Efficacy and Safety of OnabotulinumtoxinA for the Treatment of Crows Feet Lines: A Multicenter, Randomized, Controlled Trial

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BACKGROUND This study was part of a Phase 3 program treating crow's feet lines (CFL) with onabotulinumtoxinA.

OBJECTIVE To evaluate the efficacy and safety of onabotulinumtoxinA treatment of CFL.

METHODS This multicenter, double-blind, placebo-controlled, 5-month study randomized subjects with moderate-to-severe CFL (maximum smile) to onabotulinumtoxinA (24 U; n = 222) or placebo (n = 223). Investigators and subjects assessed CFL severity (maximum smile and rest) using the 4-grade Facial Wrinkle Scale (FWS). Co-primary end points were investigator- and subject-assessed proportion of subjects achieving a CFL FWS grade of 0 (none) or 1 (mild) at maximum smile (Day 30). Additional efficacy end points, patient-reported outcomes, and safety/adverse events (AEs) were evaluated.

RESULTS All primary and secondary end points were achieved; statistically significant differences favored onabotulinumtoxinA ($p < .001$, all comparisons vs placebo). Co-primary responder rates were 66.7% compared with 6.7% for investigator-assessed and 58.1% compared with 5.4% for subject-assessed response (onabotulinumtoxinA group and placebo, respectively; $p < .001$). A significantly greater proportion of the onabotulinumtoxinA group than placebo group achieved a 1 grade or greater improvement on the FWS (maximum smile and rest assessed by both the investigator and subject; all time points; $p < .001$). Most AEs were mild or moderate and did not result in discontinuations.

CONCLUSION Treatment of moderate-to-severe CFL with onabotulinumtoxinA was effective and well tolerated.

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The expanding role of onabotulinumtoxinA is largely because of its well-established safety, efficacy, and predictable outcomes. This article reports the results of the first large Phase 3 clinical study of

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onabotulinumtoxinA conducted in more than a decade for a new cosmetic indication, crow's feet lines (CFL). Several small clinical trials have demonstrated the efficacy and safety of onabotulinumtoxinA for treating CFL. In a double-blind, placebo-controlled, split-face study, subjects (N = 60) with bilaterally symmetrical moderate or severe CFL at maximum contraction received 6, 12, or 18 U onabotulinumtoxinA into the orbicularis oculi on 1 side of the face and placebo on the contralateral side.[1] In that study, treatment success was defined as at least a 1-grade improvement from baseline at maximum contraction on the Facial Wrinkle Scale (FWS). All doses of onabotulinumtoxinA resulted in treatment success rates that were significantly superior to placebo response rates. The adverse event (AE) rate was low, with mild bruising being the most common AE in each treatment group.

Two Phase 2 studies were also conducted to determine the optimal dose for treating CFL. In the first study, subjects (N = 162) received a single bilateral treatment with total doses ranging from 6 to 36 U onabotulinumtoxinA or placebo, 3 injections per side in the lateral aspect of the orbicularis oculi.[2] Responder rates (at least a 1-grade improvement at maximum smile on the FWS, assessed by the investigator) were significantly higher with onabotulinumtoxinA than with placebo treatment at each time point, up to Day 150 in groups treated with 24 or 36 U, up to Day 120 in those treated with 12 U, and up to Day 30 for those receiving 6 U. Subject rating of improvement based on the Subject's Global Assessment of Change in Crow's Feet Lines (SGA-CFL) consistently favored the 24 U dose than the 36 U dose. The rate of AEs did not differ among treatment groups, including placebo; the most frequent treatment-related AE was bruising at the injection site. Results from the second study were similar and confirmed that the 24 U dose is appropriate for the treatment of CFL (Data on file; Allergan, Inc., Irvine, CA). Dosing and injection patterns for this study were based on the results of these Phase 2 studies.

