Generic Core Scales	Used to measure the HRQoL in pediatric patients with any chronic condition Patient report and parent report (specific for different ages) 5-point Likert scale for patients ≥ 5 years of age 3-point Likert scale for patients < 5 years of age, anchored to happy and sad faces	Yes	Not identified	Varni et al. 1999[44] Varni et al. 2001[45] Varni et al. 2002[56]
PGA	Used to assess treatment response 9-point scale, with higher scores indicating better treatment response	No	Not identified	Study 141 CSR[22]
Subjective functional assessment of gait	Parent and investigator's subjective opinion on the functional changes of gait Assessed at every post-treatment visit	No	Not identified	Study 701 CSR[51]
TS score	Specific tool for the measurement of spasticity Takes into account the spasticity angle (X) and the spasticity grade (Y)	Yes	Not identified	Gracies et al. 2010[41] Alhusaini et al. 2010[57]

CP = cerebral palsy; CSR = Clinical Study Report; FMQ = Functional Mobility Questionnaire; FPS-R = Faces Pain Scale — Revised; GAS = goal attainment scaling; GMFM = Gross Motor Function Measure; HRQoL = health-related quality of life; LLS = lower-limb spasticity; MAS = Modified Ashworth Scale; MCID = minimal clinically important difference; PedsQL = Pediatric Quality of Life Inventory; PGA = Physician's Global Assessment; OGS = Observational Gait Scale; TS = Tardieu Scale; ULS = upper-limb spasticity; VGA = Videographic Gait Assessment.

[a] Considered meaningful according to the clinical expert consulted for this review; however, there was no literature identified to support this.

Faces Pain Scale — Revised

The FPS and Faces Pain Scale — Revised (FPS-R) were developed to measure pain in pediatric patients.[46,47] Bieri et al.[46] developed the FPS using a five-phase approach, each helping lead to the development of the seven-face (seven-point) scale construct. The final phase examined the test–retest reliability and subsequently showed that a rank correlation coefficient of 0.79 was obtained when six-year-old children rated a painful experience over a two-week time period.[46] Hicks et al.[47] undertook revising the original FPS, as the seven-point version was not easily rescaled to either a 0 to 5 or 0 to 10 metric. Instead, they adapted the FPS to include a six-face scale, with corresponding scoring of 0, 2, 4, 6, 8, and 10 (or 0, 1, 2, 3, 4, and 5). A higher score indicates more pain.[47]

The authors subsequently compared the FPS-R with a visual analogue scale (VAS) in 76 children ranging in age from five to 12 years who were undergoing a painful non-medical procedure (ear piercing). A strong positive correlation between the pain-intensity ratings of the FPS-R and the VAS was observed (Pearson correlation, r = 0.93), indicating the concurrent validity of the new FPS-R instrument. To further validate the FPS-R scale, Hicks et al.[47] used the FPS-R, the VAS, and the coloured analogue scale (CAS) to assess pain intensity in a population of 90 pediatric patients either undergoing surgical treatment or hospitalized for a non-surgical painful condition. Strong correlations were observed between the FPS-R and the VAS or the CAS (r ranging from 0.87 to 0.93 and 0.80 to 0.91, respectively) when examining different age groups (4 to 6, 7 to 9, and 10 to 12 years of age). In addition, the correlations remained strong when pain intensity was assessed for either current (r = 0.86) or recalled pain (r = 0.84).[47]

The clinical expert consulted for this review explained that pain is not normally associated with spasticity; therefore, the utility of this outcome measure remains under question. No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the FPS for pediatric patients with lower-limb spasticity (LLS). In addition, no MCID for the FPS-R in this population has been identified.

Goal Attainment Scaling

GAS is a method of integrating achievement in a number of individually set goals into a single goal attainment score.[37] It has been applied in various areas of complex interventions including spasticity management.[38] Before the treatment, one or more individual goals are established by the patient and their caregiver (if they are children)[39] and one or more researchers or practitioners (or others agreed upon by the practitioner). The clinician/researcher requires sufficient knowledge and experience when supporting patients to set realistic goals. In addition, they must be able to respect the patient's ideology and what is important to them when setting goals (and thus able to avoid projecting their own goals and what they perceive to be important onto the patient) and they must have good negotiating skills in order to manage potentially unrealistic goals set by the patient.[37] The number of goals can vary between patients in the same study and between patients in different studies. Numerical values ranging from −2 to +2 (a five-point scale) are used to describe the degree to which the goal(s) were or were not met.[37] The expected target of achievement is set by the patient and treating team and given a value of 0. Outcomes that are less than expected are given values of −1 or −2 (the most unfavourable outcome) and outcomes that are better than expected are given values of +1 or +2 (the most favourable outcome). The originators of the GAS score transformed it to a standard variable (the T score), with scores ranging from 0 to 100, a mean of 50 and a standard deviation (SD) of 10. The GAS T score is derived using the following equation:

$$T = 50 + \frac{10\ \Sigma w_i x_i}{\sqrt{(1-\rho)\Sigma w_i^2 + \rho(\Sigma w_i)^2}}$$

The goals that were used in this submission included improved endurance, looks better, improved walking pattern, increased walking speed, improved balance, decreased frequency of tripping, decreased frequency of falling, decreased foot pain, longer shoe wear, improved tolerance of the ankle-foot orthoses (AFO), and improved ease in putting on the AFO.[22,25]

In pediatric patients with upper-limb spastic hemiplegic CP (Gross Motor Performance Measure [GMPM] level I), GAS has been observed to provide consistent individualized outcome measures that were observed to be directly relevant to their rehabilitation program.[39]

The validity, in terms of responsiveness, of GAS has been demonstrated in the rehabilitation of adults with upper-limb spasticity (ULS).[40] In the context of spasticity management in 18 adult patients (analyzed retrospectively) with diffuse brain injury, stroke, and multiple sclerosis who were treated with botulinum toxin and who were considered as either responders (those patients who had a positive clinical outcome as identified by the treating physician; n = 11) or nonresponders (those patients who had a negative or non-significant clinical outcome as identified by the treating physician; n = 7) to the botulinum toxin intervention, the GAS score was observed to be consistent with their clinical response. The patients classified as responders showed a much larger response to the GAS than their nonresponder counterparts. In addition, the GAS score appeared more sensitive to change than the Barthel Index of Activities of Daily Living (which was used alongside GAS to assess response).[40] In another trial that assessed botulinum toxin in adult stroke patients with ULS, Turner-Stokes et al.[38] examined the concurrent validity of the GAS T score with the composite MAS and reported a statistically significant fair correlation between the two (Spearman rank correlation coefficient of 0.35, *P* = 0.001), thus suggesting that GAS includes a component of spasticity.

