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Botulinum Toxin

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Related Policies (if applicable)
MED201.014: Treatment of Hyperhidrosis
SUR717.001: Gender Assignment Surgery and Gender Reassignment Surgery and Related Services

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug

approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery and Related Services.

NOTE 1: On August 1, 2009, the U.S. Food and Drug Administration (FDA) established new names for the botulinum toxin products; these products are not interchangeable:

Previous Product Name	New Generic Product Name as of 8/1/2009
BotulinumtoxinA (Botox®)	OnabotulinumtoxinA
AbobotulinumtoxinA (Dysport®)	AbobotulinumtoxinA
BotulinumtoxinA (Xeomin®)	IncobotulinumtoxinA
BotulinumtoxinB (Myobloc®)	RimabotulinumtoxinB

OnabotulinumtoxinA

OnabotulinumtoxinA (Botox®) **may be considered medically necessary** for the following FDA-labeled indications:

- Treatment of strabismus in patients 12 years of age and older;
- Treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or cranial nerve VII disorders, in patients 12 years of age and above;
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication;
- Treatment of spasticity in patients 2 years of age or older;
- Treatment of cervical dystonia (also known as spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury) with:
  - Sustained head tilt or abnormal posturing with limited range of motion in the neck, AND
  - History of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles (* See additional details in Description section);

- Prophylactic treatment of headaches in adult patients with chronic migraine when the following criteria are met:
  - Patient has been diagnosed with chronic migraine for at least 3 months; AND
  - Migraine headaches last 4 hours a day or longer for ≥15 days per month; AND
  - Migraine is refractory to at least two migraine prophylactic medications from different classes (e.g., tricyclic antidepressants, anticonvulsants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, or calcium channel blockers);
- Treatment of overactive bladder (OAB) (excluding OAB as a result of interstitial cystitis [IC]), with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication or a beta-3 adrenoceptor agonist; or
- Treatment of urinary incontinence due to detrusor overactivity, either idiopathic or associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

NOTE 2: For coverage of FDA-labeled indication hyperhidrosis, see medical policy titled MED201.014 Treatment of Hyperhidrosis.

OnabotulinumtoxinA (Botox®) **may be considered medically necessary** for the following <u>off-label indications</u>:

- Achalasia (esophageal) in patients who have not responded to dilation therapy or who are considered poor surgical candidates;
- Anal fissure (chronic) in patients with a history of failure, contraindication, or intolerance to one of the following conventional therapies: topical nitrates, or topical calcium channel blockers (e.g., diltiazem or nifedipine);
- Congenital esotropia;
- Dystonia resulting in functional impairment (e.g., interference with joint function, mobility, communication, nutritional intake) and/or pain with any of the following:
  - Focal upper-limb dystonia (e.g., organic writer's cramp);
  - Oromandibular dystonia (e.g., orofacial dyskinesia, Meige syndrome);
  - Laryngeal dystonia (adductor spasmodic dysphonia);
  - Idiopathic (primary or genetic) torsion dystonia;
  - Symptomatic (acquired) torsion dystonia;
- Essential voice tremor;
- Hemifacial spasm;
- Hirschsprung disease for patients with functional obstruction caused by the inability of the internal anal sphincter to relax and who have undergone prior surgical treatment; or
- Sialorrhea (chronic) associated with amyotrophic lateral sclerosis or atypical parkinsonian disorders or cerebral palsy or Parkinson disease or stroke or traumatic brain injury AND has experienced excessive salivation for 3 or more months AND refractory to at least 2 months of continuous treatment with at least one oral pharmacotherapy (e.g., anticholinergics).

OnabotulinumtoxinA (Botox®) **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to:

- Benign prostatic hypertrophy;
- Chronic low back pain;
- Chronic motor tic disorder and tics associated with Tourette syndrome;
- Depression;
- Gastroparesis;
- Interstitial cystitis;
- Joint pain;
- Lateral epicondylitis;
- Mechanical neck disorders;
- Myofascial pain syndrome;
- Neuropathic pain;
- Pain after hemorrhoidectomy or lumpectomy;
- Anismus (pelvic floor dyssynergia);
- Prophylaxis of episodic migraine or other types of headaches (not listed above), including but not limited to tension headache, cluster headache, cervicogenic headache, and chronic daily headache;
- Temporomandibular joint disorders;
- Tinnitus;
- Essential tremor (other than voice);
- Trigeminal neuralgia; or
- Wound healing.

OnabotulinumtoxinA (Botox® Cosmetic) **is considered cosmetic** for the FDA-labeled indications of temporary improvement in the appearance of:

- Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity;
- Moderate to severe lateral canthal lines associated with orbicularis oculi activity;
- Moderate to severe forehead lines associated with frontalis muscle activity;
- Moderate to severe platysma bands associated with platysma muscle activity.

NOTE 3: Special comment regarding cosmetic services: Check member's contract for benefit coverage. Determination of benefit coverage for procedures considered to be cosmetic is based on how a member's benefit contract defines cosmetic services and their eligibility for benefit coverage.

AbobotulinumtoxinA

AbobotulinumtoxinA (Dysport®) **may be considered medically necessary** for the following FDA labeled indications:

- Treatment of cervical dystonia (also known as spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury) with:
    - Sustained head tilt or abnormal posturing with limited range of motion in the neck, AND

- History of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles (* See additional details in Description section); or
- Treatment of spasticity in patients 2 years of age and older.

AbobotulinumtoxinA (Dysport®) **may be considered medically necessary** for the following off-label indications:
- Achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates;
- Blepharospasm; or
- Hemifacial spasm.

AbobotulinumtoxinA (Dysport®) **is considered cosmetic** for the FDA-labeled indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults <65 years of age.

AbobotulinumtoxinA (Dysport®) **is considered experimental, investigational and/or unproven** for any other indication not listed above.

NOTE 4: Special comment regarding cosmetic services: Check member's contract for benefit coverage. Determination of benefit coverage for procedures considered to be cosmetic is based on how a member's benefit contract defines cosmetic services and their eligibility for benefit coverage.

IncobotulinumtoxinA
IncobotulinumtoxinA (Xeomin®) **may be considered medically necessary** for the following FDA-labeled indications:
- Blepharospasm;
- Treatment of cervical dystonia (also known as spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury) with:
  - Sustained head tilt or abnormal posturing with limited range of motion in the neck, AND
  - History of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles (* See additional details in Description section);
- Upper limb spasticity in adults;
- Upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy; or
- Chronic sialorrhea in patients 2 years of age and older.

IncobotulinumtoxinA (Xeomin®) **is considered cosmetic** for the FDA-labeled indications of treatment or improvement of the appearance of upper facial lines in adults as follows:
- Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity;

- Moderate to severe horizontal forehead lines associated with frontalis muscle activity;
- Moderate to severe lateral canthal lines associated with orbicularis oculi muscle activity.

IncobotulinumtoxinA (Xeomin®) **is considered experimental, investigational and/or unproven** for any other indication.

NOTE 5: Special comment regarding cosmetic services: Check member's contract for benefit coverage. Determination of benefit coverage for procedures considered to be cosmetic is based on how a member's benefit contract defines cosmetic services and their eligibility for benefit coverage.

RimabotulinumtoxinB
RimabotulinumtoxinB (Myobloc®) **may be considered medically necessary** for the following FDA-labeled indications:
- Treatment of cervical dystonia (also known as spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury) with:
  - Sustained head tilt or abnormal posturing with limited range of motion in the neck, AND
  - History of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles (* See additional details in Description section); or
- Chronic sialorrhea in adults.

RimabotulinumtoxinB (Myobloc®) **is considered experimental, investigational and/or unproven** for any other indication.

NOTE 6: Safety and effectiveness of Myobloc® in pediatric patients have not been established.

DaxibotulinumtoxinA-lanm
DaxibotulinumtoxinA-lamn (Daxxify®) **may be considered medically necessary** for the following FDA-labeled indication:
- Treatment of cervical dystonia (also known as spasmodic torticollis; applicable whether congenital, due to childbirth injury, or traumatic injury) in adults with:
  - Sustained head tilt or abnormal posturing with limited range of motion in the neck, AND
  - History of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles (* See additional details in Description section).

DaxibotulinumtoxinA-lamn (Daxxify®) **is considered cosmetic** for the FDA-labeled indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity.

NOTE 7: Safety and effectiveness of Daxxify® in pediatric patients have not been established.

NOTE 8: Special comment regarding cosmetic services: Check member's contract for benefit coverage. Determination of benefit coverage for procedures considered to be cosmetic is based on how a member's benefit contract defines cosmetic services and their eligibility for benefit coverage.

NOTE 9: OnabotulinumtoxinA (e.g., Botox®), abobotulinumtoxinA (e.g., Dysport®), incobotulinumtoxinA (e.g., Xeomin®), rimabotulinumtoxinB (e.g., Myobloc®), and daxibotulinumtoxinA-lamn (Daxxify®) are NOT interchangeable.

Policy Guidelines

Electromyographic guidance may be used to direct the injection of the botulinum toxin, particularly for treatment of the larynx or esophagus. Beginning in 2006, there is a CPT code for needle electromyographic guidance for chemodenervation, as well as a code for electrical stimulation guidance. Consideration of the guidance codes should be based on whether the botulinum toxin is being used for a medically necessary indication.

Description

Botulinum is a family of toxins produced by the anaerobic organism *Clostridia botulinum.* Botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings. There are 7 distinct botulinum serotypes designated as type A, B, C-1, D, E, F, and G. In the United States (U.S.), 5 preparations of botulinum are commercially available, 4 using type A serotype and 1 using type B. Although similar in certain aspects, each botulinum toxin product is chemically, pharmacologically, and clinically distinct, and is not interchangeable with any other botulinum toxin product.

The drug names of several of the botulinum toxin products were changed in 2009; trade names and product formulations did not change. The 4 formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®), and daxibotulinumtoxinA (Daxxify®). Botox has been available for the longest time in the U.S. and has been the most widely used formulation. Xeomin®, consists of the pure neurotoxin without complexing proteins and is the only product that is stable at room temperature for up to 4 years. Myobloc® contains botulinum toxin type B; the current name of this drug is rimabotulinumtoxinB.

Regulatory Status
On December 9, 1989, onabotulinumtoxinA (Botox) was approved by the U.S. Food and Drug Administration (FDA) for treatment of ocular dystonias. Since then, its use has been expanded for multiple indications.

On April 12, 2002, onabotulinumtoxinA (Botox Cosmetic) was approved by the FDA for the treatment of glabellar lines. Since then, its use has been expanded for multiple indications. (1)

On December 8, 2000, rimabotulinumtoxinB (Myobloc) was approved by the FDA for treatment of cervical dystonias. Since then, its use has been expanded for multiple indications.

On April 29, 2009, abobotulinumtoxinA (Dysport) was approved by the FDA for treatment of cervical dystonias. Since then, its use has been expanded for multiple indications.

On July 30, 2010, incobotulinumtoxinA (Xeomin) was approved by the FDA for treatment of cervical dystonias and blepharospasm. Since then, its use has been expanded for multiple indications.

On September 8, 2022, daxibotulinumtoxinA (Daxxify®) was approved by the FDA for the treatment of glabellar lines. On August 15, 2023, it was approved by the FDA for its first therapeutic indication for the treatment of cervical dystonia.

The FDA-approved indications for the various botulinum toxin products are summarized in Table 1.

Table 1. FDA-Indications of Botulinum Toxin Products[a] (2-6)

FDA Approved Indication[a]	Botox	Dysport	Myobloc	Xeomin	Daxxify
1. Overactive bladder (adults)	*				
2. Urinary incontinence (adults)	*				
3. Urinary incontinence (pediatrics)	*[g]				
4. Neurogenic detrusor overactivity (pediatrics)	*[g]				
5. Limb spasticity (adults)	*[b]	*[b]		*[c]	
6. Limb spasticity (pediatrics)	*[b, e]	*[b, e]		*[c, d]	
7. Chronic migraine (adults)	*				
8. Cervical dystonia (adults)	*	*	*	*	*
9. Blepharospasm	*[f]			*	
10. Strabismus	*[f]				
11. Chronic sialorrhea			*	*[e]	
12. Facial lines (adults)		*[h]		*	*
13. Severe axillary hyperhidrosis (adults)	*				

FDA: Food and Drug Administration.

[a] All botulinum toxin products carry black box warnings of the potential for a distant spread of the toxin effect. The warning notes that the risk of symptoms may be greatest in children treated for spasticity, but symptoms can also occur in adults.

[b] Upper and lower limb

[c] Upper limb

[d] 2 to 17 years of age

[e] ≥2 years of age

[f] ≥12 years of age
[g] ≥5 years of age
[h] <65 years of age

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This rationale does not address cosmetic indications or hyperhidrosis.

OnabotulinumtoxinA (Botox®)
FDA-Labeled Indications
Overactive Bladder (OAB)
Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 units of Botox (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 units of Botox or placebo) spaced approximately 1 cm apart into the detrusor muscle. (2)

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for Botox 100 units at the primary time point of week 12. Significant improvements compared to

placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. (2)

The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the Botox 100-unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days. (2)

Detrusor Overactivity Associated with a Neurologic Condition
Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 units of Botox (n=227), 300 units of Botox (n=223), or placebo (n=241). (2)

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for Botox (200 units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. (2)

The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2). (2)

A placebo-controlled, double-blind randomized post-approval 52-week study (Study NDO-3) was conducted in multiple sclerosis (MS) patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 units of Botox (n=66) or placebo (n=78). (2)

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for Botox (100 units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. (2)

Pediatric Detrusor Overactivity Associated with a Neurologic Condition
Study 191622-120 (NCT01852045) was a multicenter, randomized, double-blind, parallel-group clinical study conducted in patients 5 to 17 years of age with urinary incontinence due to

detrusor overactivity associated with a neurologic condition and using clean intermittent catheterization. (2) A total of 113 patients (including 99 with spinal dysraphism such as spina bifida, 13 with spinal cord injury and 1 with transverse myelitis) who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled. The median age was 11 years (range: 5 to 17 years), 49% were female; 75% were white, 10% were black. These patients were randomized to 50 units, 100 units or 200 units, not to exceed 6 units/kg body weight. Patients receiving less than the randomized dose due to the 6 units/kg maximum, were assigned to the nearest dose group for analysis. The sample size for Botox 50 units, 100 units, and 200 units were 38, 45 and 30, respectively. Prior to treatment administration, patients received anesthesia based on age and local site practice. One hundred and nine patients (97.3%) received general anesthesia or conscious sedation and 3 patients (2.7%) received local anesthesia.