Methods

Study Design and Subjects

This was a multicenter (23 sites), double-blind, randomized, placebo-controlled, parallel-group Phase 3 study (www.clinicaltrials.gov identifier: NCT01189747) that included a single treatment with either onabotulinumtoxinA (BOTOX Cosmetic; Allergan, Inc.) or placebo and a 5-month follow-up. Subjects were males or females of at least 18 years old with moderate-to-severe bilaterally symmetrical CFL at maximum contraction (smile) as assessed by both the investigator and subject using the FWS (0 = none, 1 = mild, 2 = moderate, and 3 = severe). To participate in the study, subjects had to provide written informed consent. Other key inclusion and exclusion criteria are in described in Table 1. The study was conducted in accordance with the guidelines and regulations for Good Clinical Practice and all relevant local and country privacy guidelines. Investigators obtained approval from their institutional review board or independent ethics committee in compliance with the Declaration of Helsinki. The planned enrollment was 440 subjects (220 per group).

Procedures

Eligible subjects were randomized in a 1:1 ratio to receive either onabotulinumtoxinA 24 U or placebo. OnabotulinumtoxinA purified neurotoxin complex containing 100 U botulinum toxin type A (BoNTA), 0.5 mg albumin (human), and 0.9 mg sodium chloride was reconstituted with 2.5 mL of preservative-free sterile 0.9% sodium chloride. Placebo was 0.9 mg sodium chloride, supplied in a sterile vacuum-dried form, reconstituted the same way as onabotulinumtoxinA. Reconstitution and preparation of syringes were undertaken by individuals who had no interactions with subjects.

On Day 1, all subjects received 3 injections per side, for a total of 6 injections to the lateral aspect of the orbicularis oculi muscles (Figure 1A,B). The volume of each injection was 0.1 mL and contained either 4 U onabotulinumtoxinA or placebo. All injections were performed with the needle tip pointed away from the eye and with the bevel up. Follow-up visits were at Weeks 1 and 2 and Days 30, 60, 90, and 120. The study exit was at Day 150.

Efficacy Outcome Measures

Primary

Primary efficacy outcomes were based on the FWS severity of CFL at maximum smile as assessed by both

TABLE 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria	*Exclusion Criteria*
Male or female of at least 18 years old	Concurrent or previous botulinum toxin treatment of any serotype
Bilaterally symmetrical moderate-to-severe CFL at maximum smile on the FWS as rated by both the investigator and subject on Day 1 (before study)	Specified facial treatments or procedures within particular time points before study that could interfere with treatments in this study or with interpretation of results
Sufficient visual acuity without the use of eyeglasses (contact lens use acceptable), to accurately assess their facial wrinkles	Prior upper or midfacial surgery or permanent aesthetic procedures/treatments
Female subjects of childbearing potential must have had a negative urine pregnancy test at Day 1 prior tobefore study treatment; must be using a reliable means of contraception	Marked facial asymmetry, dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, or the inability to substantially lessen lateral canthal rhytids even by physically spreading them apart, as determined by the investigator
	Presence of any clinically relevant abnormal finding as observed from the neurologic assessment
	Any eyebrow or eyelid ptosis at baseline as determined by the investigator
	History of facial nerve palsy
	Females who were pregnant, nursing, or planning a pregnancy
	Any uncontrolled systemic disease
	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
	Permanent makeup that would interfere with the assessment of facial wrinkles
	Subject had a condition or was in a situation that in the investigator's opinion may have put the subject at significant risk, confounded the study results, or interfered significantly with the subject's participation in the study

investigators and subjects. The primary time point for these measures was Day 30 posttreatment. The co-primary end points were the proportion of subjects achieving a grade of 0 (none) or 1 (mild) on the FWS as assessed independently by investigators and subjects. For the United States Food and Drug Administration (US FDA) only, the composite primary efficacy end point was the proportion of subjects achieving at least a 2-grade improvement from baseline on the FWS as assessed by both the investigator and subject on a per-subject basis. All investigator and subject FWS assessments were also analyzed separately.

