A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Repeated OnabotulinumtoxinA Treatments in Subjects With Crow's Feet Lines and Glabellar Lines

Jean Carruthers, MD,* Alexander Rivkin, MD,† Lisa Donofrio, MD,‡§
Vince Bertucci, MD, FRCPC,‖ Chris Somogyi, RN,¶ Xiaofang Lei, PhD,¶
Paula G. Davis, PhD,# Antoinette Campo,# and Frederick C. Beddingfield, MD, PhD†¶

BACKGROUND This is the third study in a Phase 3 program evaluating onabotulinumtoxinA treatment of crow's feet lines (CFL).

OBJECTIVE To assess the efficacy and safety of repeated onabotulinumtoxinA treatments of CFL alone or with glabellar lines (GL) in subjects with moderate-to-severe CFL and GL (maximum smile).

MATERIALS AND METHODS This 5-month extension of a 7-month study randomized subjects who originally received onabotulinumtoxinA 24 U (CFL only; n = 227) or 44 U (24 U for CFL + 20 U for GL; n = 260) to retreatment with the same dose. Placebo-treated subjects were rerandomized to onabotulinumtoxinA 44 U (n = 101) or placebo (n = 96). Primary efficacy end point (Day 30) was the proportion of subjects who achieved a CFL severity rating of none or mild (maximum smile) on the investigator-assessed Facial Wrinkle Scale (FWS). Additional efficacy end points and adverse events were evaluated.

RESULTS Responder rates (primary end point) were significantly greater in onabotulinumtoxinA-treated groups (24 U: 56.5%; 44 U: 63.6%; placebo: 1.1%; $p < .001$). Improvements on most patient-reported outcomes (PROs) favored the 44-U group over the 24-U group. Adverse events did not differ among groups; most were mild or moderate.

CONCLUSION Repeated onabotulinumtoxinA treatments significantly reduce CFL severity based on FWS and PROs. Adverse event profiles remain consistent with approved GL labeling.

J. Carruthers and A. Rivkin are consultants and investigators for Allergan, Inc. L. Donofrio is an investigator for Allergan, Inc. V. Bertucci is a speaker, consultant, and investigator for Allergan, Inc. X. Lei is an employee of Allergan, Inc., and receives compensation in salary, as well as stock or stock options (or both). C. Somogyi and F. C. Beddingfield were employees of Allergan, Inc. at the time of this study and received compensation in salary, as well as stock or stock options (or both). The other authors have indicated no significant interest with commercial supporters.

The US Food and Drug Administration (US FDA)–approved indication for onabotulinumtoxinA is the treatment of glabellar lines (GL). Nevertheless, treatment of other facial areas, including crow's feet lines (CFL), is common in clinical practice, and treatment of CFL has been approved by the regulatory

Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada; †Division of Dermatology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California; ‡Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut; §Department of Dermatology, Tulane University School of Medicine, New Orleans, Louisiana; ‖Division of Dermatology, University of Toronto, Toronto, Ontario, Canada; ¶Allergan, Inc., Irvine, California; #SCI Scientific Communications & Information, Parsippany, New Jersey. C. Somogyi and F. C. Beddingfield are now at Kythera Biopharmaceuticals, Inc., Calabasas, California

Sponsored by Allergan, Inc., Irvine, CA. Writing and editorial assistance was provided by SCI Scientific Communications & Information, Parsippany, NJ, and was funded by Allergan, Inc. Irvine, CA.

ISSN: 1076-0512 • Dermatol Surg 2015;41:702–711 • DOI: 10.1097/DSS.0000000000000357

authorities of some countries.[1] This study was the third in a comprehensive Phase 3 trial program designed to assess the efficacy and safety of onabotulinumtoxinA for the treatment of CFL under a number of conditions. Each study in the program was a large-scale, double-blind, placebo-controlled trial. Dosing and injection patterns for the entire Phase 3 program were based on the results of 2 Phase 2 studies of onabotulinumtoxinA treatment of the CFL and the usual approved label dose for treating GL (Data on file; Allergan, Inc., Irvine, CA).[2,3]

The first trial (Study 191622-098) evaluated a single treatment of onabotulinumtoxinA or placebo in subjects with moderate-to-severe CFL, and it demonstrated the efficacy and safety of onabotulinumtoxinA based on a broad range of investigator- and patient-reported outcome (PRO) measures.[4] The second, a 7-month study (Study 191622-099), evaluated the effects of treating the CFL alone or together with GL and included 2 treatment cycles, which are common clinical practices.[5] The results established the efficacy and safety of simultaneous treatment of CFL and GL and of a repeat treatment.

