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Tremor and Other Hyperkinetic Movements

Article

Prospective Study Evaluating IncobotulinumtoxinA for Cervical Dystonia or Blepharospasm: Interim Results from the First 145 Subjects with Cervical Dystonia

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Abstract

Background: We report the interim results from XCiDaBLE, a large, prospective, observational "naturalistic" study evaluating Xeomin® (incobotulinumtoxinA) for Cervical Dystonia or BLEpharospasm in the United States.

Methods: Subjects (≥ 18 years old) with cervical dystonia (CD) are followed for two treatment cycles and monitored via Interactive Voice/Web Response. The subject's physician must have chosen to treat with incobotulinumtoxinA prior to and independent of enrollment in this study. Subject-reported scales include the Subject Global Impression-Severity and Improvement and Cervical Dystonia Impact Profile (CDIP-58), and Work Productivity and Quality of Life (QoL) are assessed by means of an employment questionnaire and work history and the SF-12v2 Health Survey (SF-12v2). Subjects are seen by the investigator for three visits, which include a baseline visit (including the first injection), a second injection visit, and a final study visit (12 weeks after the second injection).

Results: This ongoing study includes 145 subjects with a diagnosis of CD. The majority were female (82.3%) and white (91.0%) and had previously been treated with botulinum toxins (77.2%). There were 106 employed at the time of disease onset, but 12.6 years later only 44% were still employed at the time of enrolment into the study, and 20% were either receiving or seeking disability benefits. The mean total dose/treatment of CD was 225.2 units for the first injection. The CDIP-58 total score was significantly improved 4 weeks after the first injection compared to baseline ($p \leq 0.0001$). Most subjects noted improvement in their global impression assessment. No new or unexpected adverse events occurred.

Discussion: The results from these interim analyses confirm previous controlled, single-dose studies of incobotulinumtoxinA in terms of efficacy and safety.

Keywords: incobotulinumtoxinA, botulinum toxin type A, NT 201, cervical dystonia, CDIP-58

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Conflict of interest: Please see Appendix 2.

Introduction

Cervical dystonia (CD) and blepharospasm are common forms of adult-onset focal dystonias. CD is the most common form of focal dystonia in neurologic clinics, and it is estimated that there are between 60,000 to 90,000 subjects with this disorder in the United States.[1]

Patients with CD experience pain, low self-esteem, embarrassment, impairment of social interactions, interference with activities of daily

living, reduced productivity, and employment difficulties.[2–4] Several studies have evaluated the impact of CD on employment and found that the disorder negatively affected the employment status of 55.3% of patients.[4] Neck pain, specifically, was associated with significantly altered employment ($p<0.0006$), reduced productivity ($p<0.0001$), and seeking disability benefits ($p<0.003$).[4]

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recommends botulinum toxin treatment as an option for patients with CD (based on seven class I studies; Level A).[5] *Clostridium botulinum* produces seven distinct serotypes, but only two serotypes (A and B) are commercially available for clinical use in the United States. All four available botulinum toxin products are approved by the United States Food and Drug Administration for use in patients with CD (abobotulinumtoxinA [Dysport® is a registered trademark of Ipsen Biopharmaceuticals, Inc.], incobotulinumtoxinA [Xeomin® is a registered trademark of Merz Pharma GmbH & Co. KGaA], onabotulinumtoxinA [Botox® is a registered trademark of Allergan, Inc.], and rimabotulinumtoxinB [Myobloc® is a registered trademark of Solstice Neurosciences, Inc.]).

Among the four available botulinum toxins, incobotulinumtoxinA was the most recently introduced in the United States. It received FDA approval on July 30, 2010[6] for the treatment of CD and blepharospasm in adults and on July 21, 2011 for moderate to severe glabellar lines in adults.[7] IncobotulinumtoxinA has demonstrated efficacy and safety in the treatment of subjects with CD in two Phase III clinical trials.[8–10] Additionally, the long-term safety and effectiveness of incobotulinumtoxinA in the treatment of CD have been established in one repeated dose trial.[11,12]

This prospective, observational study was designed to collect, evaluate, and report observational data regarding the clinical use of incobotulinumtoxinA in the "real-world" therapeutic setting (i.e., treating either CD or blepharospasm using patient-reported outcomes over two injection cycles). The baseline disease characteristics and results from the initial 4 weeks following the first injection are described in this paper.