The study results demonstrated within group improvements in the primary efficacy variable of change from baseline in daytime urinary incontinence episodes (normalized to 12 hours) at the primary efficacy time point (Week 6) for all 3 Botox treatment groups. Additional benefits were seen with Botox 200 units for measures related to reducing maximum bladder pressure when compared to 50 units. The decrease in maximum detrusor pressure (MDP) during the storage phase (MDP defined as the highest value in the detrusor pressure (Pdet) channel during the storage phase [e.g., the greater of the following: the maximum Pdet during the highest amplitude involuntary detrusor contraction (IDC), the maximum Pdet during a terminal detrusor contraction, the Pdet at the end of filling, or the highest Pdet at any other time during the storage phase) for Botox 200 units at Week 6 was greater than the decrease observed for 50 units. (2)

The median duration of response in this study, based on patient qualification for re-treatment was 207 days (30 weeks) for Botox 200 units dose group. To qualify for re-treatment, patients must have reported at least 2 urinary incontinence episodes over 2 days and at least 12 weeks have passed from the prior bladder injection. (2)

Chronic Migraine

Botox was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had >15 headache days lasting 4 hours or more, with >50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 units to 195 units Botox injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. Botox treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 2). (2)

Table 2. Week 24 Key Efficacy Variables for Study 1 and Study 2 (2)

Efficacy per 28 days	**Study 1**	**Study 2**

	Botox (N=341)	Placebo (N=338)	Botox (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache-on-headache days	-107*	-70	-134*	-95

N: number.
* Significantly different from placebo (p≤0.05)

Patients treated with Botox had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1, and all timepoints from Week 4 to Week 24 in Study 2, compared to placebo-treated patients. (2)

Adult Upper Limb Spasticity
The efficacy of Botox for the treatment of adult upper limb spasticity was evaluated in several randomized, multi-center, double-blind, placebo-controlled studies (Studies 1 through 6). (2)

Study 1 included 126 adult patients (64 Botox and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. Botox (a total dose of 200 units to 240 units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary, into the adductor pollicis and flexor pollicis longus. Use of an electromyography (EMG)/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks. (2)

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity). (2)

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 3. (2)

Table 3. Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1 (2)

	Botox (N=64)	**Placebo (N=62)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale [+a]	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale [++b]	-1.0*	0.0

Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale [++c]	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment[++]	2.0*	0.0

N: number.
[+] Primary endpoint at Week 6
[++] Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
[a] Botox injected into both the flexor carpi radialis and ulnaris muscles
[b] Botox injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] Botox injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of Botox with placebo and included 91 adult patients [Botox 360 units (N=21), Botox 180 units (N=23), Botox 90 units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. Botox and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii. (2)

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale but allows for half-point increments. (2)

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 4. (2)

Table 4. Primary and Key Secondary Endpoints by Muscle Group and Botox Dose at Week 6 in Study 2 (2)

	Botox low dose (90 units) (N=21)	**Botox mid dose (180 units) (N=23)**	**Botox high dose (360 units) (N=21)**	**Placebo (N=26)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale[+b]	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale[++c]	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale[++d]	-0.5	-1.0*	-0.5[a]	-0.5

Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

N: number.
+ Primary endpoint at Week 6
++ Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
[a] p=0.053
[b] Total dose of Botox injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of Botox injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of Botox injected into biceps brachii muscle

Study 3 compared 3 doses of Botox with placebo and enrolled 88 adult patients [Botox 360 units (N=23), Botox 180 units (N=23), Botox 90 units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. Botox and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii. (2)

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 5. (2)

Table 5. Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3 (2)

	Botox low dose (90 units) (N=23)	**Botox mid dose (180 units) (N=21)**	**Botox high dose (360 units) (N=22)**	**Placebo (N=19)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale+[b]	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale++[c]	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale++[d]	-0.5	-0.5	-1.0*	-0.5

N: number.
+ Primary endpoint at Week 4
++ Secondary endpoints at Week 4
* Significantly different from placebo (p≤0.05)
[b] Total dose of Botox injected into both the flexor carpi radialis and ulnaris muscles

[c] Total dose of Botox injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of Botox injected into biceps brachii muscle

Study 4 included 170 adult patients (87 Botox and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 units of Botox into the adductor pollicis and flexor pollicis longus (total Botox dose = 40 units in thumb muscles) or placebo. Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, adult patients received 15 units (low dose) or 20 units (high dose) of Botox into the adductor pollicis and flexor pollicis longus under EMG guidance (total Botox low dose = 30 units, total Botox high dose = 40 units), or placebo. The duration of follow-up in Study 4 and Study 5 was 12 weeks. (2)

The results of Study 4 for the change from baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 6. The MAS uses a similar scoring system as the Ashworth Scale. (2)

Table 6. Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

	Botox (N=66)	**Placebo (N=57)**
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale ††*	-1.0*	0.0
Median Physician Global Assessment of Response to Treatment ††	2.0*	0.0

N: number.
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.001$)
[a] Botox injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by MAS and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function] are presented in Table 7. (2)

Table 7. Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5 (2)

	Botox low dose (30 units) (N=14)	**Placebo low dose (N=9)**	**Botox high dose (40 units) (N=43)**	**Placebo high dose (N=23)**
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale†††[a]	-1.0	-1.0	-0.5*	0.0
Median Change from Baseline in Clinical	1.0	0.0	2.0*	0.0

Global Impression Score by Physician[++]				

N: number.
[++] Secondary endpoint at Week 6
[+++] Other endpoint at Week 6
[*] Significantly different from placebo (p≤0.010)
[a] Botox injected into the adductor pollicis and flexor pollicis longus muscles

Study 6 (NCT03261167) enrolled 124 post-stroke adult patients with upper limb spasticity. (2) In Study 6, 61 patients received 160 units Botox divided among 3 elbow flexors (biceps brachii, brachioradialis, and brachialis) and 63 patients received placebo. EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. The duration of follow-up was 12 weeks.

The change from baseline in elbow flexor tone measured by modified Ashworth Scale at Week 6 is presented in Table 8. (2)

Table 8. Primary Efficacy Endpoint Results for Elbow Flexors at Week 6 in Study 6

	Botox 160 Units (N=61)	**Placebo (N=63)**
Mean Change from Baseline in Elbow Flexor Muscle Tone on the modified Ashworth Scale at Week 6	-1.09[*]	-.071

N: number.
[*]Nominal p value <0.05

Adult Lower Limb Spasticity
The efficacy and safety of Botox for the treatment of adult lower limb spasticity was evaluated in Study 7, a randomized, multi-center, double-blind, placebo-controlled study. Study 7 included 468 post-stroke adult patients (233 Botox and 235 placebo) with ankle spasticity (MAS ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 units of Botox or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris with up to an additional 100 units (400 units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks. (2)

The co-primary endpoints were the average of the change from baseline in MAS ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement. (2)

Statistically significant between-group differences for Botox over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 9). (2)

Table 9. Co-Primary Efficacy Endpoints Results in Study 6 (Intent-To-Treat Population) (2)

	Botox 300 to 400 units (N=233)	**Placebo (N=235)**
Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7

N: number.

* Significantly different from placebo ($p<0.05$)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors and CGI were observed at Week 2, Week 4, and Week 6 for patients treated with Botox. (2)

Pediatric Upper Limb Spasticity

The efficacy and safety of Botox for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 1 (NCT01603602), a randomized, multi-center, double-blind, placebo-controlled study. Study 1 included 234 pediatric patients (78 Botox 3 units/kg, 77 Botox 6 units/kg, and 79 placebo) with upper limb spasticity (MAS elbow or wrist score of at least 2) because of cerebral palsy or stroke. A total dose of 3 units/kg Botox (maximum 100 units), 6 units/kg Botox (maximum 200 units), or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles. Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection. (2)

The co-primary endpoints were the average of the change from baseline in MAS principal muscle group score (elbow or wrist) at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement). (2)

Compared to placebo, significant improvements in MAS change from baseline were observed at all timepoints for Botox-treated patients (see Table 10). Although CGI scores numerically favored Botox over placebo, the difference was not statistically significant. (2)

Table 10. Co-Primary Efficacy Endpoints Results in Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) (2)

	Botox	**Botox**	**Placebo**

	3 units/kg (N=78)	6 units/kg (N=77)	(N=79)
Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the modified Ashworth Scale			
Week 4 and 6 Average	-1.92*	-1.87*	-1.21
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.88	1.87	1.66

N: number.

* Nominal p value <0.05

Pediatric Lower Limb Spasticity

The efficacy and safety of Botox for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 2 (NCT01603628), a randomized, multi-center, double-blind, placebo-controlled study. Study 2 included 381 pediatric patients (125 Botox 4 units/kg, 127 Botox 8 units/kg, and 129 placebo) with lower limb spasticity (MAS ankle score of at least 2). A total dose of 4 units/kg Botox (maximum 150 units), 8 units/kg Botox (maximum 300 units), or placebo was injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior. Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection. (2)

The co-primary endpoints were the average of the change from baseline in MAS ankle score at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4 = very marked worsening to +4 = very marked improvement). (2)

Statistically significant differences between Botox and placebo were demonstrated for the MAS and CGI for the 8 units/kg dose only (see Table 11). (2)

Table 11. Co-Primary Efficacy Endpoints Results in Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) (2)

	Botox 4 units/kg (N=125)	Botox 8 units/kg (N=27)	Placebo (N=129)
Mean Change from Baseline in Plantar Flexors on the modified Ashworth Scale			
Week 4 and 6 Average	-1.01**	-1.06*	-0.80
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.49	1.65*	1.36

N: number.

* Significantly different from placebo (p<0.05)

** Nominal p value <0.05

Compared to placebo, improvements in mean change from baseline for the MAS, and mean CGI score for lower limb spasticity were observed at timepoints up to Week 12 for Botox-treated patients. (2)

Cervical Dystonia
A randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received Botox in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of Botox. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis. (2)

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the Botox group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9-category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 12. (2)

Table 12. Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means) (2)

	Placebo (N=82)	**Botox (N=88)**	**95% CI on Difference**
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[ab]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	

Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

CDSS: Cervical Dystonia Severity Scale; N: Number.

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effect, and baseline CDSS as a covariate.

[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.

[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets. (2)

In this study the median total Botox dose in patients randomized to receive Botox (N=88) was 236 units, with 25th to 75th percentile ranges of 198 units to 300 units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The total dose and muscles selected were tailored to meet individual patient needs. (2)

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of Botox. (2)

Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 units of Botox at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired. (2)

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks. (2)

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment. (2)

Strabismus
Six hundred seventy-seven patients with strabismus treated with one or more injections of Botox were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection. (2)

Off-Label Indications
Esophageal Achalasia
Esophageal achalasia results from progressive degeneration of ganglion cells in the myenteric plexus in the esophageal wall, leading to failure of relaxation of the lower esophageal sphincter, accompanied by a loss of peristalsis in the distal esophagus. Treatment is aimed at decreasing the resting pressure in the lower esophageal sphincter to a level at which the sphincter no longer impedes the passage of ingested material and this can be achieved by two ways: 1) Mechanical disruption of the muscle fibers of the lower esophageal sphincter pneumatic dilation (PD), surgical myotomy or peroral endoscopic myotomy and 2) Pharmacological reduction in lower esophageal sphincter pressure (e.g., injection of botulinum toxin or use of oral nitrates).

A Cochrane review by Leyden et al. (2014) identified 7 RCTs (total n=178 participants) that compared onabotulinumtoxinA with endoscopic pneumatic dilation (PD). (7) Outcomes reported was symptom remission rate at 1, 6 and 12 months. Study characteristics and results are summarized in Tables 11 and 12 respectively. The meta-analysis of RCTs showed no difference in relative risk (RR) of symptom remission at one month between PD vs onabotulinumtoxinA (RR=1.11, 95% confidence interval [CI]: 0.97 to 1.27). However, at 6 and 12 months, PD resulted in higher symptom remission rates and the difference was statistically significant (RR=1.57, p<0.005; RR=1.88, p= <0.005). No serious adverse events were reported after onabotulinumtoxinA injection; however, there were three cases of perforation after PD. Authors concluded that PD resulted in superior long-term efficacy compared with onabotulinumtoxinA (at 6 and 12 months). While the overall methodological quality of the individual RCTs was reported to be good, the risk of bias was high. In particular, only one RCT was double blind, five RCTs were potentially at a risk of selection, performance or detection bias due to inappropriate allocation of concealment, blinding of participants and personnel, and outcome assessment.

Wang et al. (2009) conducted a meta-analysis of RCTs that compared the efficacy of different treatments for primary achalasia. (8) Five RCTs compared botulinum toxin A injection with PD in patients with untreated achalasia, and also examined both subjective and objective parameters of esophageal improvement in all patients over 12 months. Authors reported that symptom remission rate was significantly higher in patients treated with PD vs botulinum toxin A injection (65.8% vs 36% respectively). Proportion of patients who relapsed within a year was 16.7% with PD vs 50% with botulinum toxin injection. Moreover, relapse time of botulinum toxin injection was shorter than that of PD after first therapy. Two RCTs compared efficacy of laparoscopic myotomy with botulinum toxin A injection in patients with untreated achalasia.

Authors reported that the symptom remission rate of botulinum toxin injection rapidly decreased and nearly 50% of patients were symptomatic again after 1 year of treatment. Laparoscopic myotomy had superior efficacy to botulinum toxin injection (laparoscopic myotomy 83.3% vs botulinum toxin injection 64.9%, RR 1.28; 95% CI 1.02–1.59; P=0.03). Patients treated with onabotulinumtoxinA had more frequent relapse and shorter time to relapse than those treated with laparoscopic myotomy. Some limitations of this meta-analysis include small number of cohorts in each trial, poor randomization techniques, and inadequate follow-up.

While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy. However, patients treated with botulinum toxin have more frequent relapses and a shorter time to relapse. (8) Greater than 50% of patients with achalasia treated with botulinum toxin A require retreatment within 6 to 12 months. Repeated botulinum toxin injections may also make a subsequent Heller myotomy more challenging. (9)

Table 13. Systematic Review/Meta-Analysis Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Leyden et al. (2014) (7)	1955-2008	7	Individuals with primary achalasia with the aim to compare endoscopic pneumatic dilation vs botulinum toxin A	178 (NR)	RCT	7 trials followed up patients ranging from 1 to 12 months
Wang et al. (2009) (8)	1989-2007	17	Individuals with primary achalasia who received botulinum toxin injection, pneumatic dilation, laparoscopic myotomy, surgical intervention, or nifedipine	761 (NR)	RCT	17 trials followed up patients ranging from 8 to 68 months

NR: not reported; RCT: randomized controlled trial.

Table 14. Systematic Review/Meta-Analysis Results

Study (Year)	Symptom Remission at 1 Month	Symptom Remission at 6 Months	Symptom Remission at 12 Months
Leyden et al. (2014) (7): Endoscopic pneumatic dilation vs botulinum toxin A (onabotulinumtoxinA)			
Total N	189 (5 RCTs)	113 (3 RCTs)	147 (4 RCTs)
Pooled effect (95% CI); p-value	RR = 1.11 (0.97 to 1.27); P value = NR	RR = 1.57 (1.19 to 2.08); P value = 0.0015	RR = 1.88 (1.35 to 2.61); P value = 0.0002
I^2 (p)	0.0%	79%	42%
Wang et al. (2009) (8)	**Remission Rate Over 12 Months**	**Relapse Rate Over 12 Months**	
Endoscopic pneumatic dilation vs botulinum toxin A			
Total N	154 (5 RCTs)	154 (5 RCTs)	
Pooled effect (95% CI); p-value	65.8% vs 36%; RR= 2.20 (95% CI: 1.51 to 3.20, P<0.0001)	16.7% vs 50%; RR=0.36 (95% CI, 0.22 to 0.58)	
Laparoscopic Myotomy vs botulinum toxin A			
Total N	117 (2 RCTs)	Not reported	
Pooled effect (95% CI); p-value	83.3% vs 64.9%, RR= 1.28 (95% CI, 1.02 to 1.59; P = 0.03)	Not reported	

CI: confidence interval; N: number; NR: not reported; RCT: randomized controlled trial; RR: relative risk.

