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Tremor and Other Hyperkinetic Movements

Articles

Observational Study of IncobotulinumtoxinA for Cervical Dystonia or Blepharospasm (XCiDaBLE): Interim Results for the First 170 Subjects with Blepharospasm

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Abstract

Background: XCiDaBLE is a large, prospective, observational "naturalistic" study evaluating **X**eomin® for **C**erv**i**cal **D**ystoni**a** or **BLE**pharospasm in the United States. We report the interim results from the blepharospasm cohort of XCiDaBLE.

Methods: Subjects (≥18 years old) with blepharospasm were followed for two treatment cycles of incobotulinumtoxinA and monitored for 4 weeks after injection via interactive voice/web response system (IVRS/IWRS). The investigator-reported scale includes the Clinical Global Impression Scale-Severity subscale (CGI-S). Patient-reported outcome measures include the Patient Global Impression Scale-Severity (PGI-S) and -Improvement (PGI-I) subscales, Jankovic Rating Scale (JRS), SF-12v2® health survey, and Work Productivity and Activity Impairment questionnaire. Subjects are seen by the investigator at baseline (including the first injection), during the second injection, and at a final study visit (12 weeks after the second injection).

Results: One hundred seventy subjects were included in this interim analysis. The majority of subjects were female (77.1%) and white (91.8%), and had previously been treated with botulinum toxins (96.5%). The mean total dose (both eyes) was 71.5 U of incobotulinumtoxinA for the first injection. PGI-S, PGI-I, and JRS scores were significantly improved 4 weeks after treatment (all $p<0.0001$). No differences were noted in either quality of life (QoL) or work productivity in this short assessment period. No unexpected adverse events occurred.

Discussion: This is an interim study and assessment method based on an IVRS/IWRS. In this predominantly toxin-experienced cohort, significant benefits in specific and global measures of disease severity were seen in the immediate post-incobotulinumtoxinA injection period. It will be interesting to see if there are improvements in QoL with consistent individualized injections over a longer period.

Keywords: Open label, prospective, blepharospasm, incobotulinumtoxinA, Jankovic Rating Scale, Xeomin

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Introduction

Blepharospasm is a focal dystonia characterized by involuntary eyelid closure, usually bilaterally, with contractions of the orbicularis oculi muscles and other facial muscles.[1] The prevalence of blepharospasm in the general population is estimated at approximately five in 100,000 in the USA.[2] Because of the frequent blinking and spasmodic closure of the eyelids, subjects' daily activities, such as driving, walking, or reading, can be severely impaired.[3] Blepharospasm can also negatively affect the subject's employment status and social interactions.[3] In 2008, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recommended, based on two class II studies, Level B, botulinum toxin treatment as an "option" for patients with blepharospasm.[4] Accumulating evidence has now reported the efficacy and safety of botulinum toxin for treatment of blepharospasm.[5–8]

Clostridium botulinum produces eight distinct toxin serotypes, but only two, types A and B, are commercially available for clinical use in the USA.[9] Two type A botulinum toxins, incobotulinumtoxinA (Xeomin®, NT201) and onabotulinumtoxinA (Botox®), are approved by the Food and Drug Administration (FDA) for use in subjects with blepharospasm. IncobotulinumtoxinA is a botulinum neurotoxin formulation free from complexing proteins and received FDA approval on July 30, 2010, for the treatment of cervical dystonia (CD) and blepharospasm in adults.[10] IncobotulinumtoxinA has demonstrated efficacy and safety in the treatment of subjects with blepharospasm in two Phase III and one Phase IV clinical trials.[5–8,11] In head-to-head trials, incobotulinumtoxinA demonstrated comparable efficacy and safety to onabotulinumtoxinA.[6,11]

The ongoing **X**eomin® for **C**ervi**c**al **D**ystoni**a** or **BLE**pharospasm (XCiDaBLE) is the latest and largest multicenter, prospective, observational Phase IV clinical study in subjects treated with incobotulinumtoxinA for CD or blepharospasm (Trial Registration: NCT01287247, www.clinicaltrials.gov). The inclusion and exclusion criteria applied to subjects enrolled were broad. In XCiDaBLE, investigators used less selective and a wider range of subjects with blepharospasm; they included subjects they believed would benefit from incobotulinumtoxinA treatment. The aims of the study were to mimic "real-world" clinical practice, and capture clinical use and outcome data of subjects treated with incobotulinumtoxinA for CD or blepharospasm.