This study was designed to evaluate the efficacy and safety of repeated treatments of onabotulinumtoxinA in the CFL area, either alone or in combination with the glabellar area, for a total of 1 year.

Materials and Methods

Study Design and Subjects

This was a multicenter, 5-month, double-blind, randomized, parallel-group, placebo-controlled extension study of subjects who completed the 7-month Phase 3 study (Study 191622-099; www.clinicaltrials.gov identifier: NCT01224015). The design of this study allowed for up to 2 additional treatment cycles and for up to 1 year of treatment exposure.

OnabotulinumtoxinA-treated and placebo-treated subjects from Study 191622-099 were eligible to participate in this study. Investigators obtained approval of the study (191622-104) from an institutional review board or independent ethics committee before study initiation. Subjects had to provide written informed consent in addition to meeting other key inclusion and exclusion criteria as described for Study 191622-099.[5] The study was conducted in accordance with guidelines and regulations for Good Clinical Practice and all relevant local and country privacy guidelines.

Procedures

Randomization took place on Day 1 of this study, corresponding to the last day of Study 191622-099. Subjects who had received onabotulinumtoxinA in Study 191622-099 continued to receive the same dose (44 U for CFL + GL, 24 U for CFL alone) in this study. Subjects who had received placebo in Study 191622-099 were rerandomized in a double-blind fashion to either 44 U onabotulinumtoxinA (CFL + GL) or to placebo in a 1:1 ratio (stratified by investigation site). Therefore, this study included 4 treatment groups (Figure 1).

Medication reconstitution and administration were as previously described for Study 191622-099.[5] Subjects

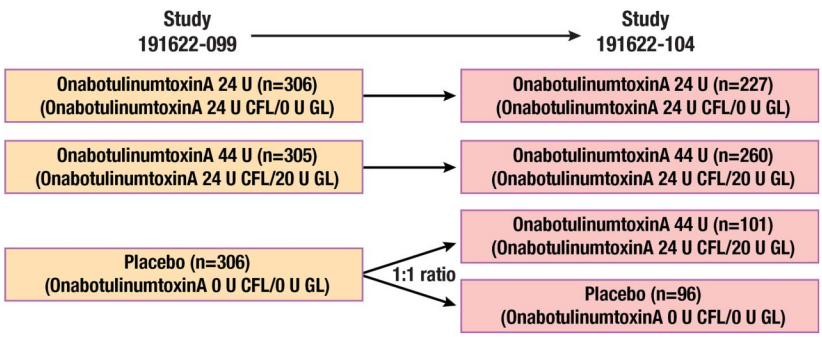

Figure 1. Randomization schedule.[5]

who successfully completed Study 191622-099 and adhered to the entry criteria were eligible to enroll in this study. In addition, subjects must have had an interval of at least 3 months (minimum of 84 days) since the previous treatment in either Study 191622-099 or this study.

Subjects could receive up to 2 additional treatments in this extension study; the first treatment (corresponding to treatment cycle 3 of the total 1-year assessment) could be on Day 1, 30, 60, or 90 of this study. Subjects who received treatment on Day 1 could have a second treatment on Day 90. Those who did not qualify for treatment on Day 1 of this study were reevaluated for retreatment monthly (Day 30, 60, or 90 time points). No treatment was allowed after the Day 90 visit of this study. Post-treatment efficacy and safety evaluations took place at Weeks 1 and 2, Day 30, and then at 30-day intervals through study exit at Day 150 or at early discontinuation (Figure 2). The first treatment cycle of this study corresponded to subjects' third treatment cycle overall, with the first 2 treatments taking place in Study 191622-099. Results were then presented according to the overall treatment cycle number, which in this study were cycles 3 and 4.

Outcome Measures and End Points

Efficacy

The primary end point was the proportion of subjects achieving a grade of none or mild at maximum smile on Day 30 of treatment cycle 3 based on investigator's Facial Wrinkle Scale (FWS) ratings. Other efficacy end points based on investigator ratings on the FWS were the proportion of subjects achieving none or mild at other time points (maximum smile), the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at maximum smile, and the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at rest, among subjects who were rated at least mild at baseline. Subject-rated end points included the proportion of subjects achieving a grade of none or mild in CFL severity at maximum smile, the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at maximum smile, and the proportion achieving an improvement from baseline of at least 1 grade in CFL severity at rest, among subjects who rated themselves at least mild at baseline.