Subsection Summary: Esophageal Achalasia

For the treatment of esophageal achalasia, two meta-analysis that included RCTs compared endoscopic PD or laparoscopic myotomy with botulinum toxin. Results showed that PD as well as laparoscopic myotomy afforded higher and statistically significant symptom remission rates. OnabotulinumtoxinA was not associated with any serious adverse events while PD resulted in perforation in few cases. While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in patients who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy.

Chronic Anal Fissure

An anal fissure is a tear or ulceration in the lining of the anal canal below the mucocutaneous junction. Chronic anal fissure is typically associated with anal spasm or high anal pressure. The initial treatment is medical management (combination of supportive measures such as high fiber diet, sitz bath, topical analgesic and one of the topical vasodilators such as nifedipine or nitroglycerin for one month). Patients who fail medical therapy are candidates for surgical

therapy that includes lateral internal sphincterotomy or botulinum toxin injection. Patients who are at a high-risk for fecal incontinence such as women who have had multiple vaginal deliveries and older patients with may have a weak anal sphincter complex are advised to undergo surgical procedures that do not require division of the anal sphincter muscle (e.g., botulinum toxin injection, fissurectomy, or anal advancement flap). Patients who are not at risk for developing fecal incontinence may undergo lateral internal sphincterotomy, which is considered the most effective treatment for anal fissure.

Chen et al. (2014) compared outcomes of onabotulinumtoxinA injection with lateral internal sphincterotomy based on 7 RCTs. (10) The study characteristics and results are summarized in Table 15 and 16. Treatment with botulinum toxin injection was associated with lower healing rate and a higher recurrence rate compared with lateral internal sphincterotomy. Sphincterotomy also resulted in higher complication rates, but the difference was not statistically significant (p=0.35). The meta-analysis suggests that internal sphincterotomy is more effective to treat anal fissure but onabotulinumtoxinA injection was associated with lower rates of incontinence. Authors reported multiple limitations in the evidence pooled for the meta-analysis including various dose of onabotulinumtoxinA used in different trials, inconsistent definition of chronic anal fissure used in the RCTs and none of the included RCTs were blinded. In addition, results of included studies were not consistent. The total complication rate varied from 0 to 64 % among the trials, while the incontinence rate varied from 0 to 48%. Nelson et al. (2012) published a Cochrane review that compared multiple treatment options for chronic anal fissure. (11) Reported results for comparison of botulinum toxin injection with sphincterotomy are consistent with those reported by Chen et al. (2014). Botulinum toxin A injection is therefore preferably used for patients who are at a high-risk of developing fecal incontinence (e.g., multiparous women or older patients).

Table 15. Systematic Review/Meta-Analysis Characteristics

Study (Year)		Dates	Trials	Participants	N (Range)	Design	Duration
Chen et al. (2014) (10)		2003-2012	7	Individuals with chronic anal fissure	489 (NR)	RCT	7 trials followed up patients ranging from 18 weeks to 3 years

N: number; NR: not reported; RCT: randomized controlled trial.

Table 16. Systematic Review/Meta-Analysis Results

Study (Year)	Healing	Complications	Incontinence	Recurrence Rate
Chen et al. (2014) (10): Botulinum A toxin injection vs lateral internal sphincterotomy				
Total N	409 (6 RCTs)	451 (6 RCTs)	489 (7 RCTs)	489 (7 RCTs)

Pooled effect (95% CI); p-value	OR = 0.15 (0.08 to 0.27); P < 0.001	OR = 0.55 (0.15 to 1.94); P=0.35	OR = 0.12 (0.05 to 0.26); P < 0.001	OR = 5.97 (3.51 to 10.17); P < 0.001
I^2 (p)	0% (0.5)	75% (0.001)	0% (0.53)	4% (0.39)
Nelson et al. (2012) (11): Botulinum A toxin injection vs sphincterotomy				
Total N	365 (5 RCTs)	Not reported	321 (4 RCTs)	Not reported
Pooled effect (95% CI); p-value	7.20[a] (3.97 to 13.07); P < 0.001	Not reported	0.11 (0.02 to 0.46); p < 0.001	Not reported
I^2 (p)	47%	Not reported	0	Not reported

N: number; NR: Not reported; CI: Confidence interval; OR: odds ratio; RCT: randomized controlled trial.
[a] Comparison indicates that sphincterotomy was 7.2 times more likely to heal than botulinum toxin injection

Subsection Summary: Anal Fissure

Two meta-analysis suggests that sphincterotomy is a more effective treatment option for chronic anal fissure compared with botulinum toxin A and results in significantly higher healing rate as well lower recurrence rate. However, these meta-analysis report higher incontinence rate with surgical procedures. Since botulinum toxin A injections are less invasive and do not require the internal sphincter muscle to be divided and thereby reduce the risk of fecal incontinence, they are preferred for patients who are not good surgical candidates or who want to minimize the likelihood of incontinence.

Congenital Esotropia

Campos et al. (2000) assessed the results of botulinum toxin treatment in 60 consecutive children with essential infantile esotropia. (12) Bilateral simultaneous injection of botulinum toxin into the medial rectus muscle was performed in 60 patients under direct visualization with an "open sky" technique. Fluothane/sevoflurane insufflation anesthesia was used. Each patient underwent a single bilateral botulinum toxin injection. Patient age at the time of injection ranged from 5-8 months. Mean patient age at the time of treatment for the 88% of patients who gained a good alignment (within +10 prism diopters [delta] of residual esotropia) was 6.5 months, while mean patient age at time of injection for the 12% of patients who were under corrected, or the deviation relapsed was 7.8 months. Follow-up averaged 5.2 years (range: 2-9 years, SD= 2). No variation of the angle of strabismus was observed after 6 months from injection. In some patients with hyperopic refraction, plus lens corrections were prescribed during follow-up to stabilize the alignment. Authors concluded that botulinum toxin can be effective in essential infantile esotropia when children are treated by age 7 months.

Alam et al. (2023) investigated the outcomes and complications of botulinum toxin injection (BTX) as the primary treatment of infantile esotropia (IET). (13) Patients with IET who underwent BTX from 2015 to 2020 were included. IET was defined as esotropia present before 12 months of age, with no significant refractive error, or limitation of rotations. Success was defined as a postoperative angle of 0-10 prism diopters (PD). Sixty-three patients met the inclusion criteria (38 male patients [60.3%]). The mean age was 18 ± 8 months (range: 10-26),

onset 6 ± 4 months (range: 2-10), and follow-up of 29 ± 25 months (range: 4-54). Amblyopia was present in 45 patients (71.4%). Number of BTX was, 1 in 42 (66.7%), 2 in 17 (27%), 3 in 4 (4.8%), and 4 in 1 (1.6%). The 1st BTX mean dose was 7 ± 3 international unit (range: 4-10) and a mean duration of 4 ± 1 min (range: 3-5). The mean preoperative angle of deviation was 42.30 ± 13.73 PD. The mean postoperative angle of deviation was 16.07 ± 16.15 PD (*P* = 0.0001). At the final follow-up, BTX was successful in 32 (51%) (success after 1st BTX 33.3%, 2nd BTX 46.03%, and 3rd BTX 50.79%). Twelve patients (19%) had undergone surgery due to the failure of BTX. Postoperative observations included transient ptosis 29 (49.2%), transient exotropia 36 (57.14%), inferior oblique overaction 13 (20.6%), vertical deviation 8 (12.7%), and persistent ptosis 1 (1.6%). Researchers found the success rate of BTX for IET was 51% and concluded that BTX can be offered as an alternative to surgery to those who cannot undergo prolonged anesthesia or where accurate measurements could not be obtained.

In regard to injection of botulinum toxin, a 2022 American Academy of Ophthalmology Preferred Pattern® on esotropia and exotropia stated: "As with conventional extraocular muscle surgery, favorable prognostic indicators include good vision in each eye, absence of restricted eye movement, a small to moderate angle of esotropia, and the potential for binocular vision. Such treatment may be an alternative to conventional extraocular muscle surgery in selected patients, but its value in managing infantile esotropia has not been definitively established." (14)

Miscellaneous Dystonias
Blitzer et al. treated 20 oromandibular dystonia (OMD) patients with botulinum toxin. Six patients had only jaw and tongue involvement; 11 had blepharospasm and jaw involvement; and three had jaw involvement as part of a more generalized dystonia. Five patients had been diagnosed originally and treated as having temporomandibular joint syndrome. All but one of the patients had improvement of their symptoms with the toxin injections. The patients averaged 47% improvement with the injections. (15)

In a 2019 meta-analysis, Dadgardoust et al. conducted a systematic search of the literature that met the following eligibility criteria were done: 1) patients treated with botulinum neurotoxin (BoNT)-A for OMD, 2) studies of high methodological quality, and 3) outcome criteria specified as regard to efficacy. Nine studies involved 387 cases in total of OMD. Results indicate that risk of dystonic movements is lower by 39.30% in the treatment group than in the control group. While cited literatures have inherent weaknesses, results show that BoNT-A is efficacious in reducing dystonic movements of patients with OMD. (16)

Courey et al. (2000) conducted a prospective analysis of the effects of botulinum toxin (BTX) on the patient's perception of voice and general health. (17) The Voice Handicap Index (VHI) and Short Form 36 (SF-36) surveys were administered to patients before treatment and 1 month after. Pretreatment and posttreatment scores were analyzed with a Student's t-test. On the VHI, improvements in the patients' perception of their functional, physical, and emotional voice handicap reached statistical significance (p < or = .0005). On the SF-36, patients had statistically significant improvements in mental health (p < or = .03) and social functioning (p < or = .04).

Treatment of spasmodic dysphonia with BTX significantly lessened the patients' perception of dysphonia. In addition, it improved their social functioning and their perception of their mental health. These outcome measures justify the continued treatment of SD with BTX.

In 2018, the American Academy of Otolaryngology – Head and Neck Surgery published an update of their guideline first published in 2009. (18) The organization recommended that clinicians should offer or refer to a clinician who can offer botulinum toxin injections for the treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia.

Kruisdijk et al. (2007) investigated the efficacy of BoNT-A injections in patients with writer's cramp in a double-blind, randomized, placebo-controlled trial and to evaluate the follow-up results. (19) Forty participants were randomized to treatment with either BoNT-A or placebo injections in two sessions. Trial duration was 12 weeks. Thirty-nine patients completed the trial. Fourteen of 20 patients (70%) receiving BoNT-A reported a beneficial effect and chose to continue treatment, versus 6 of 19 patients (31.6%) in the placebo group ($p = 0.03$). The changes on most of the clinical rating scales were significantly in favor of BoNT-A. Side effects reported were hand weakness, which was mostly mild and always transient, and pain at the injection site. After 1 year, 20 of 39 patients were still under treatment with a positive effect. Researchers concluded that Treatment with BoNT-A injections led to a significantly greater improvement compared with placebo, according to patients' opinion and clinical assessment scales.

Voice Tremor

Adler et al. (2004) evaluated the safety and efficacy of botulinum toxin type A injections as treatment for voice tremor in a randomized study of 3 doses of botulinum toxin type A with 6 weeks of follow-up. (20) Thirteen subjects (11 women, 2 men; mean age, 73 years) with voice tremor and no spasmodic dysphonia or head, mouth, jaw, or facial tremor were entered into this study. Patients received 1.25 units (n = 5), 2.5 units (n = 5), or 3.75 units (n = 3) of botulinum toxin type A in each vocal cord. All patients were evaluated at baseline and postinjection at weeks 2, 4, and 6. All patients at all dose levels noted an effect from the injection. The mean time to onset of effect was 2.3 days (range, 1-7 days). For all patients combined, mean tremor severity scale scores (rated by patients on a 5-point scale) improved 1.4 points at week 2, 1.6 points at week 4, and 1.7 points at week 6. Measures of functional disability, measures of the effect of injection, independent ratings of videotaped speech, and acoustic measures of tremor also showed improvement. The main adverse effects at all doses were breathiness and dysphagia. The authors concluded that voice tremor improves following injections of botulinum toxin type A.

Hemifacial Spasm

Poungvarin et al. (1995) performed a double-blind cross-over study of botulinum A toxin use in hemifacial spasm in 55 patients. (21) Thirteen patients decided to withdraw from the study due to a lack of efficacy, all of them were subsequently found to be in the saline injection group. The remaining 42 patients, in the botulinum A toxin injection group, reported the responses as: excellent (34 patients; 80.95%), moderate patients; (2.38%). In contrast, when given the saline

injection they reported no excellent outcome, 1 patient (2.38%) with moderate improvement, 5 patients (11.90%) with mild improvement and, 36 patients (85.71%) with no response. Side effects of botulinum toxin injections were found in 14.29% of patients compared with 9.5% of the saline injection group. The side effects of botulinum toxin injection were mild transient facial weakness (7.14%), local pain (4.76%) and excessive lacrimation (2.38%). Researchers concluded that botulinum A toxin injection was a simple and effective out-patient treatment for the management of hemifacial spasm.

Hirschsprung Disease
Hirschsprung disease is a rare genetic birth defect that results in motor disorder of the gut due to failure of neural crest cells (precursors of enteric ganglion cells) to migrate completely during intestinal development during fetal life. The resulting aganglionic segment of the colon fails to relax, causing a functional obstruction.

The published literature on use of onabotulinumtoxinA to treat Hirschsprung disease consists of case series summarized in Table 17 and 18. (22-24)

A retrospective cohort study by Svetanoff et al. (2021) included 40 patients admitted for Hirschsprung-associated enterocolitis (HAEC) from January 2010 to December 2019. (25) The aim of the study was to determine if botulinum toxin injection during HAEC episodes decreased the number of recurrent HAEC episodes and/or increased the interval between readmissions. In the 40 patients analyzed, a total of 120 episodes of HAEC occurred. Patients who received botulinum toxin during their inpatient HAEC episode had a longer median time between readmissions (p=.04) and trended toward an association with fewer readmissions prior to a follow-up clinic visit (p=.08). This study provides additional evidence that the use of botulinum injections for Hirschsprung disease among patients hospitalized for HAEC is associated with an increased time between recurrent HAEC episodes and trend toward decreasing recurrent enterocolitis incidence.

A retrospective cohort study of 41 patients consecutively treated for Hirschsprung disease in 2 academic hospitals in Amsterdam with a follow-up duration of ≥1 year after corrective surgery were analyzed. (26) All patients had obstructive defecation problems non-responsive to high-dose laxatives or rectal irrigation, 2 patients also had an episode of HAEC. Twenty-five (61%) of 41 patients had clinical improvement after a first injection. In 29 (71%) of the 41 patients, spontaneous defecation or treatment with laxatives only was achieved.