Some limitations associated with GAS include accurately predicting future success in terms of the goals (internal validity), the need for adequately trained professionals in the administration and choice of the goals in order to achieve inter-rater reliability, the possibility of floor effects (or a score lower than −2, potentially achieved if results are even worse than expected), any design issues related to the actual study (again relating to internal validity),[39] and a steep learning curve.[40]

A change in the GAS T score of more than 10 appeared clinically important in adult patients with ULS who had suffered diffuse brain injury or stroke, or who had been diagnosed with multiple sclerosis and classified by the treating physician as responders (positive clinical outcome) or nonresponders (negative or non-significant clinical outcome) relative to treatment with botulinum toxin.[40] However, no validity or reliability studies have been conducted in children and, as a result, it is unclear if the psychometric properties observed in adults (particularly the responsiveness with GAS) apply to children. No MCID was identified for GAS in pediatric patients with LLS.

Gross Motor Function Measure

The GMFM (and subsequently the GMFM-88[48,49]) is an outcome measure used to evaluate change in gross motor function over time in children with varying degrees of CP.[50] The 85 items that made up the original GMFM (and the subsequent five additional items included in the GMFM-88[48,49]) were chosen because they were the items that were the most likely to show change in patients with CP. Individuals items were combined into five separate areas of motor function in order to facilitate scoring. These dimensions include A = lying and rolling, B = sitting, C = crawling and kneeling, D = standing, and E = walking, running, and jumping.[48,50] Each individual item is scored on a four-point Likert scale (0 to 3), with assignments as follows: 0 = cannot do, 1 = initiates (< 10% of the task), 2 = partially completes (10% to < 100% of the task), and 3 = task completion (100% of the task). Each dimension contributes equal weight; therefore, dimension scores are calculated using the following formula: child's score ÷ maximum score × 100%. The total score is then obtained by adding up all of the dimension scores (per cent) and then dividing them by the total number of dimensions (five dimensions). To increase responsiveness and, if the therapist identifies specific goals, a goal-score total can also be calculated (using the same aforementioned algorithm for obtaining the total scores; however, this time, by dividing by the dimensions that were part of the goal setting).[48-50] It should be noted that the GMFM (and GMFM-88) only assesses how much of the task the child can perform (quantity) and does not measure how well the task is performed (quality).[49]

To validate the original GMFM, Russell et al.[50] included a sample of 111 children with CP, all younger than 20 years of age (with ages spread across the 20-year spectrum), 25 of who had a severe and acute head injury who were included because they were thought to show more improvement. Thirty-four children under five years of age who did not have disabilities were also included to ascertain what normal developmental change would look like in order to examine the validity of the GMFM when compared with video analysis (conducted by therapists who were unfamiliar with the children but familiar with the GMFM) and the judgments of therapists and parents as to the amount of gross motor function change they observed (scoring change at baseline and at six months by using a 15-point Likert scale that varied from −7 [a very great deal less] to +7 [a very great deal more]). All therapists were trained in the use of the GMFM. As the authors hypothesized, the total GMFM scores had the highest correlations with the video analysis (intraclass correlation coefficient [ICC] of 0.82), followed by the therapists' judgments (ICC of 0.65) and, finally, the parent's judgments (ICC of 0.54). When children were categorized as responsive or stable (looking at variation in both groups), the GMFM was able to detect significant changes in each category of child (i.e., CP, head injury, no disabilities), with the most change observed in patients with severe acute head injury, followed by children without disabilities, and then children with CP (which is what the authors hypothesized). Intra-rater, inter-rater, and test–retest reliability were all observed to show substantial agreement, with ICC's ranging from 0.92 to 0.99, 0.87 to 0.99, and 0.85 to 0.98 (therapists) and 0.67 to 0.92 (for parents test–retest reliability), respectively.[50]

Another study by Bjornson et al.[49] looked to examine the validity of the GMFM-88 (when compared with video-based evaluation) over a period of 12 to 24 months in 37 children with spastic diplegic CP who were participating in a randomized controlled trial that was examining the efficacy of selective dorsal rhizotomy (SDR). Correlations between the GMFM-88 and the video-based evaluation were moderate to strong in five (sitting, crawling/kneeling, standing, walk/jump/run, and total) of the six GMFM dimensions, with Spearman rank correlation coefficients ranging between 0.60 and 0.75. The only dimension

that showed a weak correlation (0.15) was the lying/rolling dimension, but this was hypothesized to be due to the fact that children with spastic diplegic CP have relatively high skills.[49]

In a sample of 41 children with diplegic CP who had undergone SDR, Lundkvist et al.[48] set out to ascertain the longitudinal construct validity of the GMFM-88 total and goal-total scores over a five-year follow-up. The children were examined in three subgroups: patients classified as Gross Motor Function Classification System (GMFCS) levels I to III and GMFCS levels IV and V. At 12 months, for children at GMFCS levels I to III, large changes were observed in both the GMFM-88 total scores and GMFM-88 goal-total scores (effect size [ES] of 0.8 with a standard response mean [SRM] of 1.3 and ES of 0.9 with an SRM of 1.2, respectively). Large changes were also observed in the GMFM-88 total scores and goal-total scores at 18 months (ES of 0.8 for both scores, SRM of 1.1 and 0.9, respectively) and at three and five years post-surgery (ES ranging from 1.0 to 1.6 with an SRM ranging from 1.0 to 1.2). A similar trend of large changes in the GMFM-88 total and goal-total scores was also observed in the GMFCS level IV to V subgroup, as well.[48]

No MCID was identified in the literature for the GMFM-88 with regard to pediatric patients with LLS.

Leeds Functional Mobility Questionnaire

In Study 701[51] (study of Dysport Therapeutic for the treatment of pediatric dynamic equinus spasticity), the investigators used the Leeds FMQ 50-item questionnaire, which was developed to identify and assess changes in the patient's ability to manage everyday activities that are typically impaired in patients with LLS. It is administered as a structured interview with the patient's parents and was administered at 0, 4, and 16 weeks post–Dysport Therapeutic treatment. It is subdivided into three separate domains as follows:

- sitting and standing
- mobility
- other activities.[51]

There is no overall score for this rating instrument and each question is summarized and analyzed separately. Categorical data are generated from each question to assess the degree of difficulty when performing certain activities. The data for each activity is summarized at each time point, with the change from baseline analyzed using logistic regression. A lower score indicates improved function.