Methods

XCiDaBLE is a multicenter, prospective, observational clinical study designed to capture "real-world" clinical use and outcomes of incobotulinumtoxinA treatment in subjects with CD or blepharospasm. The study was initiated in January 2010 and is ongoing at 89 sites in the United States, all of which received Institutional Review Board/Independent Ethics Committees approval prior to screening subjects. The study is registered with clinicaltrials.gov (www.clinicaltrials.gov, identification number: NCT01287247).

Subjects

XCiDaBLE includes subjects with CD who the physician chose to treat with incobotulinumtoxinA prior to and independent of study enrollment. All subjects signed and dated written informed consent prior to study inclusion. As this study was meant to approximate "real-world" clinical practice, there were limited inclusion or exclusion criteria. However, subjects had to be 18 years or older, could not have been enrolled in a clinical trial within the past 3 months, and did not have any contraindications to treatment with incobotulinumtoxinA according to the United States Prescribing Information for incobotulinumtoxinA.

Randomization

This was a prospective, observational study, and no randomization was used.

Study drug and injection technique

The selection of incobotulinumtoxinA dosage, dilution, muscles to be injected, and the use of guidance techniques were at the discretion of the treating physician. The dose for both injections and the timing of the second injection were individualized and administered at the physician's discretion, but the second injection could not occur less than 6 weeks after the first injection. The muscles injected for CD included in this report are: sternocleidomastoid, semispinalis capitis, longissimus, scalene complex, trapezius, splenius capitis, splenius cervicis, levator scapulae, and oblique capitis inferior.

Study visits

Subjects were assessed at the baseline visit and, if they met eligibility criteria, received an injection of incobotulinumtoxinA at that time. Information regarding the injection was collected and included the number of muscles injected, dose per muscle, and the dilution ratio of preserved normal saline to incobotulinumtoxinA. Demographic information, as well as disease and employment history, was collected at the baseline visit prior to injection. Additionally, previous use and outcomes of prior botulinum toxin treatment or other local or surgical treatments were collected. Subjects used interactive voice/web response (IVRS/IVWS) throughout the trial for assessments. IVRS is a technology that allows the use of a telephone to interact with subjects using a computer-generated voice that asks questions, and the subject uses the telephone keypad to respond. Interactive web response system (IWRS) allows subjects to use a secure website where they can respond to questions by filling in responses using the computer keyboard. While IVRS and IWRS are widely used, they have not been specifically validated in subjects with CD. According to and dependent on clinical practice, subjects are seen by the investigator for three visits, which include a baseline visit (including the first injection), a second injection visit, and a final study visit (12 weeks after the second injection).

Physician-reported outcome measures

Physician Global Impression-Severity (PGI-Severity). PGI-severity was rated by the treating physician at each injection. The PGI-Severity measured overall illness severity using a one-item, seven-point Likert scale (where 1=normal, 2=borderline, 3=mildly, 4=moderately, 5=markedly, 6=severely, and 7=extremely).

Subject-reported outcome measures efficacy

Subject Global Impressions (SGI). SGI-Severity was collected at each injection visit, and SGI-improvement was collected at 4 weeks

post-injection and the trial endpoint. SGI-Severity measured overall illness severity using a one-item, 7-point Likert scale (in which 1=normal, 2=borderline, 3=mildly, 4=moderately, 5=markedly, 6=severely, and 7=extremely). SGI-Improvement measured global improvement for the area being treated using a one-item, 7-point Likert scale (where 1=very much improved, 2=much improved, 3=minimally improved, 4=no improvement, 5=minimally worse, 6=much worse, and 7=very much worse).