A retrospective case series by Han-Geurts et al. (2014), included 33 children with surgically treated Hirschsprung disease treated with intrasphincteric botulinum toxin A injections for obstructive symptoms was analyzed with a retrospective chart review between 2002 and 2013 in the Netherlands. (27) The mean age at time of botulinum toxin A treatment was 3.6 years and median follow-up was 7.3 years (range 1 to 24). A median of two (range 1–5) injections were given. Initial short-term improvement was achieved in 76%, with a median duration of 4.1 months (range 1.7 to 58.8). Proportion of children hospitalized for enterocolitis decreased after treatment from 19 to 7. More than half (51%) of patients reported good or excellent long-term

outcomes after a median follow-up of 126 months. Two children experienced complications: transient pelvic muscle paresis with impairment of walking. In both children symptoms resolved within four months without treatment.

A prospective case series by Minkes and Langer (2000), included 18 children (median age, 4 years) with persistent obstructive symptoms after surgery for Hirschsprung disease. (23) Patients received injections of onabotulinumtoxinA into four quadrants of the sphincter. The total dose of onabotulinumtoxinA during the initial series of injections was 15 to 60 U. Twelve (67%) of 18 patients improved for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had one to five additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A retrospective case series by Patrus et al. (2011) reviewed outcomes in 22 patients with Hirschsprung disease treated over 10 years; subject had received a median of 2 (range, 1-23) onabotulinumtoxinA injections for postsurgical obstructive symptoms. (24) Median follow-up (time from first injection to time of chart review) was five years (range, 0-10 years). At chart review, 2 (9%) of 22 patients had persistent symptoms. Eighteen (80%) children had a "good response" to the initial treatment (not defined), and 15 (68%) had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after onabotulinumtoxinA injection (median, 0) compared with preinjection (median, 1.5; p=0.003). The authors did not report whether patients received other treatments during the follow-up period in either case series.

Table 17. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Author (Year)	Study Type	Country/ Institution	Dates	Participants	Treatment 1	F/U
Minkes et al. (2000) (23)	Prospective	U.S./University of Washington	NR	Children with Hirschsprung's disease who have persistent obstructive symptoms after operation	Onabotulinum-toxinA (Botox) N=18	4 yrs
Patrus et al. (2010) (24)	Retrospective	Canada/Hospital for Sick Children	1998-2008	Children with Hirschsprung's disease who have persistent obstructive symptoms after operation	Onabotulinum-toxinA (Botox) N=22	10 yrs
Han-Geurts et	Retrospective	Netherlands/ University	2002-2013	Children with Hirschsprung's	Onabotulinum-toxinA (Botox)	7.3 yrs

al. (2014) (27)		Medical Centers of Maastricht and Nijmegen		disease who have persistent obstructive symptoms after operation	N=33	
Roorda et al. (2021) (26)	Retrospective	Netherlands/ Academic Medical Centre and VU Medical Centre	2003-2017	Children with Hirschsprung's disease who have persistent obstructive symptoms after operation	Onabotulinum-toxinA (Botox) or abobotulinum-toxinA (Dysport) N=41 Note: Botox and Dysport represented 69% and 31% of all injections, respectively	8 yrs
Svetanoff et al. (2021) (25)	Retrospective	U.S./Children's Mercy Hospital	2010-2019	Children with Hirschsprung's disease who required an inpatient Hirschsprung-associated enterocolitis admission	Onabotulinum-toxinA (Botox) N=21	NR

F/U: follow-up; N: number; NR: not reported; U.S.: United States; yr(s): years.

Table 18. Summary of Key Nonrandomized Trials or Observational Comparative Study Results

Study (Year)	Outcomes (Efficacy)
Minkes et al. (2000) (23)	
Total N	18
OnabotulinumtoxinA	**Clinical response after 1 month** 67% (12/18)
Patrus et al. (2010) (24)	
Total N	22
OnabotulinumtoxinA injection	**Median number of hospitalizations for obstructive symptoms:** Prior to treatment: 1.5 (IQR: 1 to 3) Post treatment: 0 **Clinical Response After 1st dose: 80%**
p-value	P <0.05
Han-Geurts et al. (2014) (27)	
Total N	33
OnabotulinumtoxinA	**Short-term improvement**

	76% (25/33) **Long-term improvement** Poor = 19% (6) Fair = 30% (10) Good = 27% (9) Excellent = 24% (8)
Difference (95% CI); p-value	NR
Roorda et al. (2021) (26)	
Total N	N=41 (botulinum toxin) N=90 (no botulinum toxin)
OnabotulinumtoxinA or abobotulinumtoxinA	**Clinical improvement after 1st dose**: 61% (25/41), p<.001 (significant within-group difference pre-post intervention) **Mean duration of improvement after 1st dose**: 3.7 months (SD, 3.0) **Spontaneous defecation or defecation with laxatives after botulinum toxin injections**: 71% (29/41)
Svetanoff et al. (2021) (25)	
Total N	N=21 (botulinum toxin) N=19 (no botulinum toxin)
OnabotulinumtoxinA	**Time between HAEC episodes for botulinum toxin vs. non-botulinum toxin injection group:** 146 days (IQR, 100 to 326) vs. 68 days (IQR, 16 to 173), p=.03 **Less recurrence of HAEC episodes for botulinum toxin vs. non-botulinum toxin injection group:** 45% vs. 76% ; p=.02 Injection of botulinum toxin was associated with a longer time between recurrent HAEC episodes (p=.04) No difference in the number of recurrent HAEC episodes based on the use of botulinum toxin injections was seen (p=.08)

CI: confidence interval; HAEC: Hirschsprung-associated enterocolitis; IQR = interquartile range; N: number; NR: not reported; SD: standard deviation.

Subsection Summary: Hirschsprung Disease

Hirschsprung disease is a rare disease where the mainstay of treatment is surgery. However, patients may develop obstructive symptoms after surgery. The published literature on use of onabotulinumtoxinA to treat Hirschsprung disease consists of case series with a total of 135 patients with median follow-up of more than 7 years in 3 out of 5 published case series. A consistent short-term response was seen in more than 75% of patients in 2 of the 5 case series. Long-term follow-up is suggestive of durability of response.

Sialorrhea

In a double-blind, randomized, placebo-controlled study, Lagalla et al. (2006) enrolled 32 Parkinson's disease (PD) patients complaining of excessive drooling. (28) Patients received either 50 units of Botox in each parotid gland or placebo without using ultrasound guidance. Subjects treated with BoNT-A experienced a reduction in both drooling frequency and familial and social disability (TimexGroup effect: $P<0.01$), as well as in saliva production (Time x Group effect: $P<0.0001$). No adverse events were recorded. Authors concluded that BoNT-A injections are safe and effective treatment for the management of PD-related drooling.

Chinnapongse et al. (2012) enrolled 54 PD subjects with troublesome sialorrhea into a multicenter, randomized, double-blind, sequential-dose escalation design in which subjects received a single intraglandular treatment with botulinum toxin type B (doses of 1,500 Units [0.3 mL]; 2,500 Units [0.5 ml]; or 3,500 Units [0.7 ml]) or placebo. (29) Postinjection, subjects were followed acutely for 4 weeks and long-term for up to 20 weeks. Safety/tolerability, as assessed by adverse events, was the primary outcome measure. Efficacy, as assessed by the Drooling Frequency and Severity Scale and unstimulated salivary flow rate, was secondary. Gastrointestinal-related adverse events occurred more frequently in the active groups versus placebo group (31% vs 7%), with dry mouth being most common (15%). There were no serious adverse events attributed to botulinum toxin type B or discontinuations due to adverse events from treatment. At 4 weeks postinjection, Drooling Frequency and Severity Scale scores significantly improved versus placebo (-1.3 ± 1.3) in a dose-related manner (-2.1 ± 1.2, $P = 0.0191$; -3.3 ± 1.4, $P < 0.0001$; -3.5 ± 1.1, $P < 0.0001$, respectively) and unstimulated salivary flow rates significantly decreased in all active groups versus placebo ($P \leq 0.0009$). Furthermore, treated subjects appeared to have more sustained improvement in sialorrhea than placebo subjects. Researchers concluded that intraglandular injection of botulinum toxin type B was safe, tolerable, and efficacious in treating sialorrhea in PD patients.

In a randomized, controlled trial, Reid et al. (2008) assessed the effectiveness of BoNT-A injections into the submandibular and parotid glands on drooling in children with cerebral palsy (CP) and other neurological disorders. (30) Secondary aims were to ascertain the duration of any such effect and the timing of maximal response. Of the 48 participants (27 males, 21 females; mean age 11y 4mo [SD 3y 3mo], range 6-18y), 31 had a diagnosis of CP and 15 had a primary intellectual disability; 27 children were non-ambulant. Twenty-four children randomized to the treatment group received 25 units of BoNT-A into each parotid and submandibular gland. Those randomized to the control group received no treatment. The degree and impact of drooling was assessed by carers using the Drooling Impact Scale questionnaire at baseline and at monthly intervals up to 6 months postinjection/baseline, and again at 1 year. Maximal response was at 1 month at which time there was a highly significant difference in the mean scores between the groups. This difference remained statistically significant at 6 months. Four children failed to respond to the injections, four had mediocre results, and 16 had good results.

Scheffer et al. (2010) conducted a prospective cohort study to address the efficacy of botulinum toxin and the duration of its effect when used on a large scale for the treatment of drooling in children with neurological disorders. (31) Patients included a total of 131 children diagnosed as

having cerebral palsy or another nonprogressive neurological disorder and who also have moderate to severe drooling. The intervention was injection of botulinum toxin to the submandibular glands. Main outcome measures included direct observational drooling quotient (DQ) (0-100) and caretaker visual analog scale (VAS) scores (0-100). A clinically notable response was found in 46.6% of children, reflected in a significant mean reduction in DQ from a baseline of 29 to 15 after 2 months and 19 after 8 months (P < .001). The mean VAS score decreased from 80 at baseline to 53 after 2 months and increased to 66 after 8 months (P < .001). Kaplan-Meier analysis showed that patients who initially responded to treatment experienced relapse after a median of 22 weeks (interquartile range, 20-33 weeks). Authors concluded that the study provides further support for botulinum toxin's efficacy for treatment of drooling in approximately half of patients for a median of 22 weeks.

AbobotulinumtoxinA (Dysport®)

FDA-Labeled Indications

Cervical Dystonia

The efficacy of Dysport was evaluated in two randomized, double-blind, placebo-controlled, single-dose, parallel-group studies in treatment-naive cervical dystonia patients. The principal analyses from these trials provide the primary demonstration of efficacy involving 252 patients (121 on Dysport, 131 on placebo) with 36% male and 64% female. Ninety-nine percent of the patients were Caucasian. (3)

In both placebo-controlled studies (Study 1 and Study 2), a dose of 500 units of Dysport was given by intramuscular injection divided among two to four affected muscles. These studies were followed by long-term open-label extensions that allowed titration in 250-unit steps to doses in a range of 250 to 1000 units, after the initial dose of 500 units. In the extension studies, re-treatment was determined by clinical need after a minimum of 12 weeks. The median time to re-treatment was 14 weeks and 18 weeks for the 75^{th} percentile. (3)

The primary assessment of efficacy was based on the total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) change from baseline at Week 4 for both studies. The scale evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain. The adjusted mean change from baseline in the TWSTRS total score was statistically significantly greater for the Dysport group than the placebo group at Week 4 in both studies. (3)

Upper Limb Spasticity in Adults

The efficacy and safety of Dysport for the treatment of upper limb spasticity in adults was evaluated in a randomized, multicenter, double-blind, placebo-controlled study that included 238 patients (159 Dysport and 79 placebo) with upper limb spasticity MAS score $\geq$2 in the primary targeted muscle group for toxin-naive patients or MAS score $\geq$3 in the primary targeted muscle group for toxin non-naive patients at least 4 months after the last botulinum toxin injection, of any serotype) who were at least 6 months post-stroke or post-traumatic brain injury. The median age of the patients in this study was 55 years (range 18 to 78 years), 64% were male, and 86% were Caucasian. (3)

Dysport 500 units (N=80), Dysport 1000 units (N=79), or placebo (N=79) was injected intramuscularly into the affected upper limb muscles. After injection of the primary targeted muscle groups (PTMG), the remainder of the dose was injected into at least two additional upper limb muscles determined by the patient's individual presentation. Table 20 provides the mean and range of Dysport doses injected and the number of injections into specific muscles of the upper limb. (3)

The co-primary efficacy variables were muscle tone assessed by the MAS at the primary targeted muscle group at Week 4 and the Physician Global Assessment (PGA; ranges from –4 = markedly worse to +4 = markedly improved) at Week 4 (see Table 19). (3)

Table 19. Primary Endpoints (PTMG MAS and PGA) and MAS by Muscle Group at Week 4 in Adults with Upper Limb Spasticity (3)

	Placebo (N=79)	**Dysport**	
		(500 units) (N=80)	**(1000 units) (N+79)**
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	-0.3	-1.2*	-1.4*
LS Mean PGA of Response to Treatment	0.7	1.4*	1.8*
LS Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-0.3 (n=54)	-1.4 (n=57)	-1.6 (n=58)
LS Mean Change from Baseline in Finger Flexor Muscle Tone on the MAS	-0.3 (n=70)	-0.9 (n=66)	-1.2 (n=73)
LS Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-0.3 (n=56)	-1.0 (n=61)	-1.2 (n=48)

LS: least square; N: number; PTMG: primary targeted muscle groups; MAS: Modified Ashworth Scale; PGA: Physician Global Assessment.

