Efficacy and Safety of a 2 mL Dilution of AbobotulinumtoxinA Compared With Placebo in Adult Patients With Cervical Dystonia

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Introduction

- Cervical dystonia (CD) is a chronic adult-onset movement disorder characterized by involuntary contractions of the cervical muscles of the neck[1]
- Symptoms include painful contractions or intermittent spasms of the neck muscles that result in abnormal head position[1,2]
- AbobotulinumtoxinA (aboBoNT-A; Dysport®, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA) is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the treatment of adults with CD[3]
- The efficacy and safety of aboBoNT-A for CD has been established in two randomized, controlled clinical trials and their open-label safety extensions, which have shown that treatment provides symptomatic relief, including improvement in head posture and reduction of pain[4,5]
- Clinical trial data supporting a 500 U/2 mL dilution would offer clinicians more flexibility with injection volume to better meet the needs of their patients with CD

Objective

- To determine efficacy and safety of a 500 U, 2 mL dilution of aboBoNT-A vs placebo in CD subjects

Methods

- The study was a 12-week phase IIIb multicenter, randomized, double-blind, placebo-controlled trial initiated in 43 centers (of which 38 recruited subjects) in the United States

Subjects

- Adult subjects with a primary diagnosis of CD at least 9 months since onset were eligible
- Subjects could be botulinum neurotoxin-naïve, or currently on treatment with onabotulinumtoxinA (ONA) if they had:
  - Received a total dose of 100 to 200 U, and ≤60 U of ONA in the sternocleidomastoid muscle, since the last injection cycle
  - A satisfactory treatment response during the last two sequential cycles of ONA within the past 18 months
  - Not received ONA for at least 12 weeks
- Non-naïve subjects may have received any other formulation of botulinum neurotoxin, including aboBoNT-A, prior to study entry as long as their last two injection sessions were with ONA and they had a satisfactory clinical response to both of those sessions
- Subjects must have had a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total score ≥20 and a TWSTRS-severity subscale score ≥10 at baseline
- Subjects were excluded if they had a diagnosis of pure retrocollis or pure anterocollis or if they anticipated concomitant treatment that may have interfered with the evaluation of study treatment

Study Design

- Study subjects were randomized in a ratio of 2:1 to receive either aboBoNT-A or placebo
- Randomization was stratified according to whether the subject was ONA treatment-naïve or had been successfully treated with ONA for CD

Treatment

- All subjects received a single intramuscular injection treatment of either aboBoNT-A or placebo
- Subjects randomized to the aboBoNT-A group received:
  - 500 U/2 mL of aboBoNT-A if they were ONA treatment-naïve; aboBoNT-A was injected into at least two clinically affected muscles
  - 250–500 U/2 mL of aboBoNT-A at a 2.5:1 ratio to their previous ONA dose into muscles injected during prior treatments

Endpoints

- The primary efficacy endpoint was change from baseline in TWSTRS total score at Week 4
- Secondary efficacy endpoints included:
  - Change in TWSTRS total score at Week 2
  - Clinical Global Impression of Change (CGIC) at Weeks 2 and 4
  - Treatment response at Weeks 2 and 4, defined as at least a 30% reduction in the TWSTRS total score after treatment
- Patient Global Impression of Change (PGIC) at Weeks 2 and 4 was a tertiary endpoint

Statistical Methods

- The estimated study sample size was calculated to demonstrate the superiority of aboBoNT-A to placebo assuming a minimum clinically relevant difference in the adjusted least squares mean change from baseline to Week 4 in TWSTRS total score between treatments of 5.5, a common standard deviation in the change from baseline in TWSTRS total score at Week 4 of 8.8, with a 90% power, a two-tailed type I error equal to 0.05, and a 10% dropout rate
- All statistical tests were performed two sided with a type I error rate set at 5%