The Leeds FMQ was developed by the Regional Child Development Centre at St James's University Hospital, Leeds, UK; however, it is still in the process of development.[51] Hence, there has been no literature identified regarding the psychometric properties (validity, reliability, or responsiveness) of the Leeds FMQ for pediatric patients with LLS. In addition, no MCID for the Leeds FMQ in this population has been identified.

Leeds Videographic Gait Assessment

In Study 701[51] (study of Dysport Therapeutic for the treatment of pediatric dynamic equinus spasticity), the investigators used the Leeds VGA to observe patient gait, viewed in both the sagittal and coronal planes. It was developed by the Leeds Regional Child Development Centre at St James's University Hospital in Leeds, UK.[51] Patients walked along a walkway both with and without their normal splints and footwear at weeks 0, 4, and 16. The video clips were blinded and randomized to be reviewed by a panel of clinicians and

physiotherapists who had experience in the management of children with walking difficulties associated with muscle spasticity. A standard score sheet was used to rate the following parameters, with each leg scored separately:

- **initial foot contact** scored as: 0 = heel strike, 1 = flat foot, 2 = toe strike, 3 = mild toe (metatarsal = medium equinus), or 4 = marked toe (phalanges = severe equinus)
- **degree of knee flexion** scored as: 0 = neutral/slightly flexed 0 to 20 degrees, 1 = hyperextended > 5 degrees, or 2 = marked knee flexion > 20 degrees
- **presence/absence of rocker-bottom foot** scored as: 0 = not present or 1 = present
- **hindfoot deformity (presence of valgus or varus)** scored as: 0 = neutral, 1 = occasionally neutral, 2 = valgus, or 3 = varus
- **walking aids used** (descriptive).[51]

Each assessment was made by a central panel of four assessors, with the modal score being used as the summary statistic. Lower scores indicate a more normal gait.

No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the Leeds VGA for pediatric patients with LLS. In addition, no MCID for the Leeds VGA in this population has been identified.

Modified Ashworth Scale

The MAS is commonly used to measure increased muscle tone and spasticity due to different pathologies and neurologic conditions.[31] The MAS was derived from the original Ashworth Scale to measure muscle resistance while moving the affected joint through its full range of movement in order to passively stretch the muscle.[31] It provides a semi-quantitative measure of this resistance to passive movement.[32,33] The MAS is easy to use, as it requires no additional equipment; hence, it is one of the most commonly used tools to measure spasticity and muscle rigidity in patients with CP[34] or hypertonia.[35] It is administered by a physician or therapist during the patient visit and comprises a six-point scale used to measure the degree of spasticity (intensity of muscle tone) as follows:

- **0**: No increase in muscle tone.
- **1**: Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part(s) is moved in flexion or extension.
- **1+**: Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement.
- **2**: More marked increase in muscle tone through most of the range of movement, but the affected part(s) is easily moved.
- **3**: Considerable increase in muscle tone; passive movement is difficult.
- **4**: Affected part(s) rigid in flexion or extension.[25,35,36]

The MAS score is normally a categorical variable; however, for this review it was treated as a continuous variable and, hence, needed to be transformed. The derived MAS scores that were used in this review were 0, 1, 2, 3, 4, and 5, which corresponded to the aforementioned original MAS scores of 0, 1, 1+, 2, 3, and 4 (as previously described), respectively.[25] A higher MAS score indicates increased muscle tone, rigidity, or spasticity.

Moderate to good reliability has been reported when assessing ULS in adult populations with cerebral lesions due to cerebrovascular accident, multiple sclerosis, or traumatic brain injuries. These correlations, however, have been reported to be lower when examining LLS in adults.[35] A systematic review and meta-analysis by Meseguer-Henarejos et al.,[31] that was performed to assess both the inter-rater and intra-rater reliability of the MAS when examining the upper and lower extremities in pediatric, adolescent, and adult populations with spasticity, reported moderate inter- and intra-rater reliability (ICC = 0.686 and 0.644, respectively) in the lower extremities and high ICCs for upper extremities (ICC = 0.781 and 0.748, respectively). The authors also noted the large heterogeneity in the results pertaining to the inter-reliability ICCs in the lower limbs.[31] Studies in children have also reported good inter-rater reliability for the MAS in the upper extremities (particularly the elbow flexors).[35]

There have been many studies that have assessed the inter-rater reliability and intra-rater/observer or test–retest reliability in the lower limbs of pediatric populations with CP of different severities (mild, moderate, or severe spastic type)[34,36,54,55] or hypertonia.[35] In summary, the inter- and intra-rater reliability of the MAS are highly variability across studies (ICCs ranging from 0.27 to 0.87) and appear to be affected by the muscle assessed and patient-specific characteristics. With respect to responsiveness, the MAS has been shown to be less responsive compared with other measures (such as electromyography). No information regarding the validity of the MAS in the pediatric population was identified; however, the measure is routinely used regardless of this.

Fosang et al.[36] reported poor inter-rater reliability (measured using the ICC) of the MAS assessments of the hamstrings, calf, and hips of 18 children with mild, moderate, or severe spastic CP who were seen multiple times (with ICCs ranging from 0.37 to 0.48 in hamstrings, 0.27 to 0.45 in calves, and 0.54 to 0.56 in the hip adductors). When examining the test–retest ICCs in this same population, the authors noted high variability between raters and stipulated the importance of obtaining reliability and error margins, even within one rater.[36] They did note that the sources of the variability may be from both the rater and the patient; however, they also inferred that, due to the poor inter-rater reliability observed in their study, they were uncertain whether or not it was acceptable for this tool was to be used by different raters on the same patients.[36] Yam et al.[55] aimed to replicate the results of Fosang et al., but focused on the hip adductors and ankle plantar flexors in their population of 17 children with CP. Low inter-rater reliability was observed regardless of the strict standardization of the child's supine and head position, and the authors recommended caution when using the MAS with different raters.[55]