* $p \leq 0.05$

Lower Limb Spasticity in Adults

The efficacy of Dysport for the treatment of lower limb spasticity was evaluated in a randomized, multicenter, double-blind, placebo-controlled study that included 381 patients (253 Dysport and 128 placebo). Patients had lower limb spasticity MAS score ≥2 in the affected ankle joint for toxin-naive patients, or MAS score ≥3 in the affected ankle joint for toxin non-naive patients, and were at least 6 months post-stroke or post-traumatic brain injury. In the study, the gastrocnemius and soleus muscles, and at least one additional lower limb muscle were injected, according to the clinical presentation. The primary efficacy variable was muscle tone assessed by the MAS at the ankle joint at Week 4. The first secondary endpoint was the PGA at Week 4 (see Table 20). (3)

Table 20. Primary Endpoint Change in MAS and the First Secondary Endpoint PGA at Week 4 in Adults with Lower Limb Spasticity (3)

LS Mean Change from Baseline on the	**Dysport 1000 units**	**Dysport 1500 units**	**Placebo**

Modified Ashworth Scale	**(N=125)**	**(N=128)**	**(N=128)**
Week 4	-0.6	-0.8*	-0.5
LS Mean Physician Global Assessment Score Investigator			
Week 4	0.9	0.9	0.7

LS: least square; MAS: Modified Ashworth Scale; N: number; PGA: Physician Global Assessment.
* p<0.05

Upper Limb Spasticity in Pediatric Patients
The efficacy of Dysport for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age was evaluated in a double-blind, low dose controlled, multicenter study (NCT02106351). A total of 208 toxin naive or non-naive (66% had prior treatment with a botulinum toxin) patients weighing at least 10 kgs, with a baseline MAS of grade 2 or greater (99% patients) at the PTMG, were enrolled in the modified intention to treat population (mITT). Patients received Dysport 16 units/kg (n=70), Dysport 8 units/kg (n=69), or Dysport 2 units/kg (n=69) injected into the upper limb. The elbow flexors and wrist flexors respectively were the PTMG in 57% and in 43% of patients. The median age of the patients in this study was 9 years (range 2 to 17 years; 57% were between 2 and 9 years of age); 60% of patients were male, and 75% were white. (3)

The primary efficacy endpoint was the mean change from baseline in MAS in the PTMG at Week 6 (see Table 21). The secondary efficacy endpoint was the mean PGA score assessed at Week 6 (Table 22). Although PGA scores numerically favored Dysport treatment over the low-dose control, the difference was not statistically significant. (3)

Table 21. Modified Ashworth Scale (MAS) Score in the PTMG Change from Baseline at Week 6 in Pediatric Patients with Upper Limb Spasticity (mITT Population) (3)

	Control Group	**Treatment Groups**	
	Dysport 2U/kg (N=69)	**Dysport 8U/kg (N=69)**	**Dysport 16U/kg (N=70)**
Baseline			
Mean (SD)	3.1 (0.3)	3.1 (0.3)	3.1 (0.5)
Week 6			
LS[a] mean change from baseline in PTMG[b] on MAS	-1.6	-2.0	-2.3
Difference from control in LS[a] means		-0.4	-0.7
p-value[c]		0.0118[d]	<0.0001
Week 16			
LS[a] mean change from baseline in PTMG[b] on MAS	-0.9	-1.2	-1.5

Difference from control in LS[a] means		-0.3[d]	-0.6[d]

mITT: modified intention-to-treat; N: number; SD: standard deviation.
[a] LS: least square
[b] PTMG: primary targeted muscle group
[c] p-value is derived from ANCOVA on ranked MAS score change from baseline with treatment, baseline score, age range at baseline, prior botulinum toxin treatment status at baseline, and center as explanatory variables
[d] Nominal p-value <0.05

Table 22. Physician Global Assessment (PGA) of Treatment Response at Week 6 in Pediatric Patients with Upper Limb Spasticity (mITT Population) (3)

	Control Group	**Treatment Groups**	
	Dysport 2U/kg (N=69)	**Dysport 8U/kg (N=69)**	**Dysport 16U/kg (N=70)**
Week 6			
Mean score (SD)	1.7 (0.9)	2.0 (0.9)	2.0 (0.9)
LS[a] mean in PGA	1.8	2.0	2.0
Difference from control in LS[a] means		0.2	0.2
p-value[b]		0.2043	0.1880
Week 16			
Mean score (SD)	1.7 (1.0)	1.6 (1.1)	1.9 (1.2)
LS[a] mean in PGA	1.8	1.7	1.9
Difference from control in LS[a] means		-0.1	0.1
p-value[b]		0.7001	0.4041

mITT: modified intention-to-treat; N: number; SD: standard deviation.
[a] LS: least square
[b] PTMG: primary targeted muscle group
[c] p-value is derived from ANCOVA on ranked PGA score with treatment, age range at baseline, prior botulinum toxin treatment status at baseline, and center as explanatory variables

Lower Limb Spasticity in Pediatric Patients

The efficacy of Dysport for the treatment of lower limb spasticity in patients 2 to 17 years of age was evaluated in a double-blind, placebo-controlled, multicenter study in patients 2 to 17 years of age treated for lower limb spasticity because of cerebral palsy causing dynamic equinus foot deformity. A total of 235 (158 Dysport and 77 placebo) toxin-naive or non-naive patients with a MAS of grade 2 or greater at the ankle plantar flexors were enrolled to receive Dysport 10 units/kg/leg (n=79), Dysport 15 units/kg/leg (n=79) or placebo (n=77) injected into the gastrocnemius and soleus muscles. Forty-one percent of patients (n=66) were treated bilaterally and received a total lower limb Dysport dose of either 20 units/kg (n=37) or 30 units/kg (n=29). The median age of the patients in this study was 5 years (range 2 to 17 years); 60% of patients were male, and 73% were Caucasian. The primary efficacy endpoint was the mean change from baseline in MAS in ankle plantar flexor at Week 4; a co-primary endpoint was the mean PGA score at Week 4 (see Table 23). (3)

Table 23. MAS and PGA Change from Baseline at Week 4 in Pediatric Patients with Lower Limb Spasticity (ITT Population) (3)

		Placebo (N=77)	Dysport 10 units/kg/leg (N=79)	Dysport 15 units/kg/leg (N=79)
LS Mean Change from Baseline in Ankle plantar flexor Muscle Tone on the MAS	Week 4	-0.5	-0.9*	-1.0*
	Week 12	-0.5	-0.8*	-1.0*
LS Mean PGA of Response to Treatment	Week 4	0.7	1.5*	1.5*
	Week 12	0.4	0.8*	1.0*

ITT: intention-to-treat; LS: least square; MAS: modified Ashworth Scale; N: number; PGA: Physician Global Assessment.

* $p<0.05$

Off-Label Indications

Achalasia

Mikaeli et al. (2001) compared abobotulinumtoxinA injection with pneumatic dilation in a randomized trial. (32) Forty adults with newly diagnosed achalasia were randomized to receive botulinum toxin (n=20) or pneumatic dilatation (n=20). Symptom scores were evaluated at 1, 6 and 12 months. Clinical relapse was defined as a symptom score greater than 50% of baseline. Relapsers received a second botulinum toxin injection or pneumatic dilatation. The cumulative 12-month remission rate was significantly higher after a single pneumatic dilatation (53%) compared to a single botulinum toxin injection (15%) ($P < 0.01$). The 12-month estimated adjusted hazard for relapse and need for retreatment for the botulinum toxin group was 2.69 times that of the pneumatic dilatation group (95% confidence interval: 1.18-6.14). When a second treatment was administered to the relapsers in each group, the cumulative remission rate 1 year after initial treatment was significantly higher in the pneumatic dilatation group (100%) compared to the botulinum toxin group (60%) ($P < 0.01$). There were no major complications in either group. Although pneumatic dilatation is more efficacious than botulinum toxin in providing sustained symptomatic relief in patients with achalasia, for patients who do not respond to pneumatic dilatation or are not surgical candidates, botulinum toxin should be considered. The efficacy of a single pneumatic dilatation is similar to that of two botulinum toxin injections.

Blepharospasm

In 2008, Truong et al. conducted a large-scale, multicenter, randomized clinical trial on the efficacy and safety of botulinum toxin (Dysport; 40, 80, and 120 units/eye) versus placebo in bilateral benign essential blepharospasm (BEB). (33) Findings supported the high efficacy and good safety profile of Dysport, with improvement in functional impairment, reduced frequency and intensity of facial spasms, and fewer withdrawals through lack of efficacy in the active treatment group compared with controls. The best balance of sustained efficacy and favorable safety profile was provided by 80 units of Dysport per eye in this study.

Hemifacial Spasm

Jitpimolmard et al. (1998) designed a prospective descriptive study on the long-term efficacy and side effects of the treatment of hemifacial spasm with Dysport. (34) Of 175 cases, 17 were lost to follow up and were excluded. 855 treatments were injected in the remaining 158 patients with a median of 4 treatments. The response rate was 97%. Of 855 treatments, the adjusted mean peak and duration of improvement was 77.2% (95% CI 74.7-79.4) and 3.4 (95% CI, 3.2-3.6) months respectively. In 158 patients (complete group), the long-term results from the first to the 12th treatment showed that the mean peak improvement ranged from 72.70 to 80.10% and the duration of improvement was 2.60 to 3.71 months. It remained constant throughout (p=0.40, p=0.87, respectively). The most common side effect was ptosis. Of the 158 patients, 21 completed 12 treatments (subgroup). A separate analysis of this group disclosed a mean peak and duration of improvement from the first to 12th treatments ranging from 70.00 to 78.10% and 2.65 to 4.31 months respectively. Analysis of variance with repeated measures showed no significant variation of peak and duration of improvement over the first to the 12th treatments (p=0.38, p=0.38, respectively). Only 3% of the treatments were unsuccessful but responded to subsequent treatments.

IncobotulinumtoxinA (Xeomin®)

FDA-Labeled Indications

Chronic Sialorrhea in Adult Patients

The efficacy and safety of Xeomin for the treatment of chronic sialorrhea in adult patients were evaluated in a double-blind, placebo-controlled clinical trial that enrolled a total of 184 patients with chronic sialorrhea resulting from Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury, that was present for at least three months. Patients with a history of aspiration pneumonia, amyotrophic lateral sclerosis, salivary gland or duct malformation, and gastroesophageal reflux disease were excluded. The study consisted of a 16-week main phase, followed by an extension period of dose-blinded treatment with Xeomin. (4)

In the main phase, a fixed total dose of Xeomin (100 units or 75 units) or placebo was administered into the parotid and submandibular salivary glands in a 3:2 dose ratio. The coprimary efficacy variables were the change in unstimulated Salivary Flow Rate (uSFR, Table 10) and the change in Global Impression of Change Scale at Week 4 postinjection. A total of 173 treated patients completed the main phase of the study. For both the uSFR and GICS, Xeomin 100 units was significantly better than placebo. Xeomin 75 units was not significantly better than placebo. (4)

Chronic Sialorrhea in Pediatric Patients

The efficacy and safety of Xeomin for the treatment of chronic sialorrhea in pediatric patients were evaluated in a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial that enrolled and treated a total of 216 pediatric patients 6-17 years of age with chronic sialorrhea associated with cerebral palsy, other genetic or congenital disorders, or traumatic brain injury. An additional 35 patients 2-5 years of age were treated with open-label Xeomin in that study. The study consisted of a 16-week main phase, followed by an open-label extension period of treatment with Xeomin where patients could receive up to 3 additional

treatments with Xeomin every 16 ± 2 weeks for a total exposure duration of up to 64 weeks (222 patients completed the extension period). (4)

In the main phase, patients 6-17 years of age were administered a total dose of Xeomin according to body weight (up to 75 units), or placebo, into the parotid and submandibular glands in a 3:2 dose ratio, using ultrasound guidance. Patients 2-5 years of age all received open-label treatment with Xeomin, according to body weight, using ultrasound guidance. Patients with a body weight <12 kg were excluded.

The primary efficacy analysis was conducted in the 6-17 years of age patient group. The co-primary endpoints were the change in unstimulated Salivary Flow Rate (uSFR, Table 24) and carer's Global Impression of Change Scale (GICS, Table 25) at Week 4 post-injection.
For both the uSFR and GICS, Xeomin was statistically significantly better than placebo (see Table 24 and Table 25).

Table 24. Mean Change in uSFR (g/min) from Baseline at Week 4, 8, 12, and 16 of Main Phase

	Xeomin (6-17 years) N=148	**Placebo (6-17 years) N=72**
Week 4*	-0.14	-0.07
Week 8	-0.16	-0.07
Week 12	-0.16	-0.06
Week 16	-0.15	-0.08

N: number; uSFR: unstimulated Salivary Flow Rate.
*p=0.0012

Table 25. Mean Carer's GICS at Week 4, 8, 12, and 16 of Main Phase

	Xeomin (6-17 years) N=148	**Placebo (6-17 years) N=72**
Week 4*	0.91	0.63
Week 8	0.94	0.54
Week 12	0.87	0.47
Week 16	0.77	0.38

GICS: Global Impression of Change Scale; N: number.
*p=0.0320

Efficacy in pediatric patients 2 to 5 years of age is extrapolated from the finding of efficacy in older pediatric patients.

Upper Limb Spasticity in Adult Patients
The efficacy and safety of Xeomin for the treatment of upper limb spasticity in adult patients were evaluated in two Phase 3, randomized, multicenter, double-blind studies. (4)

Study 1 and Study 2 were both prospective, double-blind, placebo-controlled, randomized, multicenter trials with an open-label extension period (OLEX) to investigate the efficacy and

safety of Xeomin in the treatment of poststroke spasticity of the upper limb. For patients who had previously received botulinum toxin treatment in any body region, Study 1 and Study 2 required that ≥ 12 months and ≥ 4 months, respectively, had passed since the most recent botulinum toxin administration. (4)

Study 1 consisted of a 12-week main phase followed by three 12-week OLEX treatment cycles for a total exposure duration of 48 weeks. The study included 317 treatment-naïve patients who were at least three months poststroke in the main study period (210 Xeomin and 107 placebo). During the main period, Xeomin (fixed total dose of 400 units) and placebo were administered intramuscularly to the defined primary target clinical pattern chosen from among the flexed elbow, flexed wrist, or clenched fist patterns and to other affected muscle groups. 296 treated patients completed the main phase and participated in the first OLEX cycle. Each OLEX cycle consisted of a single treatment session (Xeomin 400 units total dose, distributed among all affected muscles) followed by a 12-week observation period. (4)

Study 2 consisted of a 12 to 20-week main phase followed by an OLEX period of 48– 69 weeks for up to 89 weeks of exposure to Xeomin. The study included 148 treatment-naïve and pretreated patients with a confirmed diagnosis of poststroke spasticity of the upper limb who were at least six months poststroke (73 Xeomin and 75 placebo). During the main period, for each patient, the clinical patterns of flexed wrist and clenched fist were treated with fixed doses (90 units and 80 units, respectively). Additionally, if other upper limb spasticity patterns were present, the elbow, forearm and thumb muscles could be treated with fixed doses of Xeomin per muscle. 145 patients completed the main phase and participated in the OLEX period, during which time the dosing of each involved muscle could be adapted individually. During the main and OLEX periods, the maximum total dose per treatment session and 12-week interval was 400 units.

In Study 1, the primary efficacy variable was the change from baseline in Ashworth Scale (AS) score of the primary target clinical pattern determined by the investigator at the Week 4 visit. The AS is a clinical measure of the severity of spasticity by judging resistance to passive movement. The spasticity of the elbow flexors, wrist flexors, finger flexors, and thumb muscles as well as the forearm pronators was assessed on the 0 to 4-point AS at each visit. (4) The co-primary efficacy variable of Study 1 was GICS after 4 Weeks of treatment with Xeomin or placebo. The GICS is a global measure of a subject's functional improvement. Investigators were asked to evaluate the subject's global change in spasticity of the upper limb due to treatment, compared to the condition before the last injection. The response was assessed using a 7-point Likert scale that ranges from –3 (very much worse) to +3 (very much improved). Xeomin was considered to be superior to placebo in Study 1 only if statistical significance was reached in both the AS and GICS variables.

The primary efficacy results are displayed in Table 26.