Results

Study Populations

- The intent-to-treat (ITT) population (n=134) included all randomized subjects; the modified ITT (mITT) population (n=129) included randomized subjects with both a baseline and Week 4 post-treatment TWSTRS total score assessment
- A total of 134 subjects (aboBoNT-A, n=89; placebo, n=45) were randomized (ITT population) and 129 (aboBoNT-A, n=84; placebo, n=45) completed the Week 4 primary endpoint evaluation (mITT population)

Table 1. Baseline characteristics (ITT Population)

	AboBoNT-A, 2 mL n=89	Placebo n=45
Female gender, n (%)	59 (66.3)	28 (62.2)
Age (years; mean±SD)	57.3±11.11	56.5±11.74
Caucasian/white race, n (%)	84 (94.4)	42 (93.3)
Type of CD, n (%)		
Torticollis	75 (84.3)	39 (86.7)
Laterocollis	54 (60.7)	30 (66.7)
Anterocollis	17 (19.1)	7 (15.6)
Retrocollis	20 (22.5)	8 (17.8)
Lateral shift	22 (24.7)	14 (31.1)
Sagittal shift	9 (10.1)	8 (17.8)
Previous exposure to botulinum neurotoxin, n (%)		
Yes	57 (64.0)	29 (64.4)
No	32 (36.0)	16 (35.6)
Previous botulinum neurotoxin treatments for CD, n (%)		
n[a]	57	29
OnabotulinumtoxinA	56 (98.2)	28 (96.6)
AbobotulinumtoxinA	2 (3.5)	1 (3.4)
IncobotulinumtoxinA	6 (10.5)	2 (6.9)
RimabotulinumtoxinB	5 (8.8)	2 (6.9)
Most recent CD treatment with ONA[b]		
n	55	25
Mean dose (U; mean±SD)	177.0±34.0	176.2±42.2
Mean time since last injection (months; mean±SD)	4.8±19.1	3.6±16.3

CD, cervical dystonia; ONA, onabotulinumtoxinA, SD, standard deviation.
[a]Subjects may have been previously treated with more than one botulinum neurotoxin.
[b]In subjects who were non-naive for ONA treatment.

aboBoNT-A Treatment Exposure

- The median aboBoNT-A dose was 500 U (**Table 2**)
- The most frequently injected muscles were the splenius capitis, sternocleidomastoid, trapezius, and levator scapulae

Table 2. AboBoNT-A treatment exposure

	AboBoNT-A, 2 mL n=89	Placebo n=45
Median dose (range)	500 U (0-500 U)	500 U (250-500 U)
Mean dose (SD)	451.8 U (83.59)	459.0 U (79.55)
Mean number of muscles injected (SD)	4.0 (1.23)	4.0 (1.11)
Injection site, n (%)[a]		
Splenius capitis	76 (85.4)	39 (86.7)
Sternocleidomastoid	60 (67.4)	35 (77.8)
Trapezius	58 (65.2)	28 (62.2)
Levator scapulae	60 (67.4)	28 (62.2)
Scalenus (medius and anterior)	26 (29.2)	11 (24.4)
Semispinalis capitis	30 (33.7)	18 (40.0)
Longissimus	20 (22.5)	8 (17.8)
Other	23 (25.8)	13 (28.9)

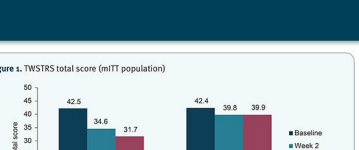
SD, standard deviation.
[a]Multiple categories could be selected.

Primary Efficacy Analysis

TWSTRS Total Score

- In the ITT population, subjects receiving aboBoNT-A experienced significantly greater changes from baseline vs placebo in TWSTRS total score at Week 4 (weighted overall treatment difference -8.1, $P<0.001$)
- The difference between treatments was significant as early as Week 2 (weighted overall treatment difference -5.4, $P=0.001$)
- In the mITT population, the results were similar (**Figure 1**) (weighted overall treatment difference -8.3, $P<0.001$)

Figure 1. TWSTRS total score (mITT population)