Cervical Dystonia Impact Profile (CDIP-58). The Cervical Dystonia Impact Profile (CDIP-58)[13–16] was assessed at each injection visit, 4 weeks post-injection, and the trial endpoint. The CDIP-58 is a validated, disease-specific scale composed of 58 items that fall into eight subscales (head and neck, pain and discomfort, sleep, upper limb activities, walking, annoyance, mood and psychosocial function), which are categorized into three conceptual domains (symptoms, daily activities, and psychosocial sequelae) to yield a total score. The CDIP score was transformed to have a common range of 0 (no impact) to 100 (most impact). The CDIP-58 has been found to be more sensitive in detecting statistical and clinical changes than comparable subscales of the SF-36 Health Survey (SF-36), and Toronto Western Spasmodic Rating Scale (TWSTRS).[13]

Quality of Life. Quality of life (QoL) was assessed using the SF-12V2®, which was completed by the subject at each injection and at the end of the trial. The SF-12V2® Health Survey is a shorter version of the SF-36® that consists of 12 questions that measure functional health and well being from the subject's point of view. Possible SF12v2® scores range from 0 to 100, with higher scores representing better QoL for both mental and physical components.[17]

Work History. Work history was assessed using the validated Work Productivity and Activity Impairment (WPAI) Questionnaire, which was completed by the subject on a weekly basis throughout the study.[18] The WPAI consists of six questions and is a patient-reported quantitative assessment of the amount of absenteeism, presenteeism, and daily activity impairment attributable to general health or a specific health problem. Each question is evaluated individually; there is no total score. All visits were assessed to determine potential differences/fluctuations during the treatment cycle (e.g., peak effect, waning).

Safety

Subjects were asked to report all adverse events (AEs).

Statistical Methodology

Sample Size Determination. Due to the prospective, observational design of this study, no formal sample size calculation was utilized. Subject enrollment for both CD and blepharospasm were unrestricted for a total enrollment of up to 1200 subjects from up to 120 sites. The initial data for preliminary analysis includes a total of 232 patients with CD. Only subjects who had a confirmed 4 week post-injection datapoint for the CDIP were included in the analysis, yielding an analysis sample size of 145 CD subjects.

Data Analyses. Subject demographic and baseline disease characteristics; injection patterns and guidance techniques; and efficacy assessments, including measures of work productivity, QoL, and safety assessments per injection session are descriptively summarized. Categorical variables are summarized as counts and percentages using the number of observations available as the denominator for percent calculations. Continuous variables are summarized using means and standard deviation (SD), median, and minimum and maximum values. No imputation for missing data was performed.

CDIP-58 Analysis. The CDIP-58 score was transformed to have a common range of 0 (no impact) to 100 (most impact). CDIP-58 score differences were assessed with the Student's t-test.

Results

Subjects. As of February 1, 2012, 145 subjects (120 females) who had a diagnosis of CD have participated in this study. The baseline demographics and disease characteristics are listed in Table 1. The mean estimated duration of disease was 12.6 years, the mean age of disease onset was 43.3 years, and the mean age of the subjects in the study was 54.9 years. The majority of subjects (77.2%) had previously received treatment with botulinum toxin, whereas less than a quarter (22.8%) was toxin-naive. The majority of subjects (75.2%) reported a positive or partial response to prior treatment with botulinum toxin. Overall, 73.1% were employed at the time of disease onset, and 44.2% were employed at the start of the study.

Dosing. Total dose, dilution, muscles injected, and dosing per individual muscles are summarized in Table 2. The mean total dose of incobotulinumtoxinA for the first injection was 225.2 U (mean of 159.2 U for toxin-naive subjects; mean of 244.7 U for previously treated subjects) with a SD of 150.8. Among the toxin-naive subjects, 16 (48.5%) received ≤120 U of incobotulinumtoxinA, 6 (18.2%) received 121 to 180 U, and 11 (33.3%) received >180 U. The most frequent dilution scheme was 1.0 ml of normal saline per 100 U of incobotulinumtoxinA; however, the range was 1–10 ml per 100 U of incobotulinumtoxinA. Electromyography (EMG) was used by 58.6% of injectors for muscle identification, 49.7% used anatomical landmarks and palpation, and a small proportion used either electrical stimulation (2.8%) or sonography (0.7%).