XCiDaBLE is ongoing and here we report findings from the first 170 subjects with blepharospasm enrolled in the clinical trial, including baseline demographic, clinical characteristics and results from the initial 4 weeks after first injection. The findings from the first 145 subjects with CD enrolled in XCiDaBLE, including baseline demographic and clinical characteristics and results from the initial 12 weeks after injections, have been published previously.[12]

Methods

Subjects

To be included, subjects had to be 18 years old or older, could not have been enrolled in a clinical trial within the past 3 months, and did not have any contraindications according to the US Prescribing Information for incobotulinumtoxinA. All subjects signed a written informed consent prior to inclusion in the study.

Randomization

XCiDaBLE was a prospective, observational study and no randomization was performed.

Study drug and injection technique

Subjects underwent two injection sessions of incobotulinumtoxinA in the study. The dose for both injections, the timing of the second injection, the dilution with normal saline, the muscles to be injected with incobotulinumtoxinA, and the choice of guidance techniques used in this trial were at the discretion of the treating investigator. The second injection was to occur at least 6 weeks after the first injection. In this study, incobotulinumtoxinA was administered in the orbicularis oculi, procerus, and corrugator supercilii muscles.

Study visits

Subjects were assessed at the baseline visit and if they met eligibility criteria received an injection of incobotulinumtoxinA. Information regarding the injection was collected and included: number of muscles injected, dose per muscle, and dilution of incobotulinumtoxinA. Previous use and outcomes of prior botulinum toxin treatment and other local or surgical treatments were collected. Demographic information, disease and employment history were collected. Subjects were asked to rate the efficacy of their previous botulinum toxin treatment(s) (i.e., none, partial, positive, unknown). According to, and dependent on, clinical practice, subjects were seen by the investigator at three visits, which included a baseline visit (including the first injection), a second injection visit, and a final study visit (12 weeks after the second injection).

Investigator-reported outcome measures

Clinical global impression scale-severity subscale. The Clinical Global Impression Scale-Severity subscale (CGI-S) was completed by the treating investigator at each injection. The CGI-S measures the overall illness severity using a one-item, 7-point Likert scale (where 1=normal, 2=borderline, 3=mildly, 4=moderately, 5=markedly, 6=severely, 7=extremely).

Patient-reported outcome measures

Subjects used an interactive voice/web response system (IVRS/IWRS) throughout the trial to report assessments.

Efficacy

Patient global impression scale-severity (PGI-S) and -improvement (PGI-I) subscales. The PGI-S was completed at each injection visit and the PGI-I was completed 4 weeks post injection and at the trial endpoint. The PGI-S measures the overall illness severity using a one-item, 7-point Likert scale (where 1=normal, 2=borderline, 3=mildly, 4=moderately, 5=markedly, 6=severely, 7=extremely). The PGI-I

measures 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, 7=very much worse).

Jankovic rating scale. The Jankovic Rating Scale (JRS) was assessed at each injection visit, 4 weeks after injection, and at the trial endpoint by the subject. The JRS is a validated, disease-specific scale used to rate the severity and frequency of blepharospasm on a scale of 0 to 4 points (where severity: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe; frequency: 0=none, 1=slightly increased, 2=eyelid fluttering, 3=eyelid spasm, 4=functionally "blind"). The overall score (JRS Sumscore) is the sum of the scores from these two subscales (maximum 8 points).[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. SF-12v2 is a shorter version of the Medical Outcomes Study Short-Form (36-item) Health Survey (SF-36®) composed of 12 questions to measure functional health and well-being from the subject's point of view.[14] The SF12v2 score ranges from 0 to 100, with higher scores representing better QoL in both mental and physical components.

Work history. Work history was assessed using the validated Work Productivity and Activity Impairment (WPAI) questionnaire. The WPAI questionnaire consists of six questions and is a patient-reported quantitative assessment of the level of absenteeism, presenteeism, and daily activity impairment attributable to general health or a specific health problem.[15] Each question is evaluated individually and there is no total score. Subjects rated their health affecting non-work activities on a scale of 0 to 10 (where 0=no effect to 10=significant effect). The WPAI questionnaire was completed by the subject on a weekly basis throughout the study. 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) that occurred in the observation period after their first injection.