Clopton et al.[35] assessed the inter- and intra-rater reliability of the MAS for quantifying spasticity in 17 children with spasticity due to CP (n = 13), developmental delay (n = 2), or traumatic brain injury (n = 2). The authors reported good inter- and intra-rater reliability in the hamstring assessments (ICC = 0.79 and 0.80, respectively); however, there was an absence of increased tone in a large number of the hamstrings tested, thereby potentially artificially increasing the reliability). The inter-rater reliability was observed as poor for the assessments of the hip adductors (ICC = 0.33), quadriceps (ICC = 0.40), gastrocnemius (ICC = 0.45), and soleus (ICC = 0.33). The intra-rater reliability (test–retest) was reported as moderate for the hip adductors (ICC = 0.63), quadriceps (ICC = 0.67), gastrocnemius (ICC = 0.64), and soleus (ICC = 0.54).[35] Low to moderate intra-observer ICCs were reported in the assessments of the hip adductors, hamstrings, gastrocnemius, and soleus muscles (ranging from 0.26 to 0.66) along with low test–retest ICCs in a cohort of 37 children with CP.[54]

In contrast to the other studies, Mutlu et al.[34] reported moderate to good inter-rater reliability ICCs for the assessments of the hip flexors, hip adductors, internal rotators, hamstrings, and gastrocnemius muscle groups (ICCs ranging from 0.64 to 0.87). Intra-rater reliability ICCs for the aforementioned muscle groups ranged widely from poor to good (ICC = 0.41 to 0.83).[34] The authors suggest caution when interpreting the MAS results due to the large variability in their intra-rater reliability results.[34]

Some investigators have speculated that the variability in the inter- and intra-rater assessments might be attributable to the following: the cooperation, attention span, or emotional status of the child,[35,36,55] the age of the cohort,[34] the subtleness associated with muscle tone either between sessions or within the same session,[36] the compliance of stretching when wearing orthotics prior to the sessions,[36] environmental factors (such as the room temperatures) that may affect mood and participation,[36] the asymmetrical tonic neck reflex and clonus,[35] the effect of primitive reflexes on the distribution of muscle tone,[35] the length of the extremity,[31] and the lack of standardization and training across therapists.[34-36]

With respect to responsiveness, in 31 children with CP, Bar-On et al.[58] reported that MAS demonstrated less responsiveness when compared with the instrumented assessment when examining children who have received botulinum toxin type A injections. They hypothesized that the MAS clusters the muscles into broad categories and, hence, reduces its ability to detect any difference in response to treatment.[58] In addition, contributions of neural and non-neuronal spasticity components are not distinguishable by the MAS, especially when compared with electrophysiological or biomechanical assessments.[58]

There appears to be a paucity of data on the assessment of validity regarding the MAS in children with spasticity. Even though the MAS is commonly used for measuring spasticity, evidence in adults suggests that resistance to passive movement is not an exclusive measure of spasticity (content validity).[59] In addition, a poor correlation was reported between the MAS and surface electromyography (which is the gold standard for spasticity) when comparing healthy adults and stroke patients.[59] Regardless of this apparent lack of evidence of validity in the pediatric population, the MAS continues to be one of the most commonly used measures for assessing spasticity in both pediatric and adult populations.

The clinical expert consulted for this review indicated that a one-point difference in the MAS (in either direction) was clinically relevant; however, no peer-reviewed evidence was identified regarding an MCID for the MAS in the pediatric population with LLS.

Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales

The original PedsQL was developed as a health-related quality-of-life (HRQoL) measure that addressed the paucity of appropriately validated and reliable instruments incorporating both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates generic and disease- and symptom-specific items that are appropriate for the assessment of pediatric chronic conditions.[44] The PedsQL 4.0 Generic Core Scales comprises 23 items under the following modules: Physical Functioning (eight items), Emotional Functioning (five items), Social Functioning (five items), and School Functioning (five items).[45] These Generic Core Scales comprise both a parent-proxy report and a child self-report that assess health perceptions. The child self-report format is specifically for three age groups: five to seven, eight to 12, and 13 to 18 years of age, while the corresponding parent-proxy reports are specifically for toddlers (ages two to four, for which there is no child self-assessment report), young children (ages five to seven),

children (ages eight to 12), and adolescents (ages 13 to 18). The questions ask how much of a problem each item has been in the past month. A five-point Likert response scale is used across the child reports (from ages eight to 18) and the corresponding parent report, and includes the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a three-point scale is used for simplification and ease of use for children aged five to seven years (0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem), with each of the response choices on the scale anchored to a happy, neutral, or sad face.[45] The scores, which are reversed scored, are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0, with higher scores indicative of a higher HRQoL. To account for missing data, the sum of the items divided by the number of items that are answered is computed to ascertain the scale score. If more than 50% of the items within the scale are missing, then the scale score cannot be obtained. To ascertain the Psychosocial Health Summary Score (composed of 15 items), the sum of the items is divided by the items answered in the School Functioning, Emotional, and Social subscales.[45] There are currently more than 60 translations of the PedsQL 4.0 Generic Cores Scales that have been validated.[60,61]

To validate the PedsQL Generic Core Scales, a sample of chronically ill (as reported by their parents in a specialty clinic [n = 683]), acutely ill (parents reported no presence of chronic illness and attended a specialty clinic [n = 207]), and healthy children (identified at their physician's office during regular visits or using telephone calls [n = 730]) between the ages of two and 18 years were included.[45] Construct validity was ascertained using the known-groups method, whereby scale scores were compared across groups that are known to differ in the specific health constructs being examined (in this case, healthy versus acute or healthy versus chronic conditions). Varni et al. noted that the PedsQL differentiated between the different health states (healthy, acutely ill, and chronically ill) and it also correlated with illness burden and morbidity measures.[45] Internal consistency reliabilities generally exceeded the standard alpha coefficients of 0.70. The Total Scale score across the ages for the self-report and proxy report were 0.88 and 0.90, respectively, thus indicating that this as an appropriate primary analysis summary score. The Physical Health and Psychosocial Health Summary scores were greater than 0.8 for the self-report and the proxy report; hence, the authors determined they were best for secondary analyses. The Emotional, Social, and School Functioning subscales generally obtained alpha coefficients of approximately 0.70; therefore, the authors suggested these be used for descriptive or exploratory analyses.[45]

Several studies have assessed the validity and responsiveness of the PedsQL in specific pediatric populations.[56,62] Among pediatric patients with heart failure, the PedsQL has shown construct validity, as scores on the PedsQL were able to classify patients with less and more severe cardiac disease appropriately, based on New York Heart Association (NYHA) classifications.[56] Moreover, *c*onstruct validity was further demonstrated, as patients with no chronic illness (or their parents as proxies) scored higher on the total score, physical domain, and psychosocial domain when compared with patients with either complex or non-complex chronic illness.[62]

With respect to responsiveness, in several different populations (i.e., orthopedic patients and patients discharged from hospital), the PedsQL showed moderate responsiveness to change in patients who improved over time based on other validated measures specific to those populations, demonstrating the ability of the PedsQL to be moderately responsive to changes.[56]

However, whether the validity and responsiveness of the PedsQL hold true in pediatric patients with LLS is unknown, as the PedsQL has never been evaluated in this population and, currently, no known MCID exists for the PedsQL in pediatric patients with LLS.