Secondary

The primary time point for secondary end point analyses was also Day 30 posttreatment. Two secondary end points were based on the FWS severity of CFL as assessed by investigators. Responder rates for these 2 end points were defined as the proportion of subjects with at least a 1-grade improvement at maximum smile and at least a 1-grade improvement at rest.

Several patient-reported outcome (PRO) measures for evaluating facial lines, which assessed psychological impact, satisfaction, and subjects' perception of global change, were also specified as secondary end points. These included the Facial Line Outcome questionnaire (FLO-11), the Self-Perception of Age (SPA), the SGA-CFL, and the Subject Assessment of Satisfaction of Appearance. The FLO-11 and SPA have been used previously to assess BOTOX treatment of facial lines, including glabellar and CFL, and are validated instruments developed in accordance with the US FDA Guidance for Industry—Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.[3–6] The FLO-11 measures subjects' perceptions of the effect of their facial lines on their appearance. Qualitative research demonstrated that FLO-11 item 2 (look older), item 5 (look less attractive), and item 8 (look tired) reflect the psychological impact of CFL appearance and their treatment among

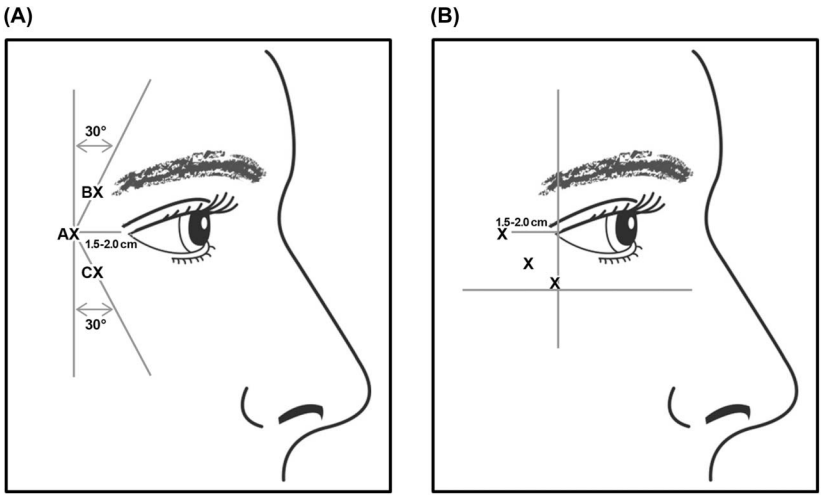

Figure 1. Injection pattern and allowed modification for the treatment of CFL. (A) CFL injection pattern. The first injection was in the orbicularis oculi at the level of the lateral canthus, at least 1.5–2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim (marked as AX). The second injection was 1.0–1.5 cm above this first injection site and at an approximate 30° angle medially (marked as BX). The third injection was 1.0–1.5 cm below the first injection site at an approximate 30° angle medially (marked as CX). (B) Modified CFL injection pattern. If the lines in the crow's feet region were primarily below the lateral canthus, the injector had the option to inject below the lateral canthus. Injections were given in a line angling from anteroinferior to superoposterior, with the most anterior injection point lateral to a line drawn vertically from the lateral canthus and the most inferior injection superior to the maxillary prominence.

subjects with moderate-to-severe CFL (Data on file; Allergan, Inc.). The SPA assesses subjects' SPA within the context of current age, reporting if they perceive themselves to look their current age, younger than their current age, or older than their current age, and the years younger or older that they perceive themselves to look. The SGA-CFL is a 7-point scale for evaluating the change in appearance of the CFL (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse). The Subject Assessment of Satisfaction of Appearance is a 5-point scale (1 = very unsatisfied; 5 = very satisfied).

Duration of response was estimated by Kaplan–Meier analysis for subjects deemed to be responders at Day 30, based on 2 measures as assessed by investigators: those subjects achieving a grade of none or mild on the FWS or those having at least a 1-grade improvement on the FWS at maximum smile.