Other PROs included the Subject's Global Assessment of Change in Crow's Feet Lines (SGA-CFL), the validated Facial Line Outcomes Questionnaire (FLO-11) psychological impact (Items 2, 5, and 8), and Self-Perception of Age (SPA) and the Subject Satisfaction of Appearance.

Safety and Tolerability

Safety and tolerability were assessed as previously described for Study 191622-099, including adverse events (AEs), neurologic assessments, and analysis of key AEs possibly associated with spread of toxin. Serum samples were tested for binding and neutralizing antibodies to botulinum toxin type A, also as described previously.[5]

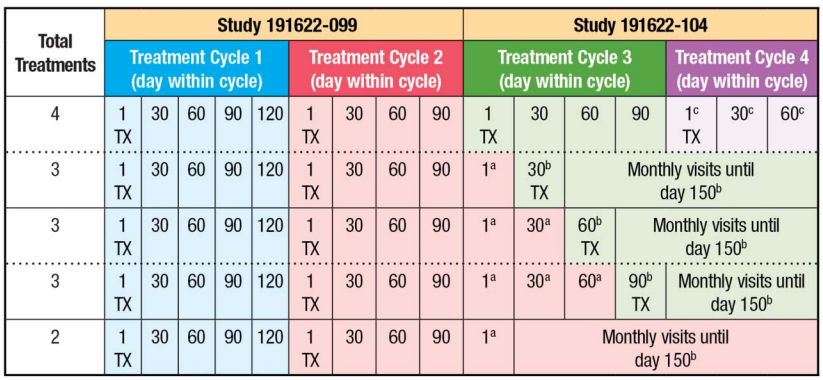

Figure 2. Treatment and evaluation schedule. Treatment cycle 3 is the first treatment in this study (Study 191622-104). No treatment was allowed after the Day 90 visit of the study. TX, study drug treatment administered. [a]Visits assigned to treatment cycle 2. [b]Visits assigned to treatment cycle 3. [c]Visits assigned to treatment cycle 4.

Data Analyses

Data analyses were performed as previously described for Study 191622-099.[5]

Results

Subjects and Treatments

Of 684 subjects enrolled, 641 (93.7%) completed this study (Figure 3). A total of 667 subjects (97.5%) received the third treatment. Most subjects who received a third dose (80.2%; 535/667) received their dose at Day 1 visit of Study 191622-104. A total of 414 subjects (60.5%) received 2 treatments (treatment cycles 3 and 4): 149 onabotulinumtoxinA 24 U/24 U, 123 onabotulinumtoxinA 44 U/44 U, 69 placebo/onabotulinumtoxinA 44 U, and 73 placebo/placebo. In this study, 253 subjects (37.0%) received only 1 treatment (treatment cycle 3): 74 onabotulinumtoxinA 24 U/24 U, 126 onabotulinumtoxinA 44 U/44 U, 31 placebo/onabotulinumtoxinA 44 U, and 22 placebo/placebo. Seventeen subjects failed to meet retreatment criteria after they received treatment 2 in Study 191622-099 and therefore did not receive any treatment in this study: 4 onabotulinumtoxinA 24 U/24 U, 11 onabotulinumtoxinA 44 U/44 U, 1 placebo/onabotulinumtoxinA 44 U, and 1 placebo/placebo.

Baseline demographics and subject characteristics were collected and tabulated at the beginning of Study 191622-099.[5] No significant between-group differences in demographics (Table 1), CFL or GL severity (Table 2), or PRO measures of CFL appearance were observed in subjects who enrolled in the extension phase of the trial.

Efficacy Outcomes

To present the results of this study, the authors combined the efficacy data for all subjects who received 44 U of onabotulinumtoxinA (onabotulinumtoxinA 44 U/onabotulinumtoxinA 44 U and placebo/onabotulinumtoxinA 44 U) (Figure 1).

Responder Rates Based on Achieving None or Mild on Facial Wrinkle Scale (Investigator Ratings)
Based on investigator ratings at maximum smile, the responder rates on Day 30 (the primary efficacy end point) were significantly greater for onabotulinumtoxinA treatment than for placebo treatment ($p < .001$): onabotulinumtoxinA 44 U, 63.6%; onabotulinumtoxinA 24 U, 56.5%; and placebo, 1.1%. Responder rates during treatment cycles 3 and 4 were also significantly greater ($p \leq .004$) for the onabotulinumtoxinA groups than for the placebo group at all other time points assessed (Figure 4). Although onabotulinumtoxinA 44 U tended to result in numerically higher responder rates than 24 U, including the Day 30 time point, the differences were not statistically significant.