Statistical methodology

Sample size determination. Owing to the prospective, observational design of this study, no formal sample size calculation was utilized. Subject enrollment for both blepharospasm and CD was unrestricted up to a total 1,200 subjects from up to 120 sites. The initial data-cut for the preliminary analysis included a total of 258 subjects with blepharospasm. Only subjects who had confirmed 4-week post-injection data for the JRS were included in the analysis. In the event of missing data, percentages were computed based on non-missing data, whenever applicable.

Statistical analysis. Subject demographic, baseline disease characteristics, injection patterns, guidance techniques, efficacy assessments (including global impression measures, JRS, QoL, and measures of work productivity), and safety assessments per injection session were summarized descriptively. Categorical variables were summarized as counts and percentages using the number of observations available as the denominator for calculation of percentages. Continuous variables were summarized using mean and standard deviation (SD), median, and range. Comparisons were made with paired *t* tests. No imputation for missing data was performed.

Results

Subjects

Data are reported from an interim analysis of the first 170 subjects (131 females) who had a diagnosis of blepharospasm, enrolled from 29 centers across the USA and who completed 4 weeks of follow-up assessments. The majority were female (77.1%) and white (91.8%).

At the time of the first visit, the mean estimated duration of disease for the enrolled subjects was 10.9 years; mean age at disease onset was 53.9 years; and mean age at enrollment was 63.7 years. The majority of subjects (59.2%) were employed at the time of symptom onset but only 31.7% were employed at the time of enrollment in the study.

The majority of subjects (96.5%) had previously received treatment with botulinum toxin, e.g., Xeomin® (incobotulinumtoxinA), Botox® (onabotulinumtoxinA), Myobloc® (rimabotulinumtoxinB), or Dysport® (abobotulinumtoxinA). Only 3.5% of participants were botulinum toxin-naïve subjects diagnosed with blepharospasm. Most subjects (74.4%) reported a near complete/full response while 20.6% subjects reported only a partial response to previous botulinum toxin treatments. The remaining 5% rated their treatment as unknown. The baseline demographics and disease characteristics are listed in Table 1.

Dosing

In almost all cases, the orbicularis oculi muscles were injected. In 69.4% of cases, the corrugator supercilii muscles were also injected, but only 45.3% of subjects received injections also in the procerus muscles. The mean total dose (both eyes) per treatment for blepharospasm was 71.5 U for the first injection in this study. The most frequent dilution scheme was 2 mL of normal saline per 100 U incobotulinumtoxinA; however, it ranged from 1 mL to 10 mL. Total dose, incobotulinumtoxinA dilution, muscles injected, and dosing per muscle are summarized in Table 2.

Clinical global impression scale-severity subscale

Investigators rated the subject's illness using the CGI-S at baseline (Table 3). The investigator rating at baseline shows the majority (68.1%) of subjects were moderately to severely ill (moderately: 42.0%, markedly: 17.2%, severely: 8.9%) and investigators rated 7.1% of the subjects as normal. Subjects rated as "normal" had symptoms rated within the normal range of the CGI-S scale. They were still included in the study and treated, as the investigators believed they would benefit from incobotulinumtoxinA treatment.

Table 1. Subject Demographics and Disease Characteristics

Characteristic	Blepharospasm N=170
Female gender, n (%)	131 (77.1)
Race,[1] n (%)	
Asian	5 (2.9)
Black	7 (4.1)
White	156 (91.8)
Other	2 (1.2)
Age at enrollment (years), mean (SD)	63.7 (11.4)
Age at onset (years), mean (SD)	n=169 53.9 (12.6)
Estimated duration of disease (years), mean (SD)	n=169 10.9 (8.3)
Age at first botulinum toxin treatment prior to enrollment on this study (years), mean (SD)	n=157 58.7 (11.1)
Time since most recent botulinum toxin injection (months), mean (SD)	n=163 4.3 (9.7)
Subjects with previous botulinum toxin therapy, n (%)	164 (96.5)
Previous botulinum toxin treatments[2]	
AbobotulinumtoxinA, n (%)	4 (2.4)
Mean number of treatments (SD)	n=4 2.3 (1.3)
IncobotulinumtoxinA, n (%)	43 (25.3)
Mean number of treatments (SD)	n=43 1.6 (1.1)
OnabotulinumtoxinA, n (%)	162 (95.3)
Mean number of treatments (SD)	n=152 21.8 (19.1)
RimabotulinumtoxinB, n (%)	6 (3.5)
Mean number of treatments (SD)	n=6 10.7 (20.8)
Effect of previous botulinum toxin treatment	
None	1 (0.6)
Partial	35 (20.6)
Near complete/full	127 (74.7)
Unknown	7 (4.1)
Previous botulinum toxin duration (days), mean (SD)	n=157 79.0 (31.6)
Baseline employment	
Employed at time of onset	N=169
Yes	100 (59.2)