Safety Measurements

Adverse Events

Adverse events were monitored throughout the study and were classified as mild, moderate, or severe. Investigators determined the relationship to study the drug. Serious AEs were any events at any dose that were deemed life threatening or resulted in death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Other events could be considered serious if they could have jeopardized the patient and required intervention to prevent one of the outcomes above. Allergan, Inc. also classifies all cancer AEs and abortions as serious events.

Neurologic Assessments

At the request of the US FDA, standardized neurologic assessments were conducted prospectively at each visit to identify events indicating possible local or distant spread of toxin. Neurologic symptoms were assessed by a focused symptom questionnaire that asked subjects about problems with ocular, lingual/pharyngeal, and systemic muscle functions and by a focused neurologic examination.

Immunogenicity

Blood samples were collected from each subject on Day 1 (pretreatment) and on Days 30 and 90 or at earlier discontinuation. Samples were assessed for BoNTA-binding antibodies (enzyme-linked immunosorbent assay), and positive samples were then screened for neutralizing antibodies to BoNTA (mouse protection assay).

Data Analyses

All efficacy analyses were performed on the intent-to-treat (ITT) population, which included all subjects randomized to the study. Missing values for the primary efficacy variable were imputed using the last observation carried forward. For the primary ITT FWS responder analysis for the US FDA only, subjects with missing data at a given time point were deemed nonresponders for that visit. Safety analyses were conducted on all subjects who received the study drug.

Results

Subjects

Disposition and exit status is shown in Figure 2. At baseline, treatment groups did not differ significantly in their demographics (Table 2), in investigator- or subject-rated CFL severity on the FWS, which was moderate-to-severe for all subjects (Table 3). The groups were also similar in baseline FLO-11 scores and perceived age on the SPA measure (data not shown). At baseline, 72.4% of subjects in the onabotulinumtoxinA treatment group and 73.5% of subjects in the placebo treatment group were unsatisfied or very unsatisfied with their appearance based on the Subject Assessment of Satisfaction of Appearance.

Efficacy

For all primary and secondary end points, responder rates were significantly higher in the onabotulinumtoxinA treatment group than in the placebo group. Both the co-primary and composite primary end points were achieved.

Co-primary End point

At the primary efficacy time point of Day 30, the proportion of subjects achieving a CFL grade of none or mild on the FWS at maximum smile was significantly greater for the onabotulinumtoxinA-treated subjects than for placebo-treated subjects (Figure 3A,B). At that time point, the investigator-rated responder rate was 66.7% for the onabotulinumtoxinA group compared with 6.7% for placebo group ($p < .001$). The corresponding subject-rated responder rate was 58.1% for onabotulinumtoxinA compared with 5.4% for placebo ($p < .001$). Statistically significant differences favoring onabotulinumtoxinA treatment were maintained at all visits through Day 150 ($p < .001$, all comparisons). Investigator-assessed responder rates were slightly greater numerically, but not statistically, than subject-assessed rates through Day 90 and peaked at Week 2, in contrast to subject-assessed response rates, which peaked at Day 30.

Composite End point

At Day 30, the composite responder rate was significantly greater for onabotulinumtoxinA-treated subjects than for placebo-treated subjects (25.7% onabotulinumtoxinA 24 U group compared with 1.3% placebo group; $p < .001$). Responder rates on the investigator and subject assessments alone were also significantly