Responder Rates Based on Subjects Achieving an Improvement From Baseline of at Least 1 Grade on the Facial Wrinkle Scale (Investigator Ratings)
At both maximum smile and at rest, responder rates were significantly greater ($p < .001$) in the onabotulinumtoxinA-treated groups compared with the placebo-treated group at Day 30 of treatment cycles 3 and 4 (Figure 5). Responder rates at maximum smile and at rest were also significantly greater ($p < .001$ and $p \leq .004$, respectively) for the onabotulinumtoxinA-treated groups than for placebo at all other time points in treatment cycles 3 and 4 (data not shown).

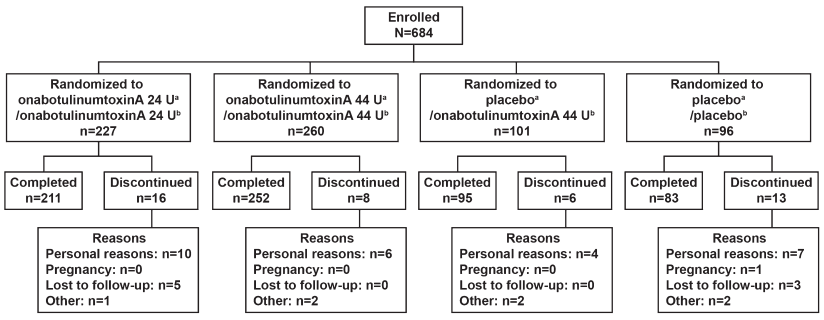

Figure 3. Subject disposition. [a]Randomized treatment assignment in Study 191622-099.[5] [b]Randomized treatment assignment in Study 191622-104.

TABLE 1. Baseline Demographics

	OnabotulinumtoxinA 44 U/44 (n = 260)	*OnabotulinumtoxinA 24 U/24 U (n = 227)*	*Placebo/OnabotulinumtoxinA 44 U (n = 101)*	*Placebo/Placebo (n = 96)*	*Total (N = 684)*	*p*
Age, yrs*						.902
N	260	227	101	96	684	
Mean	49.7	49.4	49.4	49.1	49.4	
SD	9.48	9.35	9.23	9.32	9.36	
Sex, *n* (%)						.495
Male	34 (13.1)	24 (10.6)	12 (11.9)	16 (16.7)	86 (12.6)	
Female	226 (86.9)	203 (89.4)	89 (88.1)	80 (83.3)	598 (87.4)	
Race, *n* (%)						.964
White	232 (89.2)	200 (88.1)	89 (88.1)	84 (87.5)	605 (88.5)	
Non-white	28 (10.8)	27 (11.9)	12 (11.9)	12 (12.5)	79 (11.5)	

*Age was calculated from date of birth to date of the subject's randomization visit in Study 191622-099.

Responder Rates Based on Achieving None or Mild on Facial Wrinkle Scale (Subject Ratings)

On Day 30 of treatment cycle 3, subject-assessed responder rates of none or mild on the FWS were significantly greater ($p < .001$) in the onabotulinumtoxinA treatment groups than in the placebo groups: onabotulinumtoxinA 44 U, 51.6%; onabotulinumtoxinA 24 U, 45.3%; and placebo 3.2%. Similar results were seen in treatment cycle 4 (data not shown).

Responder Rates Based on Subjects Achieving an Improvement From Baseline of at Least 1 Grade on the Facial Wrinkle Scale (Subject Ratings)

Similar to investigator ratings, responder rates at maximum smile and at rest were significantly greater ($p < .001$) in the onabotulinumtoxinA-treated groups compared with the placebo-treated group at Day 30 of treatment cycles 3 and 4 (Figure 6). Responder rates at maximum smile were also significantly greater ($p \leq .003$) for the onabotulinumtoxinA-treated groups than for placebo at all other time points in treatment cycles 3 and 4 (data not shown). For time points other than Day 30, responder rates at rest were significantly greater in the onabotulinumtoxinA groups compared with the placebo group ($p \leq .013$) except for Day 150, treatment cycle 3, for the onabotulinumtoxinA 24-U group.

Subject's Global Assessment of Change in Crow's Feet Lines

On Day 30 of treatment cycle 3, the proportion of subjects rating themselves as very much improved or much improved were 59.6% (208/349), 56.5% (126/223), and 5.3% (5/95) for the onabotulinumtoxinA 44-U, onabotulinumtoxinA 24-U, and placebo treatment groups, respectively. The differences between each onabotulinumtoxinA treatment group and the placebo group were statistically significant ($p < .001$). Furthermore, statistically significant differences ($p \leq .020$) were observed at all time points (except Days 120 and 150 of treatment cycle 3 for the onabotulinumtoxinA 24-U group) in onabotulinumtoxinA-treated subjects compared with placebo-treated subjects.