Physician-Reported Outcomes

Global Impressions. Physicians rated their global impression of illness severity (Table 3). According to the investigator rating at baseline, the majority (81.4%) were quite ill; in fact, investigators rated the subjects as moderately (49.7%), markedly (24.8%), severely (6.2%), or extremely ill (0.7%).

Subject-Reported Outcomes

Global Impressions. Subjects rated their global impressions of illness severity and the improvement following treatment (Table 3). According to the subject rating at baseline, the majority (64.5%) were quite ill, and the remaining were rated as moderately (25.4%),

Table 1. Subject Demographics and Disease Characteristics

	N=145
Female Gender, n (%)	120 (82.3)
Race, n (%)	
Asian	0
Black	11 (7.6)
White	132 (91.0)
Other	2 (1.4)
Age (years), mean (SD)	54.9 (12.6)
Age at onset (years), mean (SD)	n=140
	43.3 (13.7)
Estimated duration of disease (years), mean (SD)	n=140
	12.6 (9.7)
Age at first botulinum toxin treatment (years), mean (SD)	n=112
	52.7 (13.0)
Time since most recent botulinum toxin injection (months), mean (SD)	n=111
	6.7 (15.2)
Number of subjects with previous botulinum toxin therapy, n (%)[1]	112 (77.2)
Previous botulinum toxin treatments: Serotype and mean number of treatments[2]	
AbobotulinumtoxinA, n (%)	10 (8.9)
Mean (SD)	n=10
	3.0 (1.6)
IncobotulinumtoxinA, n (%)	36 (32.1)
Mean (SD)	n=36
	9.3 (32.8)
OnabotulinumtoxinA, n (%)	100 (89.3)
Mean (SD)	n=97
	13.9 (14.1)
RimabotulinumtoxinB, n (%)	20 (17.9)
Mean (SD)	n=19
	4.1 (3.9)
Effect of previous botulinum toxin treatment	
None	3 (2.1)
Partial	38 (26.2)

Table 1. Continued

	N=145
Positive	71 (49.0)
Unknown	33 (22.8)
Previous Botulinum Toxin Duration	
Days, Mean (SD)	n=96
	75.9 (27.2)
Baseline Employment	
Employed at Time of Onset[3]	N=145
Yes	106 (73.1)
If Yes to Employed at Onset Was Employment Status Affected[4]	
Different job with less responsibility	5 (4.7)
Loss of employment	20 (18.9)
No	69 (65.1)
Same job, less pay	7 (6.6)
Unknown	5 (4.7)
Receiving or Seeking Disability Benefits?[3]	N=140
Yes	28 (20.0)

[1]Subjects may have been on more than one serotype and the total of the n's are greater than the total number of subjects
[2]Percentages are based on the number of people who responded to have previous botulinum toxin therapy
[3]Percentages are based on non-missing values
[4]The "n" and percentage is based on the number of individuals who responded "yes" or "no" indicating employment. Those who indicated that they are not employed or those with missing data were excluded from the percentage calculation
Abbreviations: N/n, total subject population/subset of total subject population; %, percentage; SD, standard deviation

markedly (19.6%), severely (15.9%), or extremely ill (3.6%). At 4 weeks post-injection, 43.1% subjects reported much or very much improvement.

CDIP-58 [For Subjects with CD]. Subjects rated their CD symptoms using the CDIP-58 (Table 4). The scores have been standardized (with 50 as a mean) for ease of interpretation. The mean total CDIP-58 score was 46.0 at baseline and 36.2 4 weeks after the first injection ($p<0.0001$; *t*-test of change from baseline to Week 4).

SF12v2® and Work Productivity and Activity Impact. Subjects rated their QoL using the SF12v2®. There were no differences in the mental or physical QoL at week 4 compared to baseline.