Physician's Global Assessment

In the pivotal study of this submission, the PGA of treatment response was conducted by the investigator by scoring responses to the question: "How would you rate the response to treatment in the patient's lower limb(s) since the last injection?" on a nine-point categorical scale where −4 = markedly worse, −3 = much worse, −2 = worse, −1 = slightly worse, 0 = no change, +1 = slightly improved, +2 = improved, +3 = much improved, and +4 = markedly improved. Assessment of the PGA was undertaken independently by an investigator who was different from the one who assessed the MAS.[22] No literature was identified regarding the psychometric properties (validity, reliability, or responsiveness) of the PGA for pediatric patients with LLS. In addition, no MCID for the PGA in this population has been identified.

Observational Gait Scale

The OGS is an objective outcome measure used to document gait changes (or impairments) of the upper motor syndrome in young children who have received injections of botulinum toxin.[22,43] It was derived from the Physician's Rating Scale by expanding the scale from six to eight sections, including putting more emphasis on the knee-to-foot relationship during the standing phase. The gait parameter sections that make up the OGS include knee position in mid stance, initial foot contact, foot contact mid stance, timing of heel rise, hindfoot at mid stance, base of support, gait assistive devices, and change. The maximum score is 22 for each leg, which denotes a normal gait. In older children, the standard of assessing gait includes instrumented three-dimensional gait analysis (3-DGA); however, this is not always appropriate for children due to their potential to be uncooperative and their small size.[43] The child is recorded while walking and the investigator (e.g., someone with extensive knowledge of gait analysis) looks at the video recording in order to score each component.[43] The components for each leg (the scoring is specific for each individual leg) are scored as follows:

1. Knee position mid stance:
   - crouch: 0 = severe (> 15 degrees); 1 = moderate (10 to 15 degrees); 2 = mild (< 10 degrees); 3 = neutral
   - recurvatum: 0 = severe (> 10 degrees), 1 = moderate (10 to 15 degrees); 2 = mild (< 5 degrees)
2. Initial foot contact:
   0 = toe; 1 = forefoot; 2 = foot flat; 3 = heel
3. Foot contact at mid stance:
   −1 = toe/toe (equinus); 0 = foot flat / early heel rise; 1 = foot flat/no early heel rise; 2 = occasional heel / foot flat; 3 = heel/toe (normal roll over)
4. Timing of heel rise:
   0 = no heel contact (fixed equinus); 1 = before 25% stance (very early); 2 = between 25% and 50% (slightly early); 3 = at terminal stance; 0 = no heel rise (after foot flat, i.e., crouch)

5. Hindfoot at mid stance:
   0 = varus; 1 = valgus; 2 = neutral

6. Base of support:
   0 = frank scissoring; 1 = narrow base (poor knee clearance); 2 = wide base;
   3 = normal base (width of shoulders)

7. Gait assistive devices:
   0 = walker (forward/posterior) with assistance; 1 = walker (independent); 2 = crutches, sticks; 3 = none, independent for 10 m

8. Change:
   −1 = worse; 1 = none; 2 = better.[22]

The maximum score is 22 for each leg, which denotes a normal gait.[43]

To assess the intra- and inter-rater reliability and validity of the OGS, Mackey et al.[43] compared the results obtained from two experienced clinicians who assessed the gait of 20 children (mean age of 12 years) with spastic diplegic CP using both a split-screen video recording of a 3-DGA (the criterion standard) and the OGS. Moderate to substantial inter-rater (weighted kappa ranging from 0.43 to 0.86) and intra-rater (weighted kappa ranging from 0.53 to 0.91) was demonstrated in the knee position mid-stance section, the foot contact at mid-stance section, the initial foot contact section, and the timing of the heel-rise section. When examining the concurrent validity of the OGS compared with the 3-DGA (examined in only the four aforementioned sections that showed moderate to substantial reliability), the authors noted moderate to strong correlations (weighted kappas) ranging from 0.38 to 0.94.[43]

No MCID was identified in the literature regarding pediatric patients with LLS.

Subjective Functional Assessment of Gait

A subjective functional assessment of gait was conducted by both the parent and investigator at each post-treatment visit to assess functional changes in response to treatment with Dysport Therapeutic.[51] Specifically, the parent and the investigator each provided a rating (scored separately) on the child's functional change in response to treatment. The available choices were as follows:

- good response
- minimal response
- no response
- worse response
- not recorded.[51]

No literature was identified regarding any psychometric properties (validity, reliability, or responsiveness) of the subjective functional assessment of gait for pediatric patients with LLS. In addition, no MCID for the outcome measure in this population has been identified.

Tardieu Scale Score

The TS score was developed by Tardieu et al. in 1954 to clinically measure spasticity by measuring the different angles of reaction when passing the muscle through stretches at different predefined velocities.[41,42] This outcome measure was developed to more closely align with the 1979 Lance definition of spasticity, specifically, a "motor disorder

characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone), with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome."[41] Spasticity is thus rated by examining the reaction difference of the muscle in question between the slowest and fastest stretch speed, both of which are performed by the same practitioner at the same time of day with the muscle in the same resting position.[41] The slow stretch assesses the passive range of motion and is slow enough to avoid producing a significant stretch reflex. The stretch at the fastest velocity is performed to maximize the involvement of the stretch reflex, thus producing a catch-and-release sensation (also termed clonus) that is dependent on the amount of spasticity present.[41] Two parameters are used to measure the muscle spasticity, namely the spasticity angle X (which is the difference between the slow-speed angle of arrest [V_1] and the clonus or catch-and-release angle at the highest speed [V_3]) and the spasticity grade Y (the grading of the intensity of the muscle reaction to the fastest stretch [V_3] and is an ordinal variable). Larger spasticity angles correspond to more spasticity in the muscle. The spasticity is graded as follows: grade 0 = absence of spasticity as defined by a catch that is not followed by a release; grade 1 = passive movement is slowed down by mild resistance; grade 2 = passive movement (the catch and release) is transiently interrupted; grades 3 and 4 = severe spasticity; and non-ratable = a catch that is not followed by an obvious release occurring at inconsistent angles.[41]