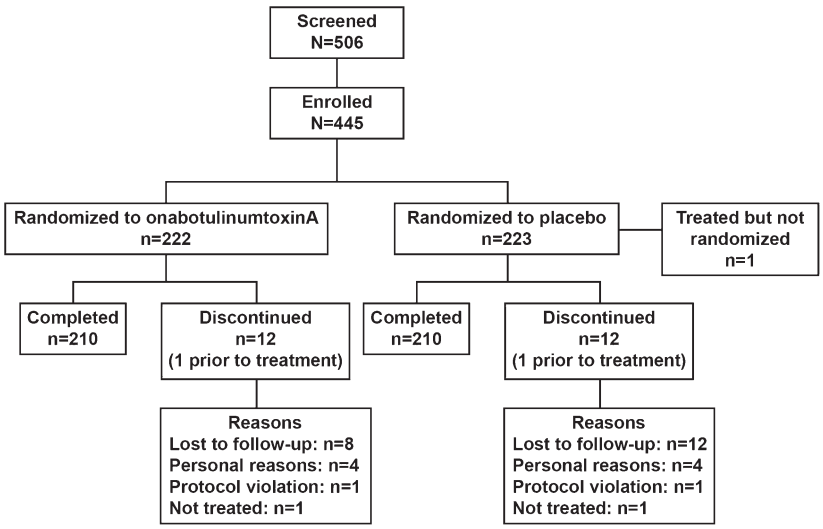

Figure 2. Subject disposition and exit status.

TABLE 2. Baseline Demographics

	OnabotulinumtoxinA	*Placebo*	*Total*
	(n = 222)	*(n = 223)*	*(N = 445)*
Mean age, y (range)	46.7 (22–75)	46.2 (22–74)	46.4 (22–75)
Sex			
Female, %	86.9	85.7	86.3
Race, %			
White	88.7	88.8	88.8
Black	3.2	3.1	3.1
Asian	1.8	2.2	2.0
Hispanic	5.4	4.9	5.2
Other*	0.9	0.9	0.9

*Other category included mixed race, white/Hispanic, Native American, Latin, and First Nations.

greater for onabotulinumtoxinA-treated subjects at Day 30 than for placebo-treated subjects (investigator-assessed, 40.5% onabotulinumtoxinA 24 U group compared with 1.8% placebo group; subject-assessed, 32.4% onabotulinumtoxinA 24 U group compared with 1.3% placebo group; both $p < .001$).

Investigator-Assessed Responder Rates on the FWS

The proportion of subjects with at least a 1-grade improvement in CFL severity on the FWS as assessed by the investigator was significantly greater for the onabotulinumtoxinA group than for the placebo group at Day 30 and at all visits through Day 150. These significant improvements were seen both at maximum smile and at rest ($p < .001$; Figure 4).

PRO: FLO-11 (Psychological Impact Items 2, 5, and 8), SPA, SGA-CFL, and Subject Assessment of Satisfaction of Appearance

For FLO-11, the proportion of responders for each item (2, 5, and 8) was significantly greater for onabotulinumtoxinA-treated subjects than for subjects

TABLE 3. Baseline CFL Severity

	OnabotulinumtoxinA 24 U	*Placebo*	*Total*
	(n = 222), n (%)	*(n = 223), n (%)*	*(N = 445), n (%)*
Investigator's FWS rating at maximum smile			
Moderate	109 (49.3)	112 (50.2)	221 (49.8)
Severe	112 (50.7)	111 (49.8)	223 (50.2)
Subject's FWS rating at maximum smile			
Moderate	109 (49.3)	112 (50.2)	221 (49.8)
Severe	112 (50.7)	111 (49.8)	223 (50.2)
Investigator's FWS rating at rest			
None	8 (3.6)	8 (3.6)	16 (3.6)
Mild	88 (39.8)	88 (39.5)	176 (39.6)
Moderate	90 (40.7)	91 (40.8)	181 (40.8)
Severe	35 (15.8)	36 (16.1)	71 (16.0)
Subject's FWS rating at rest			
None	8 (3.6)	8 (3.6)	16 (3.6)
Mild	82 (37.1)	80 (35.9)	162 (36.5)
Moderate	104 (47.1)	100 (44.8)	204 (45.9)
Severe	27 (12.2)	35 (15.7)	62 (14.0)