Subjects reported work productivity and activity impact using the WPAI Questionnaire (Table 5). Among the 138 subjects who responded at baseline, only 61 were employed. On a scale of 0–10 (0=no effect and 10=significant effect), subjects rated health affecting non-work activities as a mean of 5.1 (SD 3.1). Among working subjects, health affected mean productivity had a mean of 3.4 (SD 2.6). There were minimal changes seen in every area measured by the WPAI during the first 4 weeks of treatment.

Safety. Overall, there were only seven subjects who reported any AEs. Subjects could report more than one AE. There were very few definitely related or probably related AEs reported, and these included decreased joint range of motion, musculoskeletal pain, neck pain, and localized swelling. The majority of definitely related or probably related AEs were mild to moderate in severity.

Discussion

The typical patient with CD that entered this trial was female, had a mean age of 55 years, and experienced the onset symptoms of CD at around 43 years of age. While the majority of subjects were employed at the time of symptom onset, they were not when they enrolled in this study. More than two-thirds had previously received injections of botulinum toxin, with the majority reporting a positive or partial response. Subjects reported slightly less severe baseline disease than

Table 2. Summary of IncobotulinumtoxinA Dosing In Subjects with Cervical Dystonia

	Treatment Naive Subjects N=33	Pre-Treated Subjects N=112	All Subjects N=145
Dose at first Injection Visit			
Mean (SD)	159.2 (102.5)	244.7 (157.5)	225.2 (150.8)
Volume of Saline/100 U IncobotulinumtoxinA at first Injection Visit			
Range (Min, Max)	(1,8)	(1,10)	(1, 10)
Dosing by Muscle			**Injection N=145 Mean (SD)**
Sternocleidomastoid	n=17	n=75	n=92
	37.2 (25.3)	49.7 (56.3)	47.3 (52.1)
Semispinalis Capitis	n=15	n=56	n=71
	18.0 (8.8)	37.0 (28.3)	33.0 (26.6)
Longissimus	n=8	n=38	n=46
	20.1 (18.0)	21.9 (17.0)	21.6 (17.0)
Scalene Complex	n=10	n=41	n=51
	27.7 (27.6)	36.2 (29.6)	34.5 (29.2)
Trapezius	n=27	n=78	n=105
	35.0 (21.6)	46.6 (33.9)	43.6 (31.5)
Splenius Capitis	n=23	n=91	n=114
	34.3 (34.2)	46.6 (36.7)	44.1 (36.4)
Splenius Cervicals	n=8	n=34	n=42
	14.5 (8.9)	32.3 (26.1)	28.9 (24.7)
Levator Scapula	n=19	n=67	n=86
	23.2 (15.7)	34.6 (21.3)	32.1 (20.6)
Oblique Capitis Inferior	n=5	n=11	n=16
	11.2 (8.0)	28.8 (30.5)	23.3 (26.6)
Summary of Muscle Identification[1]			
Anatomical Location	20 (60.6)	52 (46.4)	72 (49.7)
Electromyography	15 (45.5)	70 (62.5)	85 (58.6)
Electrical Stimulation	1 (3.0)	3 (2.7)	4 (2.8)
Sonography	1 (3.0)	0 (0)	1 (0.7)

[1]Multiple techniques may have been chosen for an individual subject; therefore, totals do not equal column totals

Abbreviations: N/n, total subject population/subset of total subject population; %, percentage; SD, standard deviation; U, Units

Table 3. Global Impressions (Investigator and Subject)

	Cervical Dystonia			
	SEVERITY			IMPROVEMENT
	Baseline (First Injection Visit) Investigator Severity	Baseline (First Injection Visit) Subject Severity[1]		4 Weeks Post First Injection Subject Improvement[2]
Categories	N=145 n (%)	N=138 n (%)	Categories	N=137 n (%)
Not assessed	0	2 (1.5)	Not assessed	1 (0.7)
Normal (1)	5 (3.5)	17 (12.3)	Very much Improved (1)	15 (11.0)
Borderline (2)	5 (3.5)	9 (6.5)	Much Improved (2)	44 (32.1)
Mildly (3)	17 (11.7)	21 (15.2)	Minimally Improved (3)	42 (30.7)
Moderately (4)	72 (49.7)	35 (25.4)	No change (4)	21 (15.3)
Markedly (5)	36 (24.8)	27 (19.6)	Minimally Worse (5)	6 (4.4)
Severely (6)	9 (6.2)	22 (15.9)	Much Worse (6)	6 (4.4)
Extremely (7)	1 (0.7)	5 (3.6)	Very much Worse (7)	2 (1.5)