Table 1. Continued

Characteristic	Blepharospasm N=170
If employed at onset, was employment status affected	
Different job with less responsibility	4 (4.0)
Loss of employment	11 (11.0)
No	75 (75.0)
Same job, less pay	1 (1.0)
Unknown	9 (9.0)
Receiving or seeking disability benefits?	n=161
Yes	19 (11.8)

Abbreviation: SD, Standard Deviation.
[1]A subject may select multiple races.
[2]Subjects may have received more than one serotype and thus the total number of subjects per treatment sums to more than the total number of subjects.
Percentages are based on non-missing values.

Patient global impression scale-severity and -improvement subscales

Subjects used the PGI-S to rate their illness at baseline and 4 weeks after injection (Table 3). At baseline, 20.6% of subjects rated themselves as normal and 47.2% rated themselves as moderately, markedly, severely, or extremely ill. The mean subject rating of disease severity was less severe than the mean investigator rating. The correlation analysis showed that the subject and physician ratings were significantly different (correlation coefficient = 0.33959; $p<0.0001$). At 4 weeks after injection, 51% of subjects reported "much" or "very much" improvement.

Jankovic rating scale

Subjects rated their blepharospasm symptoms using the JRS. At baseline, the mean (SD) severity, frequency, and total scores were 2.5

Table 2. Summary of IncobotulinumtoxinA Dosing

	Blepharospasm N=170
Dose at first injection visit, mean units (SD)	71.5 (50.6)
Most frequent volume (mL) of saline/100 U incobotulinumtoxinA at 1st injection visit [range]	2 (1–10)
Dosing by muscle for both eyes: total at first injection visit,[1] mean units (SD)	
Orbicularis oculi, n=168	26.2 (14.7)
Procerus, n=77	7.1 (5.7)
Corrugator supercilii, n=118	8.5 (7.1)
Summary of muscle identification at first injection visit, n (%)	
Anatomical location	168 (98.8)
Electromyography	2 (1.2)
Electrical stimulation	—
Sonography	—

Abbreviation: SD, Standard Deviation.
[1]More than one muscle could have been treated.

Table 3. Global Impressions (Investigator and Patient)

Category	Blepharospasm, n (%)			
	Severity			Improvement
	Baseline (1st Injection Visit) Investigator Severity	Baseline (1st Injection Visit) Patient Severity	Category	4 Weeks Post 1st Injection Patient Improvement
	N=169	N=165		N=159
Not assessed	0	2 (1.2)	Not assessed	5 (3.1)
Normal (1)	12 (7.1)	34 (20.6)	Very much improved (1)	24 (15.1)
Borderline (2)	10 (5.9)	18 (10.9)	Much improved (2)	57 (35.9)
Mildly (3)	32 (18.9)	33 (20.0)	Minimally improved (3)	43 (27.0)
Moderately (4)	71 (42.0)	40 (24.2)	No change (4)	17 (10.7)
Markedly (5)	29 (17.2)	23 (13.9)	Minimally worse (5)	5 (3.1)
Severely (6)	15 (8.9)	12 (7.3)	Much worse (6)	7 (4.4)
Extremely (7)	0	3 (1.8)	Very much worse (7)	1 (0.6)

(1.0), 2.4 (0.94), and 4.9 (1.7), respectively. Four weeks after injection, the mean (SD) severity, frequency, and total scores were 1.7 (1.1), 1.5 (1.2), and 3.2 (2.2), respectively. The mean (SD) change versus baseline was –0.81 (1.15) ($p<0.0001$) for the JRS severity score, −0.87 (1.2) ($p<0.0001$) for the JRS frequency score, and −1.68 (2.18) ($p<0.0001$) for the JRS Sumscore.

Quality of life and work history

Subjects rated their QoL using the SF-12v2. There were no differences in either the mental or physical components of QoL at Week 4 compared with baseline. Subjects reported work issues using the WPAI questionnaire. On a scale of 0 to 10, subjects rated health affecting non-work activities as a mean of 3.1 (SD 2.8). In working subjects, health affected productivity by a mean of 1.9 (SD 2.3). Minimal changes were seen in every area measured by the WPAI during the first 4 weeks of treatment (Table 4).