To assess the reliability of the TS in children with CP, Gracies et al.[41] performed a two-phase reliability study wherein five children with CP were assessed in the first phase (performed to assess the reliability of the TS when the practitioner has no prior training), and 16 children with CP were assessed in the second phase (performed to assess the reliability of the TS when the practitioner has prior training). Good inter- and intra-rater reliability of the TS (> 70% agreement, although there was no accounting for chance agreement [i.e., no kappa statistic or ICC was calculated]) was observed when examining all parameters (X_{V1}, X_{V3}, and their difference, X) in the elbow flexors and the ankle plantar flexors. The one day of training seemed to markedly enhance the reliability, particularly in the angle of catch at fast speed (X_{V3}) in the assessment of all muscles except the knee flexors. In addition, the authors noted that the TS could be used reliably without the use of a goniometer, as there were no reliability differences observed between the visual and goniometric assessments.[41]

Another study by Alhusaini et al.[57] examined 27 children with CP in a cross-sectional analytic study in order to investigate the content validity of the TS and the Ashworth Scale when assessing spasticity and contracture and to further compare them to electromyography and biomechanical measurements. According to the electromyography and biomechanical measurements, 21 patients in this study were found to have spasticity. However, both the TS and the Ashworth Scale produced false-negatives in this regard (three for the TS and five for the Ashworth Scale); therefore, the TS failed to identify spasticity 11% of the time. In addition, neither the TS nor the Ashworth Scale was able to determine the severity of the spasticity. The TS, however, was able to identify the presence and severity of contracture, thus enabling users of the TS to differentiate between contracture and spasticity.[57]

No MCID was identified in the literature with regard to pediatric patients with LLS.

Appendix 6: Summary of Study 147 (Extension Study)

Objective

To summarize the safety and efficacy results from the multi-centre repeat treatment open-label (OL) extension trial (Study 147). The following summary is based on both published[63] and unpublished data.[51]

Trial Description

Ambulatory (Gross Motor Function Classification System levels I to III) pediatric patients (aged 2 to 17 years of age) with cerebral palsy (CP) and dynamic equinus foot deformity who had completed the double-blind portion of Study 141 (patients had to have had at least 12 weeks of follow-up post-injection) and who had no ongoing adverse events could enrol into the OL extension study. A maximum of four treatments of abobotulinumtoxinA (aboBoNTA) of 5 U/kg to 30 U/kg occurring at 12-week intervals were administered in the OL extension, with the first one occurring at or after the week 12 visit of the double-blind study. (However, the visit could be postponed until weeks 16, 22, 28, or later according to the investigator's judgment.) The OL extension lasted for a total of 12 months (40 weeks post–treatment cycle 1; 28 weeks post–treatment cycle 2; 16 weeks post–treatment cycle 3, or four weeks post–treatment cycle 4). The primary objective of the OL extension study was to assess the long-term safety (assessed as adverse events and serious adverse events) of repeated aboBoNTA treatments for lower-limb spasticity (LLS) in CP patients. The secondary objective was to assess the efficacy of repeated aboBoNTA treatments using the Modified Ashworth Scale (MAS) at the ankle joint, the Physician's Global Assessment (PGA) of treatment response, goal attainment scaling (GAS), the Tardieu Scale (TS), the Observational Gait Scale (OGS), lower-limb pain, duration of effects, time intervals between–treatment, and quality of life. Both safety and efficacy were analyzed descriptively with no formal statistical significance analyses planned. It should be noted, however, that the dosing in the two aboBoNTA groups included a range of dosing, with ranges of 7.5 U/kg to 12.5 U/kg in the aboBoNTA 10 U/kg group, and 12.5 U/kg to 17.5 U/kg in the aboBoNTA 15 U/kg group.

Results

Patient Disposition

All 216 patients enrolled into the OL extension had completed the double-blind phase in Study 141 up to at least the week 12 follow-up visit. Two hundred and three patients (94%) started treatment cycle 1 (the first dose in Study 147), with the remaining 13 patients (6%) not eligible for re-treatment at the end of Study 141 (all of whom had received aboBoNTA) and subsequently entered the observational study phase of study 147. Four of the 13 patients eventually entered treatment cycle 1 at a later time point: three at week 6 and one at week 18 of the observational phase, while the other nine patients were not re-treated with aboBoNTA. Of the 207 patients who received at least one dose of aboBoNTA in Study 147, 69 patients had received aboBoNTA 10 U/kg and 67 patients had received aboBoNTA 15 U/kg in Study 141. A total of 194 patients (90%) completed the study, with 188 patients receiving treatment in the OL study and six patients in the observational phase. A total of 22

patients (10.2%) withdrew from the OL extension study, with 6 (8.1%) and 7 (9.9%) discontinuing in the aboBoNTA 10 U/kg and 15 U/kg arms, respectively. The most common reasons for discontinuing were withdrawn consent and other. Of note, a total of 175 patients entered treatment cycle 2, 86 patients entered treatment cycle 3, and 11 patients entered treatment cycle 4. Details of the patient disposition are presented in Table 43.

[redacted]

Table 43: Patient Disposition in Open-Label Extension Study 147 Assigned in Double-Blind Study (Dose per Leg) — Safety Population

	Placebo (N = 71[c])	AboBoNTA 10 U/kg/leg (N = 74)	AboBoNTA 15 U/kg/leg (N = 71)
Received treatment, n (%)	[redacted]	[redacted]	[redacted]
Completed study (12 months), n (%)	[redacted]	[redacted]	[redacted]
Total number of withdrawals[a]	[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]
Entered observational phase			
n	[redacted]	[redacted]	[redacted]
Withdrew from observational phase[b]			
[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.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Time From Injection to Re-Treatment

[redacted]

Table 44: Summary of Time From Injection (in Weeks) to Re-Treatment Assigned in the Double-Blind Study (Dose per Leg) — Randomized Population

Treatment Period	AboBoNTA 10 U/kg/leg	AboBoNTA 15 U/kg/leg
From DB Study to Treatment Cycle 1, N	[redacted]	[redacted]
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
From OL Treatment Cycle 1 to OL Treatment Cycle 2		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
From OL Treatment Cycle 3 to OL Treatment Cycle 3		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
From OL Treatment Cycle 3 to OL Treatment Cycle 4		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; DB = double-blind; OL = open-label; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Safety Results

Exposure

The total exposure to aboBoNTA is presented in Table 45. Patients randomized to the aboBoNTA 10 U/kg and 15 U/kg groups in the double-blind portion of Study 141 had a mean exposure of 53.5 weeks (SD of 5.1 weeks) and 53.0 (SD of 5.8 weeks), respectively. As expected, those patients originally randomized to the placebo arm had less overall exposure to aboBoNTA and, therefore, their safety and efficacy results are not presented throughout the rest of this summary.