[1]Percentages are based on non-missing values (N=138)
[2]Percentages are based on non-missing values (N=137)
Abbreviations: N/n, total subject population/subset of total subject population; %, percentage; SD, standard deviation

their physicians. The mean dose of incobotulinumtoxinA for the first injection of the study was 225.2 U overall (159.2 U among toxin-naive and 244.7 U among previously treated. It is interesting to note that among the toxin-naive subjects, 48.5% received ≤120 U (120 U is the starting dose according the US Prescribing Information);[19] 18.2% received 121 to 180 U and 11 (33.3%) received >180 U.

The four muscles most frequently injected included the splenius capitis (78.6%), trapezius (72.4%), sternocleidomastoid (63.4%), and levator scapulae (59.3%), whereas only a minority of injections targeted the longissimus (30.0%), scalene complex (29.2%), splenius cervicals (29.0%), and oblique capitis inferior (11.0%). While most injectors diluted 100 U of incobotulinumtoxinA with 1 cc of normal saline, the diluent range was 1–10 cc. A small majority (58.6%) of injectors used EMG for muscle identification, while others used anatomical location (44.8%), electrical stimulation (2.8%), or sonography (0.7%).

In this large, prospective, open-label trial, incobotulinumtoxinA effectiveness was measured by subject-reported outcomes. Most patients reported improvement 4 weeks post-injection on the subject global impression scale. Additionally, patients reported statistically significant improvement on the CDIP-58 (total, conceptual domains, and subscales). However, not surprisingly, there were no statistically significant improvements in the QoL measurements (SF12v2 or Work Productivity and Activity Impact Questionnaire) 4 weeks post-injection, which is likely due to the short nature of the report. QoL improvements usually take time. It will be interesting to see if there are improvements in QoL with consistent individualized injections over a longer period.

IncobotulinumtoxinA has previously been shown to be a safe and effective treatment for CD in large trials.[8,10] IncobotulinumtoxinA was studied in two phase 3 trials: one placebo-controlled trial (N=233, with 159 treated with incobotulinumtoxinA)[10] and one active-comparator trial (N=463, with 231 treated with incobotulinumtoxinA).[8] The placebo-controlled trial had a long-term extension in which patients were re-randomized to either incobotulinumtoxinA 120 U or 240 U.[20] All patients could receive up to five treatment cycles with flexibility to dose as early as the patient needed (but not less than 6 weeks). Unfortunately, we cannot compare the primary outcome from these studies with our results because the assessments are different; the pivotal registration trials utilized the TWSTRS[21,22] or the Cervical Dystonia Severity Scale[23] and we utilized the CDIP-58.[13]

In a study conducted by the authors of the CDIP-58, that assessment was applied to a clinic-based sample of patients receiving botulinum toxin A and compared to existing rating scales used in CD, including two TWSTRS subscales (disability and pain).[13] The patients received questionnaires before and 3 weeks post-botulinum toxin type A treatment. The results of the CDIP-58 at 3 weeks post-botulinum toxin type A injection were similar to the results described here. In fact,

Table 4. Cervical Dystonia Impact Profile (CDIP-58)