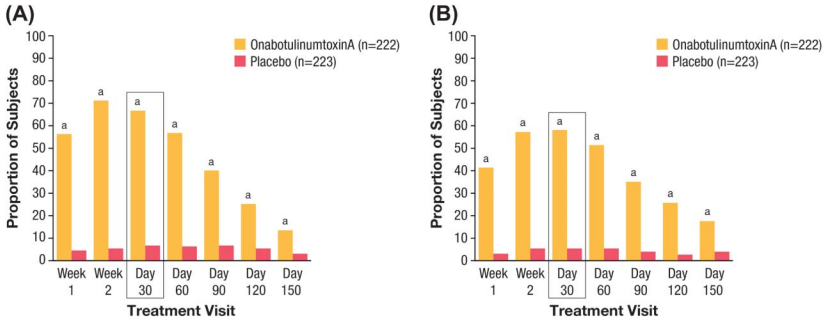

Figure 3. Co-primary end point: proportion of subjects achieving none or mild in CFL severity on the FWS. (A) Investigator's FWS rating at maximum smile. (B) Subject's FWS rating at maximum smile. The boxed bars represent the primary time point. a indicates $P < .001$.

receiving placebo at Day 30 and all visits through Day 150 ($p < .001$; data not shown).

Subjects rating themselves in a younger SPA category after treatment than at baseline were considered SPA responders. The analysis, therefore, included only those subjects who rated themselves as either looking their current age or older than their current age at baseline (onabotulinumtoxinA, n = 183; placebo, n = 185). The proportion of subjects rating themselves as looking younger compared with baseline was significantly greater for onabotulinumtoxinA-treated subjects than for placebo-treated subjects at Day 30 and all visits through Day 150 ($p < .001$; data not shown).

On the SGA-CFL, the proportion of subjects rating themselves as very much improved or much improved was significantly greater for the onabotulinumtoxinA-treated subjects than the placebo-treated subjects at Day 30 and at each visit through Day 150 ($p < .001$; Figure 5).

At Day 30, 60.1% (131/218) of the onabotulinumtoxinA-treated subjects were satisfied or very satisfied with their appearance compared with 7.5% (16/214) of placebo-treated subjects, which was a statistically significant difference ($p < .001$).

Duration of Response

The median duration of effect for responders achieving an FWS grade of none or mild (maximum smile) on Day 30 was 118 days for investigator assessments and 116 days for subject assessments. Investigator- and subject-assessed median duration of effect for Day 30 responders with an improvement from baseline of at least 1 grade on the FWS (maximum smile) was 125 and 144 days, respectively.

Safety Measures

Adverse Events

In the safety population ($N = 444$), at least 1 AE was reported by 36.0% of all subjects, 39.1% (86/220) of onabotulinumtoxinA-treated subjects and, 33.0% (74/224) of placebo-treated subjects. Most events were mild to moderate in severity. The most frequently reported AEs (reported by 1% or more of subjects) are shown in Table 4. No treatment discontinuations resulted from AEs.

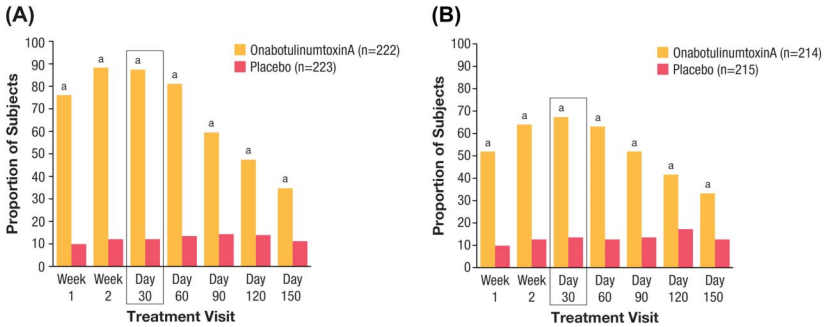

Figure 4. Proportion of subjects achieving an improvement from baseline of at least 1 grade on the FWS. (A) At maximum smile. (B) At rest. The boxed bars represent the primary time point. a indicates $P < .001$.