Facial Line Outcomes Questionnaire-11 (Psychological Impact Items 2, 5, and 8)

The proportion of responders for FLO-11 Items 2, 5, and 8 was significantly greater ($p \leq .005$) in the onabotulinumtoxinA-treated groups than in the

TABLE 2. Baseline CFL and GL Severity

Area	Variable	Number (%) of Subjects: OnabotulinumtoxinA 44 U/44 U (n = 260)	OnabotulinumtoxinA 24 U/24 U (n = 227)	Placebo/OnabotulinumtoxinA 44 U (n = 101)	Placebo/Placebo (n = 96)	Total (n = 684)	p*
CFL	Investigator FWS at maximum smile						.934†
	Moderate	95 (36.5)	89 (39.2)	38 (37.6)	35 (36.5)	257 (37.6)	
	Severe	165 (63.5)	138 (60.8)	63 (62.4)	61 (63.5)	427 (62.4)	
	Subject FWS at maximum smile						.986†
	Moderate	96 (36.9)	87 (38.3)	38 (37.6)	35 (36.5)	256 (37.4)	
	Severe	164 (63.1)	140 (61.7)	63 (62.4)	61 (63.5)	428 (62.6)	
	Investigator FWS at rest						.265
	None	10 (3.8)	7 (3.1)	3 (3.0)	4 (4.2)	24 (3.5)	
	Mild	67 (25.8)	71 (31.3)	23 (22.8)	20 (20.8)	181 (26.5)	
	Moderate	131 (50.4)	99 (43.6)	54 (53.5)	43 (44.8)	327 (47.8)	
	Severe	52 (20.0)	50 (22.0)	21 (20.8)	29 (30.2)	152 (22.2)	
	Subject FWS at rest						.807
	None	8 (3.1)	5 (2.2)	3 (3.0)	2 (2.1)	18 (2.6)	
	Mild	60 (23.1)	54 (23.8)	20 (19.8)	20 (20.8)	154 (22.5)	
	Moderate	139 (53.5)	116 (51.1)	58 (57.4)	50 (52.1)	363 (53.1)	
	Severe	53 (20.4)	52 (22.9)	20 (19.8)	24 (25.0)	149 (21.8)	
GL	Investigator FWS at maximum frown						.405
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.1)	
	Moderate	91 (35.0)	79 (34.8)	44 (43.6)	36 (37.5)	250 (36.5)	
	Severe	169 (65.0)	148 (65.2)	57 (56.4)	59 (61.5)	433 (63.3)	
	Investigator FWS at rest						.816
	None	17 (6.5)	17 (7.5)	6 (5.9)	10 (10.4)	50 (7.3)	
	Mild	79 (30.4)	74 (32.6)	39 (38.6)	26 (27.1)	218 (31.9)	
	Moderate	119 (45.8)	89 (39.2)	39 (38.6)	45 (46.9)	292 (42.7)	
	Severe	45 (17.3)	47 (20.7)	17 (16.8)	15 (15.6)	124 (18.1)	

*P-values for among-treatment comparisons were determined by Kruskal-Wallis test.

†A Pearson's chi-square test was performed to evaluate the equality of proportions between treatment groups. If 25% or more of the cells had expected counts less than 5, then Fisher's exact test was used instead.

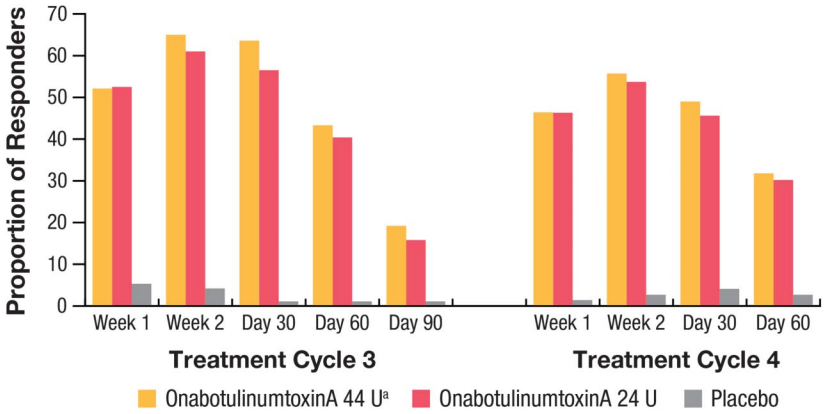

Figure 4. Proportion of subjects achieving none or mild based on investigator's FWS rating of CFL severity at maximum smile (intent-to-treat population). Day 30 of treatment cycle 3 was the primary time point for efficacy end points. The proportion of responders was significantly greater in each onabotulinumtoxinA treatment group than in the placebo group at all time points ($p < .001$). [a]Efficacy results pooled for subjects in the onabotulinumtoxinA 44/44-U group and the placebo/onabotulinumtoxinA 44-U group.