Table 26. Efficacy Results by Patterns of Spasticity in Study 1, Week 4 (4)

	Mean Change in Ashworth Scale

	Xeomin (N=171)	**Placebo (N=88)**
Total Primary Target Clinical Pattern (flexed wrist, flexed elbow, and clenched fist)	-0.9	-0.5

N: number.
The analysis is based on Last Observation Carried Forward in the Intent To Treat population.
p<0.001

Upper Limb Spasticity in Pediatric Patients
Study 1 was a prospective, double-blind, dose-response, randomized, multi-center trial with an open-label extension period to evaluate the efficacy and safety of Xeomin for the treatment of upper limb spasticity in pediatric patients. Study 1 enrolled a total of 350 pediatric patients 2 to 17 years of age with upper limb spasticity in one or both upper limbs. In the double-blind main period of Study 1, patients were randomized to one of three dosages of Xeomin: 2 units/kg (maximum 50 units per upper limb), 6 units/kg (maximum 150 units per upper limb); or 8 units/kg (maximum 200 units per upper limb). The maximum dose, if both upper limbs were treated, respectively was 4 units/kg (maximum 100 units), 12 units/kg (maximum 300 units), or 16 units/kg (maximum 400 units). For treatment of flexed elbow, injection of biceps brachii was mandatory. The investigator could select 1 of the 2 other muscles contributing to spasticity of elbow flexion (i.e., brachialis and brachioradialis) for injection. For patients needing treatment for a flexed wrist, both the flexor carpi radialis and flexor carpi ulnaris were injected. Study 1 used a dose-response design, in which the two highest dosages of Xeomin (8 units/kg and 6 units/kg) were compared to the lowest dosage (2 units/kg), which served as control. In the absence of a placebo control, the efficacy of the 2 units/kg dosage of Xeomin could not be evaluated in Study 1.

The co-primary efficacy variables in Study 1 were the change from baseline on the Ashworth Scale for the primary clinical target pattern (i.e., elbow flexors or wrist flexors), and the GICS, both at Week 4. The GICS is a global measure of a subject's functional improvement based on a 7-point Likert scale that ranges from -3 = very much worse to +3 = very much improved.

The change from baseline in Ashworth Scale score was significantly greater for patients treated with Xeomin 8 units/kg than for patients treated with Xeomin 2 units/kg. The difference in GICS score between patients treated with Xeomin 8 units/kg and those treated with Xeomin 2 units/kg did not reach statistical significance. However, the clinical meaningfulness of the difference in Ashworth Scale score changes between patients treated with Xeomin 8 units/kg and those treated with Xeomin 2 units/kg was established by a responder analysis, in which the proportion of patients with a 1-point change or greater on the Ashworth Scale was examined. In that analysis, 86% of patients treated with Xeomin 8 units/kg met the responder definition, compared to 71% of patients treated with Xeomin 2 units/kg (nominal p value = 0.0099).

There was no significant difference in change from baseline in Ashworth Scale score, GICS score, or proportion of responders between patients treated with Xeomin 6 units/kg and those

treated with Xeomin 2 units/kg. Therefore, the efficacy of a 6 units/kg dosage of Xeomin for the treatment of upper limb spasticity in pediatric patients was not established in Study 1.

Cervical Dystonia
Xeomin has been investigated in a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in a total of 233 patients with cervical dystonia. Patients had a clinical diagnosis of predominantly rotational cervical dystonia, with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥20, TWSTRS severity score ≥10, TWSTRS disability score ≥3, and TWSTRS pain score ≥1. For patients who had previously received a botulinum toxin treatment for cervical dystonia, the trial required that ≥10 weeks had passed since the most recent botulinum toxin administration. Patients with swallowing disorders or any significant neuromuscular disease that might interfere with the study were excluded from enrollment. Patients were randomized (1:1:1) to receive a single administration of Xeomin 240 units (n=81), Xeomin 120 units (n=78), or placebo (n=74). Each patient received a single administration of 4.8 mL of reconstituted study agent (Xeomin 240 units, Xeomin 120 units, or placebo). The investigator at each site decided which muscles would receive injections of the study agent, the number of injection sites, and the volume at each site. The muscles most frequently injected were the splenius capitis/semispinalis, trapezius, sternocleidomastoid, scalene, and levator scapulae muscles. (4)

Most patients received a total of 210 injections into the selected muscles. Patients were assessed by telephone at one-week postinjection, during clinic visits at Weeks 4 and 8, and then by telephone assessments or clinic visits every two weeks up to Week 20. (4)

The mean age of the study patients was 53 years, and 66% of the patients were women. At study baseline, 61% of patients had previously received a botulinum toxin as treatment for cervical dystonia. The study was completed by 94% of study patients. Three patients discontinued the study prematurely due to adverse events: two patients in the 240-unit group experienced musculoskeletal pain and muscle weakness, and one patient in the 120-unit group experienced nausea and dizziness. (4)

The primary efficacy endpoint was the change in the TWSTRS total score from baseline to Week 4 postinjection, in the intent-to-treat (ITT) population, with missing values replaced by the patient's baseline value. In the ITT population, the difference between the Xeomin 240-unit group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was 9.0 points, 95% confidence interval (CI) 12.0; 5.9 points; the difference between the Xeomin 120-unit group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was 7.5 points, 95% CI 10.4; 4.6 points.

Comparison of each Xeomin group to the placebo group was statistically significant at $p<0.001$. Initial Xeomin doses of 120 units and 240 units demonstrated no significant difference in effectiveness between the doses. The efficacy of Xeomin was similar in patients who were botulinum toxin naïve and those who had received botulinum toxin prior to this study. (4)

Blepharospasm

The efficacy and safety of Xeomin for the treatment of blepharospasm in treatment-naïve patients were evaluated in Study 1, a randomized, double-blind, placebo-controlled, multicenter trial in a total of 61 patients. Patients had a clinical diagnosis of blepharospasm, with a baseline Jankovic Rating Scale (JRS) severity subscore ≥2. Patients were defined as treatment-naïve if at least 12 months had passed since their last botulinum toxin treatment for blepharospasm. During the placebo-controlled phase, a fixed total dose of 25 Units Xeomin (n=22), 50 Units Xeomin (n=19), or placebo (n=20) was administered intramuscularly at 6 injection sites per eye. Of the 61 patients randomized, 55 patients completed the placebo-controlled phase. Patients only continued to the open-label extension (OLEX) period if they had a confirmed need for a reinjection by week 20 of the placebo-controlled phase. A total of 39 patients entered and completed the OLEX phase. (4)

The primary efficacy variable was the change from baseline in JRS Severity subscore determined at Week 6 after the injection. The 50 Unit treatment group demonstrated statistically significant improvements compared to placebo, with a difference of 1.2 (p=0.0004). The change from baseline in the JRS Severity subscore for the 25-unit treatment group 6 weeks after the injection was not statistically significant, with a difference of 0.5 (p=0.1452) compared to placebo. (4)

The efficacy and safety of Xeomin for the treatment of blepharospasm patients pretreated with onabotulinumtoxinA (Botox) were evaluated in Study 2, a randomized, double-blind, placebo-controlled, multicenter trial in a total of 109 patients. Patients had a clinical diagnosis of benign essential blepharospasm, with baseline JRS Severity subscore ≥2, and a stable satisfactory therapeutic response to previous administrations of onabotulinumtoxinA (Botox). At least 10 weeks had to have elapsed since the most recent onabotulinumtoxinA administration. Patients with any significant neuromuscular disease that might interfere with the study were excluded from enrollment. Patients were randomized (2:1) to receive a single administration of Xeomin (n=75) or placebo (n=34). Each patient in the Xeomin group received a Xeomin treatment (dose, volume, dilution, and injection sites per muscle) that was similar to the most recent onabotulinumtoxinA injection sessions prior to study entry. (4)

Patients were assessed during clinic visits at Weeks 3 and 6, and then by telephone or at clinic visits every two weeks up to Week 20.

The mean age of the study patients was 62 years, and 65% of the patients were women. The study was completed by 94% of study patients. Approximately one third of patients had other dystonic phenomena; in all but 1% this was limited to facial, cervical, perioral and mandibular muscles. No patients discontinued the study prematurely due to adverse events.

The primary efficacy endpoint was the change in the JRS Severity subscore from baseline to Week 6 postinjection, in the ITT population, with missing values replaced by the patient's most recent value (i.e., last observation carried forward). In the ITT population, the difference between the Xeomin group and the placebo group in the change of the JRS Severity subscore

from baseline to Week 6 was 1.0 (95% CI 1.4; 0.5) points. Comparison of the Xeomin group to the placebo group was statistically significant at p<0.001. (4)

RimabotulinumtoxinB (Myobloc®)

FDA-Labeled Indications

Cervical Dystonia

Two Phase 3, randomized, multi-center, double-blind, placebo-controlled studies of the treatment of cervical dystonia were conducted (Study 1 and Study 2). Both studies enrolled only adult patients who had a history of receiving botulinum toxin type A in an open-label manner, with a perceived good response and tolerable adverse effects. Study 1 enrolled patients who were perceived as having an acceptable response to type A toxin, while Study 2 enrolled only patients who had secondarily lost responsiveness to type A toxin. Other eligibility criteria common to both studies were that all patients had moderate or greater severity of cervical dystonia with at least 2 muscles involved, no neck contractures or other causes of decreased neck range of motion, and no history of any other neuromuscular disorder. Patients in Study 1 were randomized to receive placebo, Myobloc 5,000 units or Myobloc 10,000 units. Patients in Study 2 were randomized to receive placebo or 10,000 units of Myobloc. The study agent was administered to subjects in a single treatment session by investigators who selected 2 to 4 muscles per subject from the following: splenius capitis, sternocleidomastoid, levator scapulae, trapezius, semispinalis capitis, and scalene muscles. The total dose was divided between the selected muscles, and from 1 to 5 injections were made per muscle. There were 109 patients enrolled into Study 1, and 77 into Study 2. Patient evaluations continued for 16 weeks post.
injection. (5)

The primary efficacy outcome variable for both studies was the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total Score (scale range of possible scores is 0–87) at Week 4. TWSTRS is comprised of three sub-scales which examine 1) Severity—the severity of the patient's abnormal head position; 2) Pain—the severity and duration of pain due to the dystonia; and 3) Disability—the effects of the abnormal head position and pain on a patient's activities. The secondary endpoints were the Patient Global and Physician Global Assessments of change at Week 4. Both Global Assessments used a 100-point visual-analog scale (VAS). The Patient Global Assessment allows patients to indicate how they feel at the time of their evaluation compared to the pre-injection baseline. Likewise, the Physician Global Assessment indicates the physician's assessment of a patient's change from baseline to Week 4. Scores of 50 indicate no change, 0 much worse, and 100 much better. (5)

There were no statistically significant differences in results between the 5,000 unit and 10,000-unit doses in Study 1. Exploratory analyses of these two studies suggested that the majority of patients who showed a beneficial response by Week 4 had returned to their baseline status between Weeks 12 to 16 post injection. Although there was a Myobloc-associated decrease in pain, there remained many patients who experienced an increase in dystonia-related neck pain irrespective of treatment group. TWSTRS Total Score at Week 4 and Patient Global Assessment among subgroups by gender or age showed consistent treatment-associated effects across

these subgroups. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets. (5)

Myobloc was studied in two Phase 2 dose-ranging studies, Studies 3 and 4, which preceded the Phase 3 studies. Studies 3 and 4 had a study design similar to the Phase 3 studies, including eligibility criteria. Study 3 enrolled 85 patients randomized to placebo, Myobloc 400 units, Myobloc 1,200 nits, or Myobloc 2,400 units (21 or 22 patients per group). Study 4 enrolled 122 patients randomized to placebo, Myobloc 2,500 units, Myobloc 5,000 units, or Myobloc 10,000 units (30 or 31 patients per group). These studies demonstrated efficacy on the TWSTRS-Total, baseline to Week 4, at doses of 2,400 units; 2,500 Units; 5,000 units; and 10,000 units. Study 3 showed mean improvement from baseline on the Week 4 TWSTRS for placebo and 2,400 units of 2.0 and 8.5 points respectively (from baselines of 42.0 and 42.4 points). Study 4 showed mean improvement from baseline to Week 4 for placebo, Myobloc 2,500 units, Myobloc 5,000 units, and Myobloc 10,000 units of 3.3, 11.6, 12.5, and 16.4 points, respectively (from baseline of 45.5, 45.6, 45.2, and 47.5 points). Study 3 also showed less response for doses below 2,400 units. (5)

Study 5 was an open-label, intrapatient dose-escalation study of 3 treatment sessions where each patient with cervical dystonia sequentially received 10,000 units; 12,500 units; and 15,000 units of Myobloc, at periods of 12 to 16 weeks between treatment sessions irrespective of their response to their previous dose. This study enrolled 145 patients, of whom 125 received all three treatments. Although this was an open-label design where investigators and patients knew the dose at each treatment session, there were similar mean improvements on the TWSTRS-Total, from baseline to Week 4, for all three doses. In the Myobloc-treated patients (n=112) of the Phase 3 studies, 19% had 2 muscles injected, 48% had 3 muscles injected, and 33% had 4 muscles injected. (5)

Chronic Sialorrhea

Study 1 (NCT01994109) was a multicenter, randomized, double-blind, placebo-controlled study of a single treatment of chronic sialorrhea (with 13-week follow-up), followed by an open-label treatment period. 187 adult patients with chronic, troublesome sialorrhea for at least 3 months were randomized to receive treatment with Myobloc 2,500 units, Myobloc 3,500 units, or placebo. Patients had chronic sialorrhea associated with Parkinson's disease (n=122), amyotrophic lateral sclerosis (ALS; n=12), stroke (n=13), and other causes (n=40). Patients with a history of aspiration or severe dysphagia in the last 6 months and ALS patients with a forced vital capacity of less than 20% of predicted were excluded from the study. A single treatment was administered, consisting of bilateral injections of Myobloc into the parotid (1,000 units or 1,500 units per gland) and submandibular (250 units per gland) salivary glands or volume matched placebo. A total of 114 patients received 4 consecutive treatments with 3,500 units of Myobloc every 11 to 15 weeks. (5)

The co-primary efficacy endpoints for Study 1 were the change from baseline in Unstimulated Salivary Flow Rate (USFR) and the Clinical Global Impression of Change (CGI-C) assessed 4 weeks after treatment in the double-blind part of the study. The CGI-C is a seven-point Likert

scale with scores ranging from “1=very much improved” to “7=very much worse.” The change from baseline (i.e., decrease) in USFR at Week 4 was significantly greater for patients treated with Myobloc than in patients on placebo. Similarly, CGI-C scores at Week 4 were significantly lower (i.e., better) in patients treated with Myobloc than in patients on placebo. Chronic sialorrhea was ‘much improved’ or ‘very much improved’, according to CGI-C scores at Week 4 post injection, in patients treated with Myobloc 2,500 units (60%) and Myobloc 3,500 units (53%) than in patients on placebo (12%). (5)

Study 2 (NCT00515437) was a multicenter, double-blind, placebo-controlled, sequential dose-escalation study of Myobloc 1,500 units; 2,500 units; or 3,500 units versus matching placebo for the treatment of troublesome chronic sialorrhea in patients with Parkinson’s disease. Patients were randomized to receive a single treatment with Myobloc 1,500 units (n=14); Myobloc 2,500 units (n=12); or Myobloc 3,500 units (n=13). Each group also included 5 patients who received placebo (n=15). Patients were followed for up to 20 weeks after injection. The mean age of patients in the study was 71 years. In the study, 89% of patients were male, and 96% white.