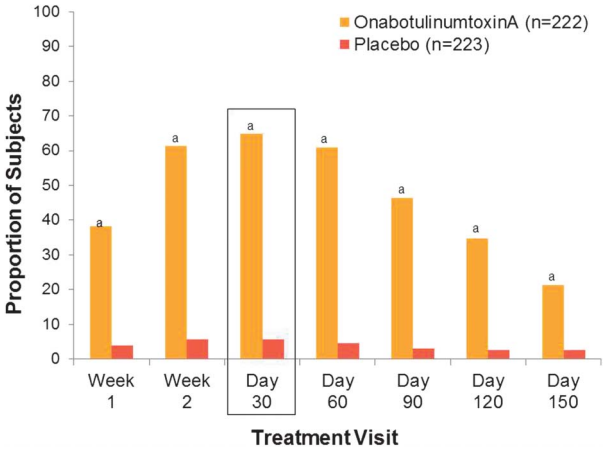

Figure 5. Proportion of subjects rating themselves as "very much improved" or "much improved" on the SGA-CFL. The boxed bars represent the primary time point. a indicates P < .001.

Treatment-related AEs were reported by 6.4% (14/220) of onabotulinumtoxinA-treated subjects and 4.5% (10/224) of placebo-treated subjects. The majority of them were mild. No clinically relevant between-group differences were observed. Headache was the most frequently reported treatment-related AE in each group (onabotulinumtoxinA, 2.7% [6/220]; placebo, 1.3% [3/224]). Injection-site hemorrhage and injection-site reaction were each reported in 2 of the 220 (0.9%) onabotulinumtoxinA-treated subjects. Injection-site hematoma and injection-site pain were each reported in 3 of the 224 (1.3%) placebo-treated subjects. One serious event, termination of a nonviable twin pregnancy early in the first trimester of pregnancy in the onabotulinumtoxinA group, was reported as treatment related.

Neurologic Assessments and Spread of Toxin

The neurologic assessment revealed no neurologic events or clinically relevant neurologic findings related to possible spread of toxin. Four subjects (1 onabotulinumtoxinA and 3 placebo) reported AEs identified as having a potential relationship to possible spread of toxin. Following detailed medical assessment, mild muscular weakness of the lower eyelid in the onabotulinumtoxinA-treated subject was considered a local pharmacological effect. No events were deemed related to distant spread of toxin.

Immunogenicity

No neutralizing antibodies to onabotulinumtoxinA were detected.

Discussion

In this first large Phase 3 study evaluating the efficacy and safety of onabotulinumtoxinA to treat CFL, all prespecified primary, secondary, and other efficacy endpoints were met. This included the most rigorous composite primary end point, which required a decrease of at least 2 grades from baseline in CFL severity at maximum smile as assessed by both the investigator and the subject on a per-subject basis. Additionally, the proportion of subjects with an investigator-assessed clinically meaningful improvement of at least 1 grade on the FWS, both at maximum smile and at rest, was significantly greater for onabotulinumtoxinA subjects than for placebo subjects through Day 150. The significant improvements in CFL severity as measured by the FWS were supported and complemented by results on a number of PRO measures. The slightly higher numeric differences in responder rates as assessed by investigators versus subjects may be attributable to several factors. First, the investigators were experienced clinicians who routinely assessed CFL in their practices. Additionally, each clinician participated in a standardized training program and gained further experience during this study. Finally, subjects looked into a mirror at an oblique angle to view their CFL compared with the direct view of the investigators. The oblique angle may have made it difficult to see subtle improvements and may thus account for the lack of agreement between the investigator and subject assessments. The inability to detect subtle improvements may also explain why subject-assessed peak response was later compared with the investigator-assessed peak response.

OnabotulinumtoxinA treatment was well tolerated in this study, with no clinically relevant between-group differences in the incidence of AEs and no discontinuations because of AEs. No neurologic findings or AEs suggested distant spread of toxin; no neutralizing antibodies to onabotulinumtoxinA were detected. One serious AE, termination of a nonviable twin pregnancy (miscarriage of 1 fetal sac and subsequent no fetal heart rate leading to termination of the other) early in the first trimester of pregnancy, was reported as treatment related, although the investigator considered the event unlikely to be related to onabotulinumtoxinA treatment. The occurrence of spontaneous abortion in