Table 45: Exposure in Weeks in the Double-Blind and Open-Label Studies Assigned in the Double-Blind Study (Dose per Leg) — Safety Population

	Placebo (N = 71)	AboBoNTA 10 U/kg/leg (N = 74)	AboBoNTA 15 U/kg/leg (N = 71)
Total Treatment Exposure			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Total aboBoNTA Exposure			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Harms

[redacted]

Table 46: Harms Following Treatment With AboBoNTA in the Double-Blind and Open-Label Studies by Total Dose Received in the Lower Limb(s) — Safety Population

	One Leg Injected		Two Legs Injected	
	AboBoNTA 10 U/kg[a] (N = 124)	AboBoNTA 15 U/kg[b] (N = 81)	AboBoNTA 20 U/kg[c] (N = 94)	AboBoNTA 30 U/kg[d] (N = 57)
Any AEs in ≥ 5 % of patients, 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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	One Leg Injected		Two Legs Injected	
	AboBoNTA 10 U/kg[a] (N = 124)	AboBoNTA 15 U/kg[b] (N = 81)	AboBoNTA 20 U/kg[c] (N = 94)	AboBoNTA 30 U/kg[d] (N = 57)
[redacted]				
[redacted]				
SAEs, n (%)				
WDAEs, n (%)				
Notable harms, n (%)				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

aboBoNTA = abobotulinumtoxinA; AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Efficacy Results

Modified Ashworth Scale Scores

[redacted]

Table 47: Modified Ashworth Scale Score in the GSC in the (Most) Affected Leg, Change From Double-Blind Baseline by Treatment Cycle and Dose Received in the GSC of the (Most) Affected Leg

Visit	AboBoNTA 10 U/kg/leg[a]	AboBoNTA 15 U/kg/leg[b]
Treatment Cycle 1,[c] N		
DB baseline, n		
Mean (SD)		
Week 4, n		
Mean change (SD)		
Week 12, n		
Mean change (SD)		
Treatment Cycle 2, N		

Visit	AboBoNTA 10 U/kg/leg[a]	AboBoNTA 15 U/kg/leg[b]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 4,[d] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; DB = double-blind; GSC = gastrocnemius-soleus complex; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Physician's Global Assessment

[redacted]

Table 48: Physician's Global Assessment of Treatment Response by Dose Received in the (Most) Affected Leg

Visit	AboBoNTA 10 U/kg/leg[a]	AboBoNTA 15 U/kg/leg[b]
Treatment Cycle 1,[c] N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 4,[d] N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Goal Attainment Scaling Scores

[redacted]

Table 49: Goal Attainment Scaling Total Score by Dose Received in the (Most) Affected Leg

Visit	AboBoNTA 10 U/kg/leg[a]	AboBoNTA 15 U/kg/leg[b]
Treatment Cycle 1,[c] N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]
Treatment Cycle 4,[d] N	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean score (SD)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Tardieu Scale Scores

Small increases from baseline with any aboBoNTA dose were observed in the angle of arrest (X_{V1}) following treatment at week 4 in treatment cycles 1, 2, and 3; however, the magnitude of the increase decreased with each treatment cycle. Increases in the angle of catch (X_{V3}) from baseline with any aboBoNTA dose were observed following treatment at weeks 4 and 12 in all treatment cycles, with the magnitude of this increase similar for each treatment cycle. Reductions in the spasticity angle (X_{V1} minus X_{V3}) from baseline increased over treatment cycles 1, 2, and 3 at weeks 4 and 12 with any dose of aboBoNTA. Reductions in the spasticity grade (Y) from baseline were observed following any aboBoNTA dose at weeks 4 and 12 in all treatment cycles. The magnitude of this reduction was similar throughout all treatment cycles. Detailed Tardieu Scale data per treatment cycle are presented in Table 50.

Table 50: Tardieu Scale Angle of Arrest (X_{V1}), Angle of Catch (X_{V3}), and Spasticity Angle (X) in the GSC in the (Most) Affected Leg, Change From DB Baseline by Treatment Cycle and Dose Received in the GSC of the (Most) Affected Leg

Visit, Statistic[a]	AboBoNTA 10 U/kg/leg[b]	AboBoNTA 15 U/kg/leg[c]
Angle of Arrest (X_{V1})		
Treatment Cycle 1,[d] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 4,[e] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Angle of Catch (X_{V3})		
Treatment Cycle 1,[d] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]

Visit, Statistic[a]	AboBoNTA 10 U/kg/leg[b]	AboBoNTA 15 U/kg/leg[c]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 4,[e] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Spasticity Angle (X)		
Treatment Cycle 1,[d] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]

Visit, Statistic[a]	AboBoNTA 10 U/kg/leg[b]	AboBoNTA 15 U/kg/leg[c]
Treatment Cycle 4,[e] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Spasticity Grade (Y)		
Treatment Cycle 1,[d] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 4,[e] N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; DB = double-blind; GSC = gastrocnemius-soleus complex; SD = standard deviation.

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Source: Study 147 Clinical Study Report.[51]

Observational Gait Scale Scores

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Table 51: Observational Gait Scale in the GSC in the (Most) Affected Leg, Change from Double-Blind Baseline by Treatment Cycle and Dose Received in the (Most) Affected Leg

Visit	AboBoNTA 10 U/kg/leg[a]	AboBoNTA 15 U/kg/leg[b]
DB Study, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 1, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 2, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 3, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Week 12, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]
Treatment Cycle 4, N	[redacted]	[redacted]
DB baseline, n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Week 4, n	[redacted]	[redacted]
Mean change (SD)	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA; DB = double-blind; GSC = gastrocnemius-soleus complex; SD = standard deviation.