Adverse events

Only eight subjects reported an AE including AEs that were definitely or probably related to treatment. They included entropion, ulcerative keratitis, contusion, dry eye, and lagophthalmos. All of the definitely or probably related AEs were mild to moderate in severity. Complete AE details will be published in the final study report.

Discussion

XCiDaBLE was a prospective, observational study designed to collect, evaluate, and report data on the clinical use of incobotulinumtoxinA in the "real-world" therapeutic setting. One hundred and seventy subjects who had a diagnosis of blepharospasm were enrolled from 29 centers across the USA. Subjects received two treatment cycles (approximately 6 months) and completed 4 weeks of follow-up assessments, via IVRS/IWRS.

The majority of subjects with blepharospasm who entered the trial were female, had a mean age of 63.7 years, and had experienced symptoms of blepharospasm for nearly 11 years. While the majority of subjects (59.2%) were employed at the time of onset of blepharospasm symptoms, only 31.7% were employed at the time of enrollment in the study. In occidental countries, many people retire at the age of 63 years. It will therefore be difficult to assess the effect of the treatment on the employment status of the subjects enrolled in this study.

Almost all subjects had previously received injections of botulinum toxin with the majority reporting a near complete/full treatment effect (74.7%). In general, subjects rated the severity of their disease as less severe than did the investigators. The mean dose for the first injection in this study was 71.5 U. These values are in line with reported doses applied during clinical trials, ranging from 26.8 to 73 U per eye and a mean of 66.9 U for both eyes being reported in the US pivotal trial.[5–7,11] All the studies conducted using onabotulinumtoxinA as an active comparator to incobotulinumtoxinA have utilized a 1:1 dosing ratio. These studies showed incobotulinumtoxinA was non-inferior in terms of efficacy and similar in terms of safety to onabotulinumtoxinA, and the effects of incobotulinumtoxinA were comparable to onabotulinumtoxinA using this dosing ratio.[6,11] The orbicularis oculi and the corrugator supercilii muscles were injected in the majority of subjects; only a minority of subjects were injected in the procerus. While most investigators diluted 100 U of incobotulinumtoxinA with 2 mL of normal saline, the dilution

Table 4. 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 0–10), mean (SD)	Hours worked in the previous week, mean (SD)	Hours missed from work due to ill health during previous week, mean (SD)	Hours missed from work due to other reasons during previous week, mean (SD)	How much did health affect productivity during previous week? (range 0–10), mean (SD)
Blepharospasm						
Baseline (N=167)	53 (31.7)	n=165 3.1 (2.8)	n=52 34.2 (17.0)	n=52 1.2 (5.7)	n=52 5.2 (11.0)	n=52 1.9 (2.3)
Week 1 (N=158)	47 (29.7)	n=150 2.9 (2.9)	n=47 33.2 (19.5)	n=47 1.4 (6.3)	n=47 5.3 (14.2)	n=43 1.6 (1.7)
Week 2 (N=154)	47 (30.5)	n=146 3.1 (3.0)	n=46 26.6 (17.1)	n=46 5.2 (19.4)	n=46 4.3 (10.8)	n=38 1.5 (2.1)
Week 3 (N=154)	46 (29.9)	n=148 2.6 (2.7)	n=46 30.3 (19.6)	n=46 1.9 (7.8)	n=46 4.6 (10.1)	n=40 1.5 (2.1)
Week 4 (N=170)	49 (28.8)	n=159 2.8 (2.8)	n=49 28.7 (19.2)	n=49 1.1 (5.9)	n=49 3.5 (8.9)	n=41 1.6 (2.0)

Abbreviation: SD, Standard Deviation.
The productivity and daily activities questions are based on a 10-point scale where 0=health problems had no effect on daily activity and 10=health problems completely prevented productivity/activities. Percentages are based on non-missing values.

range was wide (from 1 mL to 10 mL). The recommended dose for blepharospasm is 2.5–5.0 U/injection site.[16]