The change from baseline in the unstimulated salivary flow rate (USFR) and the Clinical Global Impression of Change (CGI-C) was assessed 4 weeks after treatment. There was a significant reduction in the USFR for all three dosage groups of Myobloc, compared with patients on placebo. Similarly, the CGI-C scores were significantly lower in all three Myobloc dosage groups than in patients on placebo. The mean change from baseline to Week 4 on the USFR was similar in all three Myobloc dosage groups. (5)

DaxibotulinumtoxinA-lanm (Daxxify®)

FDA-Labeled Indications

Cervical Dystonia

The efficacy of Daxxify was evaluated in a randomized, double-blind, placebo-controlled, multicenter trial in a total of 301 patients (NCT03608397). (6) The mean age of patients was 58 years, 65% were women, and 96% were White. At study baseline, 84% of patients had previously received a botulinum toxin as treatment for cervical dystonia. Patients had a clinical diagnosis of cervical dystonia with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥20, TWSTRS severity score ≥15, TWSTRS disability score ≥3, and TWSTRS pain score ≥1. For patients who had previously received a botulinum toxin treatment for cervical dystonia, the trial required that ≥14 weeks had passed since the most recent botulinum toxin administration. Patients were randomized (3:3:1) to receive a single administration of 2.5 mL of either Daxxify 125 Units (n=125), Daxxify 250 Units (n=130), or placebo (n=46), divided amongst the affected muscles as selected by the investigator. Table 27 indicates the treated muscles, along with the number of patients treated and Daxxify units.

Table 27. Summary of Muscles Treated in Each Daxxify Treatment Group (6)

Unilateral Muscle Injected	**Daxxify 125 Units**		**Daxxify 250 Units**	
	Number of patients	**Medical Units (min, max)**	**Number of patients**	**Median Units (min, max)**

Levator Scapulae	106	20 (10, 30)	105	50 (20, 60)
Longissimus Capitis and Cervices	45	15 (10, 30)	58	40 (20, 60)
Scalenus Complex	55	15 (10, 15)	44	30 (20, 30)
Splenius Capitis	120	25 (10, 50)	127	50 (20, 100)
Splenius Cervices	65	20 (10, 50)	71	40 (20, 100)
Sternocleidomastoid	115	25 (10, 25)	121	50 (20, 50)
Trapezius	105	20 (15, 40)	105	40 (30, 80)

The primary efficacy endpoint was the mean change in the TWSTRS total score from baseline averaged over weeks 4 and 6. (6) TWSTRS evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain, with a range of possible scores from 0 to 85. The mean change from baseline in the total TWSTRS score was significantly greater for both dosage groups of Daxxify than for placebo (Table 28).

Table 28. Change in TWSTRS Score Averaged over Weeks 4 and 6 in Patients with Cervical Dystonia (6)

TWSTRS Assessment	Placebo (N=46)	DAXI 125 U (N=125)	DAXI 250 U (N=130)
Baseline mean	45.3	43.1	42.6
Least squares mean change from baseline	-4.3	-12.7	-10.9
Least squares mean difference from placebo (95% CI)		-8.4 (-12.2, -4.6)	-6.6 (-10.4, -2.8)
p-value		<0.0001	0.0007

CI: confidence interval; DAXI: Daxxify; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; U: units.

A similar pattern of significant improvement versus placebo was observed in the clinician global impression of change (CGIC) and patient global impression of change (PGIC) scales.

Botulinum Toxin Use in Other Conditions

Neurological Indications

Tension and Cervicogenic Headache

The meta-analysis by Jackson et al. (2012) identified 8 RCTs evaluating onabotulinumtoxinA (6 trials) and abobotulinumtoxinA (2 trials) for treating chronic tension-type headaches; all were placebo-controlled. (35) A pooled analysis of these 8 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group vs the placebo group (difference = -1.43; 95% CI, -3.13 to 0.27; p-value=0.02). Silberstein et al. (2006) (36) randomized 300 patients to onabotulinumtoxinA (5 different doses) or placebo for the prophylaxis of chronic tension-type headache. The trial failed to demonstrate statistically significant difference between the onabotulinumtoxinA groups and the placebo group in the number of headache free days per month.

Multiple RCT's (37-40) with smaller sample size (<50) have evaluated the efficacy of onabotulinumtoxinA in patients with cervicogenic headache but either reported a lack of treatment benefit (37, 38, 40) or were methodological flawed (pain scores imbalanced at baseline) to derive meaningful conclusions. (39)

Essential Tremor

Botulinum toxin type A (BoNT-A) have been shown to provide benefit for limb tremor associated with essential tremor but have been associated with dose-dependent hand weakness. A systematic review published in 2011 (41) concluded that botulinum toxin A is possibly effective for the treatment of essential hand tremor, with a beneficial effect that was modest at best. The conclusion was drawn on the basis of 2 double-blind, placebo-controlled, parallel-design trials of botulinum toxin type A; one enrolled 25 patients and the other enrolled 133 patients. In the first trial, 11 of 12 treated patients reported mild (50%) or moderate (42%) wrist or finger weakness. (42) In the second trial, symptomatic hand weakness occurred in 30% of the low-dose group and 70% of the high-dose group. Neither the investigators nor the patients reported any subjective benefit, and there was minimal (0.5 points) change at six weeks. (43) Subsequent to this systematic review, Mittal et al. (2017) published the results of a small, randomized trial of 30 patients with essential tremor and Parkinson disease tremor to incobotulinumtoxinA in a crossover design. (44) Statistically significant improvements in clinical rating scores of rest tremor and tremor severity at four and eight weeks were reported in the treated patients and of action/postural tremor at eight weeks; however, there was no statistically significant difference in grip strength at four weeks between the two groups. The clinical significance of small benefits observed in trials that were offset by frequent adverse effects (hand weakness) do not permit conclusions about net heath benefit. A larger trial with longer term follow-up is required to replicate these findings and provide long-term follow-up to mitigate the risk of developing hand weakness over the course of time.

Tinnitus

Slengerik-Hansen et al. (2016) reported the findings of a systematic review that included 22 studies, mainly case reports and case series with a total of 51 treated patients treated with onabotulinumtoxinA for the treatment of tinnitus. (45) A small (n=30) cross over prospective study by Stidham et al. (2005) reported a statistically significant decrease in tinnitus handicap inventory scores between pretreatment and 4-month post-botulinum toxin A injection. (46) Multiple other outcomes studies showed no difference. Well-conducted RCTs with sufficiently large sample sizes are needed.

Trigeminal Neuralgia

Evidence for the efficacy and safety of botulinum toxin A for trigeminal neuralgia is limited and was summarized by Morral et al. (2016) in a systematic review that included 4 RCTs (n=178 patients). (47) The largest trial randomly assigned 80 patients to either botulinum toxin A or placebo. While the meta-analysis reported significant reductions in mean pain scores and attack frequency in the botulinum toxin A compared with the placebo group, there are concerns about small patient numbers, limited durability and quality of evidence.

Urological Indications

Benign Prostatic Hyperplasia

Marchal et al. (2012) reported the results of a systematic review on use of onabotulinumtoxinA and abobotulinumtoxinA to treat benign prostatic hyperplasia. (48) Two clinical trials with sufficient quality were selected for meta-analysis reported no difference in pre- and post-treatment of maximum flow, prostate volume, International Prostate Symptom Score and prostate-specific antigen post-voiding residue.

Interstitial Cystitis

The mechanism of the effect of Intradetrusor botulinum toxin therapy for interstitial cystitis is likely the ability of botulinum toxin to modulate sensory neurotransmission. While botulinum toxin has been shown to alleviate symptoms in multiple studies (49-51) mostly conducted outside of the U.S., there is a risk of urinary retention (50) which may be particularly devastating for a patient with a painful bladder and therefore any patient considering this treatment must be willing and able to perform intermittent self-catheterization.

The American Urological Association published guidelines for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome in 2011 based on a systematic review that included published evidence from January 1, 1983, to July 22, 2009. (52) The guideline is updated periodically by conducting incremental systematic reviews to maintain guideline currency with newly published relevant literature. Most recently, an updated literature review in 2022 (search dates, June 2013 to January 2021) was published. (53) In addition, multiple systematic reviews have been published. (54-57) There is large variability in the botulinum toxin type, dosage, frequency and site of injection and comparators among the RCTs included in the systematic reviews. Further, several studies appear to include overlapping patient groups. These limitations make it challenging to interpret the results of these meta-analysis.

Pain Due to Multiple Etiologies

Lateral Epicondylitis

Although the mechanism for action for botulinum toxin in epicondylitis is not clearly understood, it is thought to be as “proinflammatory.” Botulinum toxin has been evaluated as a treatment for epicondylitis in a number of RCTs as summarized in a number of systematic reviews. (58-60) In the systematic review and meta-analysis published by Lin et al. (2018), authors included 6 RCTs (n=321) that comparing onabotulinumtoxinA or abobotulinumtoxinA with placebo or corticosteroid injections in patients with lateral epicondylitis. (58) Four of the 6 trials enrolled less than 30 participants per treatment arm and allocation concealment was unclear in 4 out of 6 trials. Results were reported as standardized mean differences and a negative number implied a favorable effect of botulinum toxin on pain reduction.

Compared with placebo, botulinum toxin injection significantly reduced pain at all 3 time-points 2 to 4 weeks, 8 to 12 weeks and at 16 weeks or more; standardized mean difference -0.73 (-1.29 to -0.17), -0.45 (-0.74 to -0.15) and -0.54 (-0.99 to -0.11) respectively. In contrast, botulinum toxin was significantly less effective than corticosteroid 2 to 4 weeks following

injection; standardized mean difference 1.15 (0.57 to 1.34) with no difference at 8-12 weeks or 16 weeks or more time point. While the systematic reviews generally report pain relief in individual trials of botulinum toxin vs the comparator, treatment with botulinum toxin was associated with temporary paresis of finger extension.

Myofascial Pain Syndrome

Several systematic reviews of RCTs have evaluated onabotulinumtoxinA and abobotulinumtoxinA for myofascial pain syndrome. The Cochrane systematic review by Soares et al. (2014) identified 4 placebo controlled, double-blind RCTs that included 233 participants with myofascial pain syndrome excluding neck and head muscles. (61) Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the four studies found that botulinum toxin did not significantly reduce pain intensity. Major limitations included high-risk of bias due to study size in three of the four studies and selective reporting in one study. Two other systematic reviews that focused on myofascial pain syndrome involving head and neck muscles reported similar findings. Systematic review by Desai et al. (2014) included 7 trials that evaluated the efficacy of botulinum toxin type A in cervico-thoracic myofascial pain syndrome. (62) Majority of studies found negative results and except for one, six identified trials had significant failings due to deficiencies in one or more major quality criteria.

Low Back Pain

Foster et al. (2001) reported the findings of an RCT in which 31 consecutive patients with chronic low back pain of at least 6 months in duration were randomized to onabotulinumtoxinA or saline. (63) Botulinum toxin A was superior to placebo injection for pain relief and improved function at 3 and 8 weeks (50 % pain relief at 3 weeks 73.3 vs 25%; at 8 weeks 60 vs 16%, respectively). However, in most patients, benefits were no longer present after three to four months. These results should be considered preliminary, and further data from randomized trials are needed to confirm findings in a larger number of patients over a longer duration and to evaluate benefits and harms of repeated injections before this treatment can be recommended.

Temporomandibular Joint Disorders

Chen et al. (2015) summarized the evidence assessing the efficacy of botulinum toxin A for treatment of temporomandibular joint disorders in a systematic review that included 5 RCTs. (64) Sample size in majority of trials was 30 or less except for 1. Three of the five studies were judged to be at high-risk of bias. All studies administered a single injection of onabotulinumtoxinA or abobotulinumtoxinA and followed patients up at least one month later. Four studies used a placebo (normal saline) control group and the fifth used abobotulinumtoxinA to fascial manipulation. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, two of the five trials found a significant short-term (1-2 months) benefit of onabotulinumtoxinA compared with control on pain reduction.

Post Hemorrhoidectomy Pain

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A trial by Patti et al. (2005) randomized 30 patients to onabotulinumtoxinA 20 U or saline injection and reported a significantly shorter duration of postoperative pain at rest and during defecation in the treated group. (65) A trial by Patti et al. (2006), which also included 30 patients, found significant differences in postoperative maximum resting pressure change from baseline with onabotulinumtoxinA vs topical glyceryl trinitrate ($p<0.001$). (66) In addition, there was a significant reduction in postoperative pain at rest ($p=0.01$) but not during defecation. There was no difference in healing.

Pelvic and Genital Pain in Women

One double-blind, randomized, placebo-controlled trial by Abbott et al. (2006) evaluated 60 women with chronic pelvic pain and pelvic floor spasm. (67) Patients received injections of onabotulinumtoxinA or placebo. Pain scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups.

Ano-Rectal Conditions

Internal Anal Sphincter Achalasia

Friedmacher and Puri (2012) reported results of a meta-analysis that included 395 patients from 2 prospective and 14 retrospective case series that compared internal anal sphincter myectomy (n=229) with botulinum A injection (n=166). (68) Regular bowel movements (odds ratio [OR]=0.53; 95% CI, 0.29 to 0.99, $p = 0.04$), short-improvements (OR=0.56; 95% CI, 0.32 to 0.97, $p = 0.04$) and long-term improvement (OR=0.25; 95% CI, 0.15 to 0.41, $p < 0.0001$) favored myectomy compared with botulinum toxin A injection. Further, rate of transient fecal incontinence (OR=0.07, 95% C,I 0.01 to 0.54; $p < 0.01$), rate of non-response (OR 0.52, [95% CI 0.27-0.99]; $p=0.04$) and subsequent surgical treatment (OR 0.18, [95% CI, 0.07-0.44]; $p < 0.0001$) was significantly higher with botulinum A injection compared with myectomy. There was no significant difference in continued use of laxatives or rectal enemas, overall complication rates, constipation and soiling between the two procedures. Authors concluded that myectomy was more effective treatment option compared with intrasphincteric botulinum toxin A injection.

Anismus

Emile et al. (2016) reported on the results of a systematic review that assessed 7 studies comprising 189 patients with a follow-up period greater than 6 months in each study. (69) Of the seven studies, two were RCTs and the others comparative and observational studies. Both RCTs were from a single site from the same author group and conducted in Egypt, enrolling 15 and 24 patients, respectively. (70, 71) Improvement was defined as patients returning to their normal habits. The first RCT used biofeedback and the other used surgery as the comparator. In the first RCT, 50% of individuals in the biofeedback group reported improvement initially at 1 month but it dropped down to 25% by the end of year. The respective proportions of patients in the botulinum toxin arm were 70.8% and 33.3%. In the second RCT, surgery improved outcomes in all patients at 1 month but that percentage dropped to 66.6% at 1 year. The respective proportions of patients in the botulinum toxin arm were 87% and 40%, respectively.