placebo-treated group on Day 30 (treatment cycles 3 and 4; Figure 7) and up to at least Day 60 in each treatment cycle ($p \leq .013$). For example, for Day 30 of treatment cycle 3, the combined onabotulinumtoxinA responder rates for Items 2, 5, and 8 were 76.3%, 66.0%, and 61.4%, respectively, compared with 32.6%, 26.7%, and 27.3%, respectively, for the corresponding placebo group rates. In addition, the differences between the onabotulinumtoxinA 44-U and the onabotulinumtoxinA 24-U groups were statistically significant ($p \leq .010$) on Day 30 of treatment cycle 3 and at several time points in other treatment cycles.

Subject Assessment of Satisfaction With Appearance

In treatment cycle 3, the proportion of subjects who were neutral or worse at baseline and were satisfied or very satisfied with their appearance at Day 30 was 58.3% (196/336) in the onabotulinumtoxinA 44-U group, 52.5% (115/219) in the onabotulinumtoxinA 24-U group, and 7.5% (7/93) in the placebo group ($p < .001$ between each onabotulinumtoxinA group and placebo). Results in treatment cycle 4 were similar, with 56.8% (105/185), 49.0% (72/147), and 5.6% (4/71) in the same 3 groups, respectively ($p < .001$ between each onabotulinumtoxinA group and placebo).

Self-Perception of Age

Subjects rating themselves as looking their current age or older at baseline were included in the analysis. At Day 30 of treatment cycle 3, significantly greater proportions ($p < .001$) of subjects in the onabotulinumtoxinA 44-U (47.5%; 143/301) and

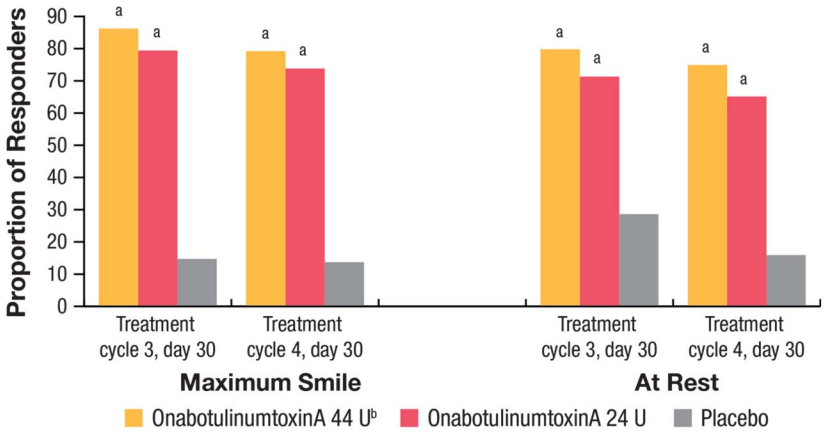

Figure 5. Proportion of subjects achieving an improvement from baseline of at least 1 grade in CFL severity (investigator ratings) at Day 30 of treatment cycles 3 and 4. [a]$p < .001$, onabotulinumtoxinA 44 U and onabotulinumtoxinA 24 U versus placebo. [b]Efficacy results pooled for subjects in the onabotulinumtoxinA 44/44-U group and the placebo/onabotulinumtoxinA 44-U group.