[redacted]

Source: Study 147 Clinical Study Report.[51]

Critical Appraisal

The main limitations of the extension phase were the OL nature of the study (which can potentially bias the reporting of the outcome measure, especially the subjective measures), the lack of a control group, the limited sample size of what is likely a highly select population (due to a large number of patients not continuing therapy in treatment cycles 2, 3, and 4), the fact that the aboBoNTA 10 U/kg group included dosing that ranged anywhere from 7.5 U/kg to 12.5 U/kg and the aboBoNTA 15 U/kg group included dosing ranging from 12.5 U/kg to 17.5 U/kg, and the fact that the aboBoNTA 10 U/kg group also included those patients initially in the placebo arm of the double-blind portion of the original study. These limitations preclude the ability to draw meaningful conclusions with regard to the efficacy of aboBoNTA 10 U/kg or aboBoNTA 15 U/kg. However, the main purpose of the extension study was to provide a long-term safety assessment of the two aboBoNTA doses. There were no new safety signals identified in the extension trials.

Summary

The OL extension study reported data from patients who continued to receive up to four treatment cycles of aboBoNTA 10 U/kg (which included patients originally randomized to the placebo group in the double-blind study and switched over, and which also included a range of aboBoNTA dosing of between 7.5 U/kg and 12.5 U/kg) or aboBoNTA 15 U/kg (which also included a range of aboBoNTA dosing of between 12.5 U/kg and 17.5 U/kg). No new safety signals were evident, with the most common adverse events being nasopharyngitis, pharyngitis, and upper respiratory tract infection. Very little can be concluded regarding the efficacy of aboBoNTA due to the aforementioned limitations associated with the OL extension phase. Therefore, no definitive conclusions can be made regarding the long-term treatment of aboBoNTA.

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

Given the absence of head-to-head studies comparing abobotulinumtoxinA (AboBoNTA, Dysport Therapeutic) against other botulinum toxin type A (BoNTA) drugs in the study population relevant for this CADTH Common Drug Review (CDR), indirect treatment comparisons (ITCs) that include aboBoNTA can provide information on the effectiveness and safety of this drug compared with existing therapies. The objective of this appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of any ITCs that compare aboBoNTA with onabotulinumtoxinA (onaBoNTA) in pediatric patients two years of age and older with lower-limb spasticity (LLS).

Methods

The manufacturer submitted one ITC[64] that was reviewed, summarized, and critically appraised. CDR conducted an independent literature search for published ITCs that compared aboBoNTA with other relevant comparators for the treatment of LLS in pediatric patients two years of age and older; no published ITCs were identified.

Description of ITCs Identified

Table 52 presents the population, interventions, comparisons, outcomes, and study design (PICOS) criteria for the manufacturer-submitted ITC.

Table 52: Inclusion and Exclusion Criteria for Selection of Studies

Criteria		Inclusion Criteria	Exclusion Criteria
Population	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Intervention	[redacted]	[redacted]	[redacted]

Criteria		Inclusion Criteria	Exclusion Criteria
Comparator			
Outcomes			
Study design			

Source: Manufacturer-supplied indirect comparison.[64]

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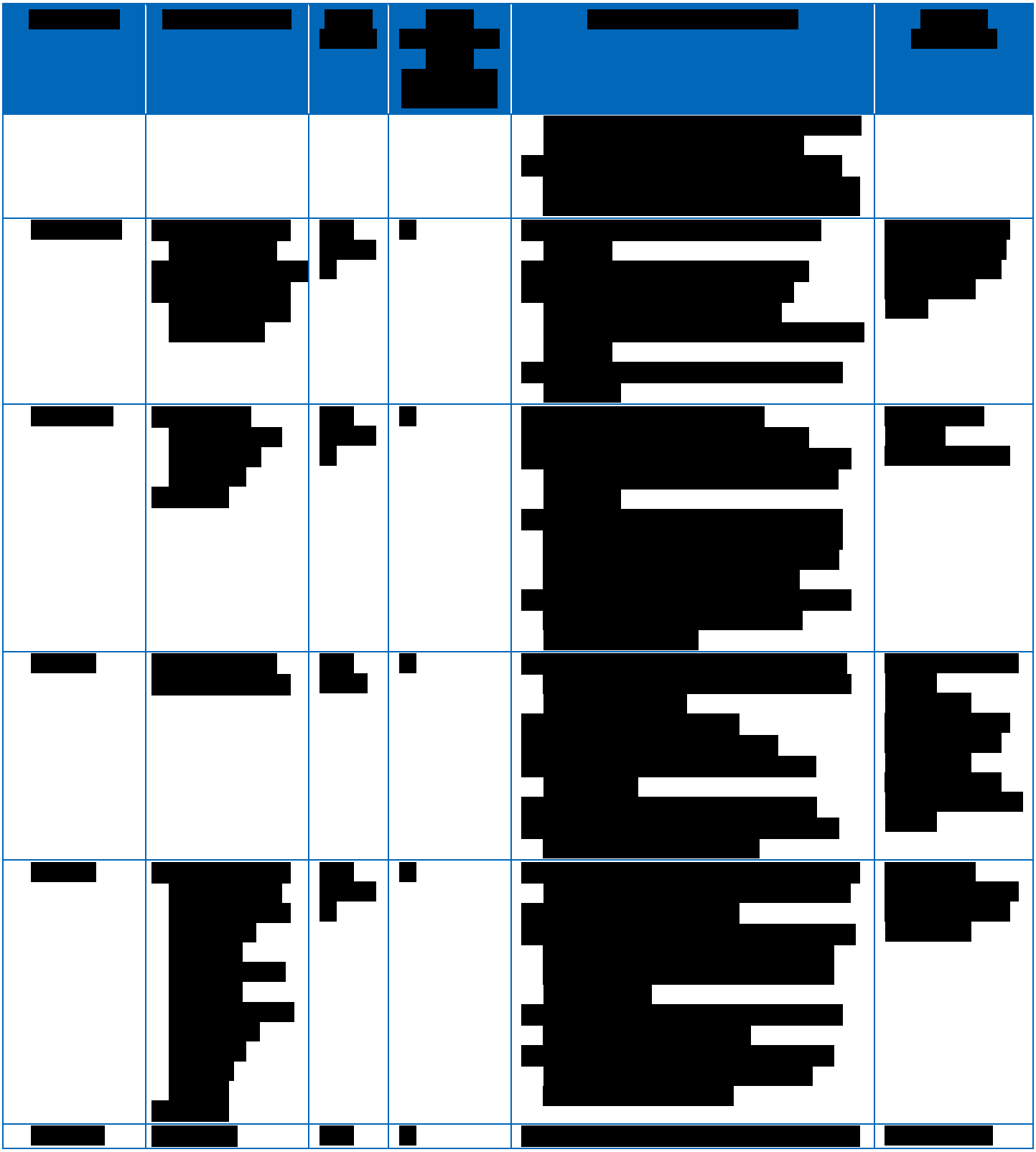

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