ITT, intent-to-treat; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.
*Weighted overall treatment difference of -8.3 between groups ($P<0.001$)

CGIC

- Physicians reported that 52.3% of their subjects treated with aboBoNT-A were "very much improved" or "much improved" at Week 4 compared with 20% of subjects treated with placebo (**Figure 2**)
- Similar differences were observed at Week 2, with physicians reporting that 45.4% of their subjects receiving aboBoNT-A were "very much improved" or "much improved" vs 6.8% of subjects treated with placebo

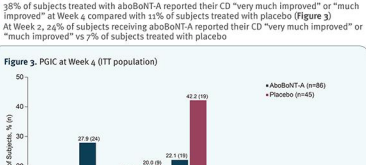
Figure 2. CGIC at Week 4 (ITT population)

CGIC, Clinical Global Impression of Change.

PGIC

- 38% of subjects treated with aboBoNT-A reported their CD "very much improved" or "much improved" at Week 4 compared with 11% of subjects treated with placebo (**Figure 3**)
- At Week 2, 24% of subjects receiving aboBoNT-A reported their CD "very much improved" or "much improved" vs 7% of subjects treated with placebo

Figure 3. PGIC at Week 4 (ITT population)



PGIC, Patient Global Impression of Change.

Responder Analysis

- A significantly greater percentage of subjects treated with aboBoNT-A vs placebo had a 30% or greater reduction in TWSTRS total score at Weeks 2 and 4 (**Table 3**) in a predefined responder analysis

Table 3. Reduction in TWSTRS total score of 30% or greater

	AboBoNT-A, 2 mL n=89	Placebo n=45	*P*-value
Week 2	27.9%	11.4%	0.033
Week 4	41.9%	11.1%	<0.001

TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

Safety Data

- Treatment-emergent adverse events were reported in 41% of subjects receiving aboBoNT-A and 22% of subjects receiving placebo (**Table 4**)
- The majority of events reported were mild to moderate in intensity
- Three subjects reported severe events related to treatment in the aboBoNT-A group. Four subjects in the aboBoNT-A group and one in the placebo group experienced serious adverse events. Only one serious adverse event of dysphagia in the aboBoNT-A group was assessed by the investigator to be treatment related.
- 1 subject in the aboBoNT-A group and no subjects in the placebo group discontinued the study due to an adverse event

Table 4. Treatment-emergent adverse events

Event, n (%)	AboBoNT-A, 2 mL n=88	Placebo n=45
All treatment-emergent adverse events	36 (40.9)	10 (22.2)
Dysphagia	8 (9.1)	0 (0.0)
Muscular weakness	8 (9.1)	0 (0.0)
Neck pain	7 (8.0)	0 (0.0)
Headache	5 (5.7)	0 (0.0)
Sinusitis	3 (3.4)	0 (0.0)
Serious adverse events	4 (4.5)	1 (2.2)
Dysphagia	1 (1.1)	0 (0.0)
Colon neoplasm	1 (1.1)	0 (0.0)
Endometrial cancer	1 (1.1)	0 (0.0)
Transient ischemic attack	1 (1.1)	0 (0.0)
Depression	0 (0.0)	1 (2.2)

CONCLUSION

- Data from this study indicate that a 2 mL dilution of aboBoNT-A was significantly more effective than placebo in CD subjects
- Treatment-emergent adverse events reported during the study were consistent with the known safety profile of aboBoNT-A for CD patients[4]

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DISCLOSURE

M.F. Lew: Dr. Lew is an advisor/consultant for Teva, US WorldMeds, UCB Pharma, Acadia, Auspex, Lundbeck, AbbVie, Impax, and Cynapsus; a speaker for Teva, US WorldMeds, UCB Pharma, Lundbeck, Acadia, AbbVie, and Impax; and a researcher for Abbott/AbbVie, Parkinson's Study Group, US WorldMeds, Michael J. Fox Foundation, Synosia Pharmaceuticals, Merz, Ipsen, Pharma two B, Civitas, Biotie, and Cynapsus.

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