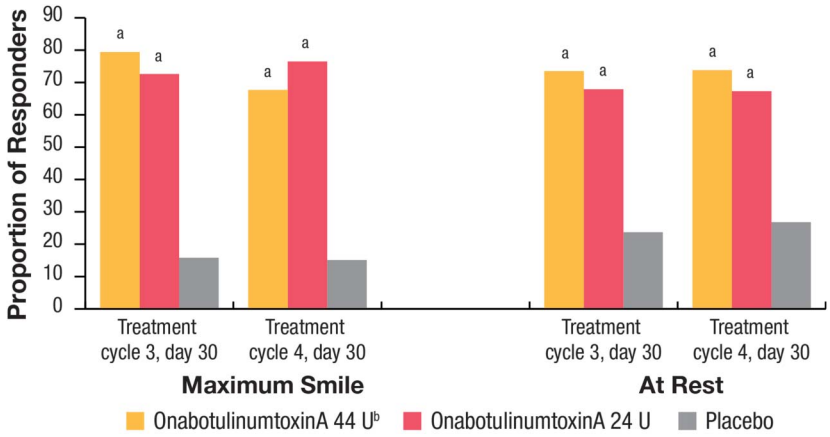

Figure 6. Proportion of subjects achieving an improvement from baseline of at least 1 grade in CFL severity (subject ratings) at Day 30 of treatment cycles 3 and 4. [a]$p < .001$, onabotulinumtoxinA 44 U and onabotulinumtoxinA 24 U versus placebo. [b]Efficacy results pooled for subjects in the onabotulinumtoxinA 44/44-U group and the placebo/onabotulinumtoxinA 44-U group.

onabotulinumtoxinA 24-U (38.7%; 75/194) groups reported that they looked younger than their current age compared with the placebo group (5.1%; 4/79). Similar results were seen in treatment cycle 4, with 47.0% (79/168), 40.8% (53/130), and 6.7% (4/60) reporting looking younger in the onabotulinumtoxinA 44-U, onabotulinumtoxinA 24-U, and placebo groups, respectively ($p < .001$, each onabotulinumtoxinA treatment group vs the placebo group).

Safety and Tolerability

Adverse Events

During the 1-year assessment period (Studies 191622-099 and 104), 58.2% of subjects reported at least 1 AE. Most of these AEs were mild or moderate in severity, and there were no differences by treatment group. The frequency of AEs was onabotulinumtoxinA 44 U/onabotulinumtoxinA 44 U, 58.5%; onabotulinumtoxinA 24 U/onabotulinumtoxinA 24 U, 56.4%; placebo/onabotulinumtoxinA 44 U, 61.4%; and placebo/placebo, 58.3%. The most frequently reported AEs by MedDRA-preferred term and treatment cycle are shown in Table 3. The majority of AEs were not considered treatment-related. The most frequently reported treatment-related AEs were injection site hematoma (including bruises), headache, and injection site hemorrhage, all of which occurred at a frequency of 3.1% or less in each of the 4 treatment cycles. No differences in the incidence of overall AEs or

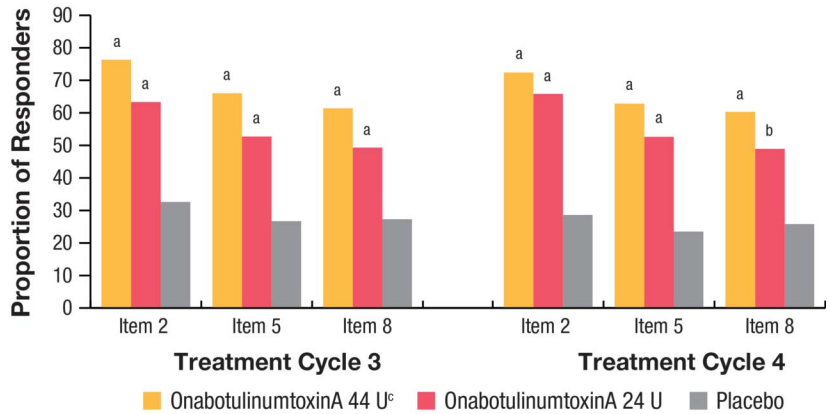

Figure 7. Proportion of responders on FLO-11 Items 2, 5, and 8 (Day 30, treatment cycles 3 and 4). The proportion of responders was significantly greater in the onabotulinumtoxinA treatment groups than in the placebo group ($p \leq .005$, all comparisons). [a]$p < .001$ and [b]$p < .005$, onabotulinumtoxinA 44-U and onabotulinumtoxinA 24-U versus placebo. [c]Efficacy results pooled for subjects in the onabotulinumtoxinA 44/44-U group and the placebo/onabotulinumtoxinA 44-U group.