TABLE 4. Most Common AEs (Reported in at Least 1% of the Subjects)

System Organ Class	Preferred Term*	OnabotulinumtoxinA 24 U (n = 220), n (%)	Placebo (n = 224), n (%)	Total (N = 444), n (%)
Overall		86 (39.1)	74 (33.0)	160 (36.0)
Gastrointestinal disorders	Overall	6 (2.7)	2 (0.9)	8 (1.8)
	Toothache	3 (1.4)	0 (0)	3 (0.7)
General disorders and administration-site conditions	Overall	12 (5.5)	9 (4.0)	21 (4.7)
	Injection-site hematoma	3 (1.4)	4 (1.8)	7 (1.6)
	Injection-site paresthesia	3 (1.4)	0 (0)	3 (0.7)
	Injection-site pain	1 (0.5)	3 (1.3)	4 (0.9)
Infections and infestations	Overall	35 (15.9)	34 (15.2)	69 (15.5)
	Nasopharyngitis	8 (3.6)	6 (2.7)	14 (3.2)
	Upper respiratory tract infection	5 (2.3)	6 (2.7)	11 (2.5)
	Bronchitis	4 (1.8)	2 (0.9)	6 (1.4)
	Sinusitis	3 (1.4)	4 (1.8)	7 (1.6)
	Influenza	2 (0.9)	4 (1.8)	6 (1.4)
	Vaginal infection†	2 (1.0)	0 (0)	2 (0.5)
Nervous system disorders	Overall	12 (5.5)	10 (4.5)	22 (5.0)
	Headache	10 (4.5)	4 (1.8)	14 (3.2)
Reproductive system and breast disorders	Overall	0 (0)	1 (0.4)	1 (0.2)
	Prostatitis‡	0 (0)	1 (3.1)	1 (1.6)
Skin and subcutaneous tissue disorders	Overall	6 (2.7)	10 (4.5)	16 (3.6)
	Dermatitis contact	3 (1.4)	3 (1.3)	6 (1.4)

*Only includes AEs with corresponding preferred terms of incidence rate of at least 1% for any of the treatment groups.
†Percentages were based on the female population.
‡Percentages were based on the male population.

this study is lower than the overall fetal loss rate of approximately 17% in the US population.[7] Two other pregnancies occurred in this study, 1 in an onabotulinumtoxinA-treated subject and 1 in a placebo-treated subject; both went to term with no complications.

Generally, treatment effects were observed by the first in-office visit at Week 1 and lasted up to 5 months, which was the end of the study. This study was not designed to assess the onset of effect, likely to have occurred before the first assessment. Durations of effect longer than 5 months also could not be determined in this study.

It has recently been stated that CFL treatment effects are best evaluated at rest.[8] Nevertheless, botulinum toxins affect the muscles, and therefore assessment of the attempted contraction of treated muscles provides reliable and relevant results. Subjects with moderate-to-severe lines at maximum smile seek onabotulinumtoxinA treatment though their lines at rest may be less severe. Also, treatment effects are clearly discernible at maximum smile, whereas assessment of treatment at rest alone may also be influenced by subtle factors such as skin care regimen and hydration. Although the primary end points in this study were based on assessment at maximum smile, the design also incorporated assessments at rest, which provides a comprehensive profile of treatment effects in both contracted and resting conditions.

In conclusion, this initial study in a robust Phase 3 program established that onabotulinumtoxinA is effective and well tolerated for the treatment of moderate-to-severe CFL based on a broad range of clinical and PRO measures. In subjects treated with onabotulinumtoxinA, significant improvements in CFL severity were measured by the FWS at Day 30 and treatment effects lasted through the end of the study, as assessed independently by the investigator or the subject, and were observed both at maximum smile and at rest. These FWS results were complemented by high subject satisfaction for the duration of the 5-month study.

Note: Dosing and results reported in this study are specific to the formulation of BoNTA manufactured by Allergan, Inc. This formulation is not interchangeable with other botulinum toxin products and cannot be converted using a dose ratio.

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