While these results would suggest temporary improvement, methodologic limitations, including small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

Other Populations

Gastroparesis

A systematic review by Bai et al. (2010) identified 15 studies on onabotulinumtoxinA to treat gastroparesis. (72) Two studies were RCTs; the remainder was case series or open-label observational studies. Reviewers stated that, while the nonrandomized studies generally found improvements in subjective symptoms and gastric emptying after onabotulinumtoxinA injections, the RCTs (73, 74) did not report treatment benefit with onabotulinumtoxinA for treating gastroparesis. The 2 RCTs were inadequately powered RCTs; one included 23 patients and the other included 32 patients. Additional adequately powered RCTs are needed.

Depression

Magid et al. (2015) published a pooled analysis (75) of individual patient data from 3 randomized trials (76-78) evaluating injections of onabotulinumtoxinA in the glabellar region (forehead) for treating unipolar major depressive disorder as an adjunctive treatment. The response rate (defined as ≥ 50% improvement from baseline scores in the depression score) was higher in the onabotulinumtoxinA group compared with placebo (54.2% vs 10.7%; OR=11.1; 95% CI, 4.3 to 28.8). The respective remission rate (defined as score ≤ 7 for the Hamilton Depression Rating scales, ≤ 10 for the Montgomery-Asberg Depression Rating Scale) was 30.5% vs 6.7% (7.3; 95% CI, 2.4 to 22.5). While the effect size of the treatment observed in the pooled analysis and individual RCTs is clinically meaningful and large, there are multiple limitations that preclude drawing meaningful conclusions about net health benefit. Limitations in study design and conduct include potential of unblinding due to changes in cosmetic appearance, small sample size, lack of power analysis, (77) short duration of follow-up in two out of three RCTs, (76, 77) lack of clarity on allocation concealment (76-78) and lack of ITT analysis. More importantly, patients with a history of major depressive order presenting with acute depression episode prior to enrollment in the trial were evaluated, it is unclear if botulinum toxin A treatment is intended to be used as a short-term treatment of a depressive episode or as a maintenance treatment for depression. Further, a large trial (NCT02116361) with 258 patients to evaluate the efficacy of OnabotulinumtoxinA as treatment for major depressive disorder in adult females was completed in 2016 but has not been published which raises concerns about potential for publication bias.

Facial Wound Healing

Ziade et al. (2013) reported results of an RCT in which 30 adults presenting to the emergency department with facial wounds without tissue loss were assigned to single an injection of onabotulinumtoxinA (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds. (79) Scars were assessed at a one-year follow-up visit by patients, an independent evaluator as well as board of six experienced medical specialists. There were no significant differences between the two groups in multiple outcomes that were assessed. Limitations of the study included relatively small sample size, lost to follow-up of 20% patients and lack of patients blinding. Gassner et al. (2006) reported the results of another RCT that randomized 31

patients to onabotulinumtoxinA- or placebo-induced immobilization of facial lacerations to improve wound healing. (80) Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analog scale at six months served as the main outcome measure. The difference in visual scores was 8.9 in the treatment arm vs 7.2 in the placebo arm (p=0.003). Limitations of the study included a single-institution study, relatively small sample size, lack of clarity on number screened/randomized/excluded from the final analysis.

Section Summary: Botulinum Toxin Use in Other Conditions

Botulinum toxin has been evaluated as a treatment option for multiple neurological, urological, pain, ano-rectal and miscellaneous clinical indications. Generally, botulinum toxin has been evaluated in clinical settings where patients have failed the standard of care or in whom standard of care interventions are contraindicated. However, in multiple indications with high prevalence rates such as benign prostate hyperplasia, low back pain, depression, tinnitus etc. where multiple effective treatments supported by adequate quality evidence base are available, studies using a placebo comparator that lack scientific rigor do not permit conclusions about net health benefit of botulinum toxin. Future studies in these clinical indications should use appropriate comparators in adequately powered prospective studies using standardized dose of treatment and adequate follow-up.

Practice Guidelines and Position Statements

American Urological Association

In 2019, the American Urological Association guideline on non-neurogenic overactive bladder stated, “clinicians may offer intradetrusor onabotulinumtoxinA (100U) as a third-line treatment in the carefully selected and thoroughly counseled patient who has been refractory to first- and second-line overactive bladder treatments. The patient must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. Standard (Evidence Strength Grade B).” (81)

In 2022, the American Urological Association guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome stated, “intradetrusor botulinum toxin A may be administered if other treatments have not provided adequate symptom control and quality of life or if the clinician and patient agree that symptoms require this approach. Patients must be willing to accept the possibility that post-treatment intermittent self-catheterization may be necessary. Option (Evidence Strength C).” (53) Options are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; options may be supported by Grade A (high certainty), B (moderate certainty), or C (low certainty) evidence.

American Academy of Neurology

The American Academy of Neurology updated their practice guideline on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache in 2016 (reaffirmed April 30, 2022). (82) Recommendations are summarized in Table 29.

Table 29. Recommendations for Use of Botulinum Toxin to Treat Various Disorders

Recommendation	LOR
Blepharospasm	
• OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered • AbobotulinumtoxinA may be considered	B C
Cervical dystonia	
• AbobotulinumtoxinA and rimabotulinumtoxinB should be offered • OnabotulinumtoxinA and incobotulinumtoxinA should be considered	A B
Focal manifestations of adult spasticity involving the upper limb	
• AbobotulinumtoxinA, incobotulinumtoxin A, and onabotulinumtoxinA should be offered • RimabotulinumtoxinB should be considered as treatment options • OnabotulinumtoxinA should be considered as a treatment option before tizanidine for treating adult upper-extremity spasticity	A B B
For focal manifestations of adult spasticity involving the lower limb	
• OnabotulinumtoxinA and abobotulinumtoxinA should be offered as treatment options • There is insufficient evidence to support or refute a benefit of incobotulinumtoxinA or rimabotulinumtoxinB for treatment of adult lower-limb spasticity	A
Headache	
• To increase the number of headache-free days, onabotulinumtoxinA should be offered as a treatment option to patients with chronic headaches • OnabotulinumtoxinA should be considered to reduce headache impact on health-related quality of life; chronic migraine refers to migraine attacks occurring 15 days or more monthly for at least 3 months, with attacks lasting 4 hours or more • OnabotulinumtoxinA should not be offered as a treatment for episodic migraines; episodic migraine refers to migraine with a lesser frequency of attack	A B A

LOR: level of recommendation.

In 2011 (reaffirmed April 30, 2022), the American Academy of Neurology updated its evidence-based guidelines that conclude botulinum toxin A is “possibly effective (Level C)” for treatment of essential tremor. (83)

American Society of Colon and Rectal Surgeon

The revision of a practice parameter on the treatment of anal fissures by the American Society of Colon and Rectal Surgeons (2023) states, “Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures, and modest improvement in healing rates as second-line therapy following treatment with topical therapies. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.” (84)

American Pediatric Surgical Association

In 2017, the American Pediatric Surgical Association published guidelines based on group discussions, literature review, and expert consensus for the management of postoperative obstructive symptoms in children with Hirschsprung disease. These guidelines recommend that if there is no mechanical obstruction and rectal biopsy is normal, botulinum toxin injection into the internal anal sphincter should be tried. If a patient shows significant improvement, the patient can receive botulinum toxin injection every 3 to 6 months as many times as necessary depending on symptoms. In most cases, the symptoms will gradually improve with age. (85)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member’s benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	31513, 31570, 31571, 43192, 43201, 43236, 46505, 52287, 64611, 64612, 64615, 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647, 64999, 67345
HCPCS Codes	C9160, J0585, J0586, J0587, J0588, S2340, S2341

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Added “OR a beta-3 adrenoceptor agonist” to the criteria statement on overactive bladder under onabotulinumtoxinA; 2) Updated cosmetic statement for Xeomin; and 3) Updated cosmetic statement for Botox Cosmetic. No new references added; some updated.
05/15/2024	Document updated with literature review. The following change was made to Coverage: Added coverage statement for daxibotulinumtoxinA-lamn (Daxxify®). Added/updated references: 1-6, 13, 25, 26, 29, 52-53, 56, 57, and 81-85.
01/15/2023	Reviewed. No changes.
11/15/2021	Document updated with literature review. The following changes were made to Coverage: 1) For Botox: a) Added new FDA label indication for neurogenic

	detrusor overactivity in pediatric patients, b) Updated language for spasticity based on new FDA label language, c) Removed statement that required that Botox not be used in combination with preventative calcitonin gene-related peptide inhibitors, and d) Removed list of spastic conditions from off-label section due to update of labeled indications; 2) For Dysport: a) Updated language for spasticity based on new FDA label language, and b) Removed "spasticity related to cerebral palsy or stroke" from off-label section due to update of labeled indications; and 3) For Xeomin: a) Updated language for use in upper limb spasticity in pediatric patients based on new FDA label language, b) Modified chronic sialorrhea to include pediatric patients as well as adults, and c) Removed NOTE regarding no approved pediatric use. Added/updated the following references: 2-5, 12, 16, and 26.
10/01/2020	Document updated with literature review. The following changes were made to Coverage: 1) Modified label, off-label and experimental, investigational and/or unproven indications for onabotulinumtoxinA; 2) Added cosmetic statement for Botox® Cosmetic; 3) Modified label indications for abobotulinumtoxinA; 4) Modified cosmetic statement for abobotulinumtoxinA; 5) Modified label indications for incobotulinumtoxinA; 6) Modified cosmetic statement for incobotulinumtoxinA; 7) Modified label indications for rimabotulinumtoxinB, 8) Multiple NOTEs added and/or modified. Added/updated the following references: 1-5, 7-8, 10-18, 22, 25-32, 36, 39, 50, 70-72.
02/01/2018	Document updated with literature review. The following indications were added to the medically necessary off-label indications: auriculotemporal syndrome, benign prostatic hypertrophy, cervicogenic headache, chronic lower back pain, congenital esotropia, essential voice tremor, treatment of Hirschsprung disease for patients with functional obstruction caused by the inability of the internal anal sphincter to relax and who have undergone prior surgical treatment, granuloma of vocal cords refractory to conventional surgical and medical therapies, hemifacial spasm, idiopathic trigeminal neuralgia-refractory, myofascial pain syndrome, lateral humeral epicondylitis (tennis elbow) for patients who did not respond to conventional treatment, anismus (pelvic floor dyssynergia), treatment of pharyngoesophageal segment spasm following total laryngectomy, dystonia that is associated with one of the following hereditary, degenerative, or demyelinating diseases of the central nervous system, and that results in functional impairment (e.g., interference with joint function, mobility, communication, nutritional intake) and/or pain: 1) focal upper-limb dystonia and 2) cerebral Palsy with lower limb spasticity, tics associated with tourette syndrome, voice failure after tracheoesophageal puncture (TEP) and prosthesis placement in patients after total laryngectomy. In addition, criteria addressing initial trial and continuing treatment removed regarding prophylaxis of headaches in adult patients with chronic migraine.

11/01/2016	Document partially updated with the following new coverage indication for AbobotulinumtoxinA (Dysport™): "Lower limb spasticity in pediatric patients 2 years of age and older."
03/15/2016	Document updated with literature review. The following was added under the medically necessary FDA indications for OnabotulinumtoxinA (Botox®) 1) For, strabismus and blepharospasm the following wording was added: "…associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above". 2) For, upper limb spasticity in adults the following was added: "…thumb flexors (adductor pollicis and flexor pollicis longus". The following was added for AbobotulinumtoxinA (Dysport™) as a FDA approved medically necessary indication: "Adults with upper limb spasticity to decrease the severity of increased muscle tone in elbow flexors, wrist flexors and finger flexors". The following was added for IncobotulinumtoxinA (Xeomin®) as a medically necessary FDA approved indication: "Upper limb spasticity in adult patients." In addition, depression and temporomandibular joint disorders were added to the listing of experimental, investigational and/or unproven indications for OnabotulinumtoxinA (Botox®).
03/01/2015	Reviewed. No changes.
11/01/2014	Document updated with literature review. A.) The following were added to Coverage for OnabotulinumtoxinA: 1) Existing criteria for chronic migraine headache was defined as for the "Initial 6-month trial (typically one treatment every 12 weeks):", and 2) "Continuing treatment beyond the initial 6-months: a) Migraine headache frequency reduced by at least 7 days per month compared to pretreatment level, or b) Migraine headache duration reduced at least 100 hours per month compared to pretreatment level. B.) The following was added to Coverage for IncobotulinumtoxinA: 1) "IncobotulinumtoxinA (Xeomin®) is considered cosmetic for the FDA-labeled indication of treatment of wrinkles. NOTE: Special comment regarding cosmetic services: Check member's contract for benefit coverage. Determination of benefit coverage for procedures considered to be cosmetic is based on how a member's benefit contract defines cosmetic services and their eligibility for benefit coverage.
03/01/2013	Document updated with literature review. Coverage unchanged; however, coverage statements about overactive bladder (OAB) and urinary incontinence due to detrusor overactivity were moved from the off-label list of medically necessary indications to the FDA labeled indications list (FDA approved January 2013). Rationale was substantially updated. This document is no longer scheduled for routine literature review and update.
05/01/2012	Criteria requiring migraine headache to be "refractory to standard pain-relieving and preventive treatment, including nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergot, antidepressants (e.g., amitriptyline, nortriptyline, doxepin); antihypertensives (e.g., propranolol, timolol); and

	antiepileptics (e.g., valproate, topiramate, gabapentin)" was changed to: Migraine is refractory to at least two migraine prophylactic medications from different classes (e.g., tricyclic antidepressants, anticonvulsants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, or calcium channel blockers).
01/01/2011	Document updated with literature review. The following changes were made: 1) Medical necessity criteria was added for use of BotulinumtoxinA (Botox) for treatment of chronic migraine headache and upper limb spasticity. 2) BotulinumtoxinA (Botox) is considered experimental, investigational and unproven for treatment of vaginismus. 3) AbobotulinumtoxinA (Dysport™) may be considered medically necessary for the following off-label indications when criteria are met: a) Achalasia; b) Blepharospasm; c) Spasticity; d) Facial nerve (7^{th} cranial nerve) disorders; 4) IncobotulinumtoxinA (Xeomin®) may be considered medically necessary for the FDA-labeled indications of blepharospasm or cervical dystonia. 5) Definition of cervical dystonia was clarified.
10/15/2009	OnabotulinumtoxinA and/or RimabotulinumtoxinB may be considered medically necessary for treatment of sialorrhea associated with advanced Parkinson's disease.
09/01/2009	Revised to allow coverage of Dysport™ for new FDA-approved indication of cervical dystonia; Dysport is considered cosmetic for treatment of glabellar lines. Added new drug names that were established by the FDA August 1, 2009.
12/01/2008	Revised/updated entire document
08/15/2008	Pricing revised
10/01/2006	Coverage revised
10/01/2005	Revised/updated entire document
08/15/2006	Revised/updated entire document
09/01/2000	Revised/updated entire document
07/01/1999	Revised/updated entire document
10/01/1996	Revised/updated entire document
09/01/1996	Revised/updated entire document
05/01/1996	Revised/updated entire document
07/01/1994	Revised/updated entire document
04/01/1993	Revised/updated entire document
07/01/1992	Revised/updated entire document
03/01/1991	New medical document