In this large, prospective, open-label trial, treatment with incobotulinumtoxinA demonstrated effectiveness 4 weeks after injection as measured by patient-reported outcomes (including PGI-S and JRS). Compared with baseline, the magnitude of improvement at 4 weeks on the JRS Sumscore was a mean of −1.7 (severity mean change was −0.8 and frequency mean change was −0.9) in this observational study ($p<0.0001$). This magnitude is significant and similar to previously reported blinded trials.[5,6] IncobotulinumtoxinA was studied in one placebo-controlled trial (N=109 with 75 being treated with incobotulinumtoxinA) and one active-comparator trial (N=256 with 129 being treated with incobotulinumtoxinA).[5,10] Additionally, a pilot active-comparator study has been conducted (N=64 with 31 being treated with incobotulinumtoxinA) along with a large, long-term, repeated-dose study (N=102, all treated with up to five treatment cycles of incobotulinumtoxinA).[6,7] The magnitudes of improvements in the Jankovic et al. placebo-controlled study at Week 3 (JRS Sumscore adjusted mean change −1.8, severity −0.9, and frequency −0.9) and Week 6 (JRS Sumscore adjusted mean change −1.3, severity −0.8, and frequency −0.6) after injection and in the Wabbels et al.[6] active-comparator controlled study at Week 4 post injection (JRS Sumscore mean change −1.5) are thus comparable to that observed in our study.[5,6] This also underscores another observation that the patient-rated JRS (performed by IVRS in this observational study) and investigator-rated JRS (performed in the blinded trials) may be comparable and therefore of value, and thus should be considered in future studies on blepharospasm.

Interestingly, despite meaningful improvement in specific and global disease severity measures, at 4 weeks after injection, there were no improvements in either QoL, as measured by the SF12v2, or in work productivity, as measured by the WPAI questionnaire. This is likely related to multiple factors including previous injections with toxin, and the short—4 weeks—duration of the follow-up period in this report. Also, the broad inclusion criteria, particularly related to employment and working type and conditions, in the study could have led to the lack of QoL improvement (e.g., a job that does not entail a lot of reading or strenuous visual activity might be less likely to improve the score of subjects most severely affected). It will be interesting to see if there are improvements in QoL with consistent individualized injections over a longer period.

There are limitations to this study. First, the study was an interim report of a much larger cohort (688 subjects, 319 subjects with blepharospasm). The sample size of this interim report on the blepharospasm subjects was small (170 subjects), which may or may not be indicative of the final study and limits the generalization of the results to the total population of patients treated with incobotulinumtoxinA for blepharospasm. Second, subjects were assessed using an IVRS/IWRS. Subjects' responses assessed by such methods were not or could not be checked by a treating clinician or by objective assessments.

IncobotulinumtoxinA has previously been shown in large trials to be a safe and effective treatment for blepharospasm.[5,7,11] In XCiDaBLE, no new or unexpected safety issues have been uncovered. IncobotulinumtoxinA was well tolerated in subjects with blepharospasm. There were very few AEs reported; fewer safety issues were reported as AEs in the present study compared with other studies, which is not surprising given the "naturalistic" setting of this study. Additionally, both the Jankovic and Roggenkämper studies involved direct questioning regarding specific AEs that the FDA were interested in, which led to a higher reported rate than self-reporting.[5,11]

Prospective, open-label studies, such as XCiDaBLE, can be useful for physicians to understand "real-world" use of botulinum toxins and how it compares to fixed, blinded trials. However, there are limitations to this type of study. This study lacks a placebo control and therefore all subjects and investigators knew the subjects were receiving active treatment and would have an expectation of improvement. An additional limitation of this study is that all of the assessments were completed by the subject via IVRS/IWRS (which has not been validated in subjects with blepharospasm). While this allows for more assessments over the treatment period, the onus is on the subject to actually complete the assessments. Nonetheless, this ongoing study is providing information on the disease characteristics of subjects with blepharospasm treated with botulinum toxin. It is worth noting that: the illness severity ratings of clinicians were worse than the subjects' rating of their own illness; the range of dilution with normal saline was large; and the patient-rated JRS improvement in this open-label study was comparable to the investigator-rated JRS improvement observed in previously blinded studies. Indeed, these interim data confirm that the magnitude of effect seen in this naturalistic study is similar to that seen in previous blinded studies with incobotulinumtoxinA.

This study reports that incobotulinumtoxinA remained well tolerated with comparable magnitude of effect over a broad spectrum of dose and dilution when used in a less selective and wider range of subjects with blepharospasm than the more selective inclusion of subjects in blinded trials employing uniform dilution and stricter dosing guidelines. Patient-rated JRS should be considered as an outcome measure in future observational studies and clinical trials for blepharospasm. Caution should be used in studies where only the PGI-S or CGI-S are utilized, as correlation between these two scales may not be optimal. Despite showing significant benefits in specific and global measures of disease severity, improvement in QoL was not captured in the short-term period of this interim report.

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