	Baseline: First Injection N=137 n Standardized Mean (SD)	Week 4 Post-Injection N=145 n Standardized Mean (SD)	Treatment Difference n 4 Week – Baseline Mean Difference (SD)	p-value
TOTAL CDIP-58	n=120	n=119	n=102	<0.001
	46.0 (21.3)	36.2 (21.5)	−10.7 (16.5)	
CONCEPTUAL DOMAINS				
Symptoms	n=129	n=125	n=112	<0.0001
	60.5 (23.2)	47.5 (24.0)	−14.3 (20.2)	
Daily Activities	n=133	n=131	n=122	<0.0001
	39.2 (27.4)	32.5 (25.2)	−7.9 (18.6)	
Psychosocial Sequelae	n=127	n=124	n=111	<0.0001
	41.6 (23.4)	31.7 (22.8)	−10.3 (18.1)	
SUBSCALES				
Head and Neck	n=133	n=131	n=121	<0.0001
	64.4 (25.0)	49.2 (24.4)	−15.0 (21.1)	
Pain and Discomfort	n=131	n=127	n=116	<0.0001
	67.4 (28.6)	52.6 (27.9)	−15.4 (25.7)	
Sleep	n=135	n=134	n=126	<0.0001
	46.8 (33.0)	36.5 (31.8)	−11.6 (24.8)	
Upper Limb Activities	n=133	n=134	n=124	0.009
	43.5 (27.6)	38.1 (26.8)	−6.0 (19.8)	
Walking	n=135	n=132	n=124	<0.0001
	34.7 (30.7)	26.6 (27.6)	−9.4 (22.8)	
Annoyance	n=134	n=128	n=120	<0.0001
	47.9 (25.6)	35.6 (26.2)	−12.9 (21.7)	
Mood	n=128	n=127	n=115	<0.0001
	36.5 (25.8)	27.1 (23.8)	−8.9 (20.7)	
Psychosocial Function	n=133	n=130	n=121	<0.0001
	40.8 (27.6)	31.2 (25.8)	−9.2 (20.1)	

The CDIP score was transformed to have a common range of 0 (no impact) to 100 (most impact)

Abbreviations: CDIP, Cervical Dystonia Impact Profile; N/n, total subject population/subset of total subject population; SD, standard deviation

Table 5. Summary of Work Productivity and Activity Impact Questionnaire

	ALL SUBJECTS		EMPLOYED SUBJECTS			
	Currently Employed (Yes) n (%)	How much did health affect non-work during the previous week? (Range 1–10) Mean (SD)	Hours worked in the previous week (Hours) Mean (SD)	Hours missed from work because of health during the previous week (Hours) Mean (SD)	Hours missed from work because of other during the previous week (Hours) Mean (SD)	How much did health affect productivity during the previous week? (Range 1–10) Mean (SD)
Baseline (N=138)	61 (44.2)	n=136	n=61	n=61	n=61	n=58
		5.1 (3.1)	32.3 (13.7)	4.0 (8.4)	2.2 (5.6)	3.4 (2.6)
Week 1 (N=126)	53 (42.1)	n=124	n=52	n=52	n=52	n=48
		4.4 (3.2)	32.5 (15.1)	2.2 (6.6)	1.4 (4.2)	2.8 (2.4)
Week 2 (N=122)	56 (45.9)	n=120	n=56	n=56	n=56	n=50
		4.1 (3.0)	31.1 (15.9)	2.1 (7.0)	1.9 (7.5)	2.8 (2.5)
Week 3 (N=124)	54 (43.6)	n=124	n=53	n=53	n=53	n=48
		4.0 (3.1)	31.8 (15.5)	1.6 (5.9)	1.7 (4.8)	3.1 (2.9)
Week 4 (N=138)	60 (43.5)	n=138	n=60	n=60	n=60	n=55
		3.7 (3.1)	30.4 (14.6)	2.6 (7.3)	2.4 (5.6)	3.0 (2.7)

Note: The productivity and daily activities questions were based on 10-point scales
Abbreviations: N/n, total subject population/subset of total subject population; SD, standard deviation

comparisons of similar subscales among the different measures revealed that CDIP-58 subscales were more sensitive to statistical and clinical changes in measuring pain, activities of daily living, and psychosocial and psychological functioning than the TWSTRS, functional disability questionnaire, and the medical outcome study short form-health survey (SF-36) The CDIP-58 was also utilized in a cross-sectional survey of patients who were being treated with either onabotulinumtoxinA or abobotulinumtoxinA and were 7–10 weeks post-injection.[24] The subscale scores for the CDIP-58 were similar to our 4 week post-injection scores, but markedly better (i.e., lower scores) than our CDIP-58 scores just prior to the first injection. In that study, the survey was completed by a trained interviewer, and the similar results suggest that the CDIP-58 can be administered by an interviewer or via IVRS/IVWS, as in the present study.

No new or unexpected safety issues were uncovered with XCiDaBLE. IncobotulinumtoxinA was well tolerated in subjects with CD. There were very few AEs reported. These findings are consistent with the post-marketing experience with incobotulinumtoxinA. To date, more than 260,000 patients have been exposed to incobotulinumtoxinA worldwide (based on sales data including samples and exposures during clinical trials), and there have been no new safety concerns identified by spontaneous reports during this time period.[12]

Comparable demographic information has been collected in a similar study conducted by Allergan, Inc. using onabotulinumtoxinA (CD PROBE).[25] Baseline information for these patients with CD included: 75.9% female (82.3% in XCiDaBLE), 93.6% Caucasian (91% in XCiDaBLE), mean age 57.6 years (54.9 in XCiDaBLE), and symptom onset at 48.3 years (43.3 years in XCiDaBLE). Furthermore, the demographics from both studies are similar to the incobotulinumtoxinA pivotal study conducted in the United States.[10] CD PROBE is slightly different from XCiDaBLE: 1) it includes three injection cycles of onabotulinumtoxinA compared to two in XCiDaBLE; 2) CD PROBE has an office visit 4 weeks post-injections and a telephone interview 6 weeks post-injections, whereas XCiDaBLE utilizes IVRS/IWRS for systematic evaluations 4 weeks post-injection; and 3) although both studies utilize CDIP-58, only CD PROBE conducted TWSTRS at baseline, the third injection, and at the final visit. Importantly, both studies collect "naturalistic"

information that will help to better understand patients with CD and their responses to botulinum toxins over time.

Prospective, open-label studies like XCiDaBLE can help physicians understand the "real-world" use and outcomes of a product; however, there are limitations to this type of study. The most important is the lack of a control group. It is interesting to note that the dosing used for subjects who had been previously treated with botulinum toxins was slightly higher (245 U) than the dosing used for toxin-naive subjects (160 U); very few toxin-naive subjects received 120 U in their initial injection session (mean dose 160 U), which is the current recommended starting dose in the United States Prescribing Information;[19] the range of dilution with normal saline was large; and sonographic-guided injections were rarely used for CD, although this localization technique is gaining more acceptance, especially in Europe. This interim data analysis confirms the effect seen in this naturalistic study as assessed by the CDIP-58 and the statistically significant improvement in this measure observed 4 weeks after an injection of incobotulinumtoxinA. The magnitude of change in the CDIP-58 is consistent with other studies that have utilized this assessment. Moreover, it remains well tolerated when used in a less selective and wider range of subjects with CD, as compared to the more selective inclusion of subjects in blinded trials.

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Appendix 1. Continued

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Appendix 2 (Author Conflict of Interest Disclosures):

First Name	Last Name	Conflict of Interest Disclosures
Hubert	Fernandez	Hubert Fernandez is a consultant for Merz Pharmaceuticals, LLC.
Fernando	Pagan	Fernando Pagan is an investigator in XCiDaBLE for Merz Pharmaceuticals, LLC.
Fabio O.	Danisi	Fabio O. Danisi is an investigator in XCiDaBLE for Merz Pharmaceuticals, LLC.
David	Greeley	David Greeley is an investigator in XCiDaBLE for Merz Pharmaceuticals, LLC.
Joseph	Jankovic	Joseph Jankovic has received research grants and compensation for services as a consultant or an advisory board committee member from Allergan, Inc.; Ipsen Limited; and Merz Pharmaceuticals, LLC. He was an investigator on the XCiDaBLE trial.
Amit	Verma	Amit Verma is an employee of Merz Pharmaceuticals, LLC.
Kapil	Sethi	Kapil Sethi is an employee of Merz Pharmaceuticals, LLC.
Pappert	Eric J.	Eric J. Pappert is a former employee of Merz Pharmaceuticals, LLC.