TABLE 3. Most Frequently Reported AEs Over 12 Months by Preferred Term and Treatment Cycle

	Number/Total n (%)			
	OnabotulinumtoxinA 44 U	*OnabotulinumtoxinA 24 U*	*Placebo*	*Total*
Injection site hematoma				
Cycle 1	5/260 (1.9)	7/227 (3.1)	4/197 (2.0)	16/684 (2.3)
Cycle 2	8/260 (3.1)	9/227 (4.0)	0/197 (0.0)	17/684 (2.5)
Cycle 3	12/349 (3.4)	6/223 (2.7)	5/95 (5.3)	23/667 (3.4)
Cycle 4	9/192 (4.7)	7/149 (4.7)	1/73 (1.4)	17/414 (4.1)
Headache				
Cycle 1	12/260 (4.6)	10/227 (4.4)	9/197 (4.6)	31/684 (4.5)
Cycle 2	7/260 (2.7)	0/227 (0.0)	3/197 (1.5)	10/684 (1.5)
Cycle 3	14/349 (4.0)	2/223 (0.9)	2/95 (2.1)	18/667 (2.7)
Cycle 4	4/192 (2.1)	1/149 (0.7)	1/73 (1.4)	6/414 (1.4)
Nasopharyngitis				
Cycle 1	14/260 (5.4)	9/227 (4.0)	7/197 (3.6)	30/684 (4.4)
Cycle 2	6/260 (2.3)	1/227 (0.4)	4/197 (2.0)	11/684 (1.6)
Cycle 3	6/349 (1.7)	5/223 (2.2)	4/95 (4.2)	15/667 (2.2)
Cycle 4	0/192 (0.0)	4/149 (2.7)	3/73 (4.1)	7/414 (1.7)
Upper respiratory tract infection				
Cycle 1	5/260 (1.9)	7/227 (3.1)	3/197 (1.5)	15/684 (2.2)
Cycle 2	3/260 (1.2)	2/227 (0.9)	2/197 (1.0)	7/684 (1.0)
Cycle 3	5/349 (1.4)	2/223 (1.3)	1/95 (1.1)	9/667 (1.3)
Cycle 4	2/192 (1.0)	1/149 (0.7)	0/73 (0.0)	3/414 (0.7)

Within each type of relationship, a subject is counted once at most. All AEs include all reported events that began during the treatment cycle, regardless of the relationship to treatment. Subjects treated with placebo in Study 191622-099 and treated with onabotulinumtoxinA 44 U in Study 191622-104 are included in the placebo group for treatment cycles 1 and 2 and in the onabotulinumtoxinA 44-U group for cycles 3 and 4.

treatment-related AEs were noted across the 4 treatment cycles. The incidence of most treatment-related AEs appeared to decline with repeated treatments. A total of 21 of the 684 subjects (3.1%) experienced 24 serious AEs, none of which were considered treatment-related. No subjects died or discontinued because of an AE.

Ten subjects (2 onabotulinumtoxinA 24 U/24 U, 5 onabotulinumtoxinA 44-U/44-U, 2 placebo/onabotulinumtoxinA 44-U, 1 placebo/placebo) experienced events that were identified as having potential relationship to possible spread of toxin. After detailed medical assessment, ptosis was considered a local pharmacologic effect. There were no events deemed related to distant spread of toxin. No seroconversions for neutralizing antibodies against onabotulinumtoxinA occurred in the samples from subjects treated up to 4 times with onabotulinumtoxinA.

Discussion and Conclusion

OnabotulinumtoxinA was evaluated for its efficacy and safety in the treatment of CFL in a large-scale comprehensive Phase 3 program comprising 3 trials. The results demonstrated that onabotulinumtoxinA treatments result in statistically significant reductions in CFL severity when compared with placebo based on a broad array of investigator- and patient-reported end points. Furthermore, treatment responses were reproducible over multiple treatment cycles. Of note, subjects who received placebo in Study 191622-099 and were thus onabotulinumtoxinA-naive in treatment cycle 3 exhibited similar response rates to those previously treated with onabotulinumtoxinA in that

same study. We believe that these findings reinforce the predictability and consistency of the results.

OnabotulinumtoxinA was well tolerated, with no differences in AE rates between groups when treatment was extended up to 1 year. Specifically, treating CFL and GL at the same time did not result in an increased incidence of AEs compared with treating CFL alone. In addition, the data showed that risks of AEs did not increase with repeated treatments. Also, there was no evidence of distant spread of toxin effects assessed from either the neurologic assessments or the analysis of key AEs per prespecified methodologies. No evidence of immunogenicity was detected over the 12-month treatment period, which included up to 4 treatment cycles.

The paradigm used in this study reflects typical clinical practice in which many patients tend to receive ongoing treatments involving more than 1 anatomic area. Observed differences on PROs between the groups receiving onabotulinumtoxinA treatment in both the CFL and GL and those receiving onabotulinumtoxinA only in the CFL suggest that benefits to subjects are greater when more than 1 area is treated. These findings are consistent with those of Study 191622-099, including the observation that there are nonresponders to treatment. Subjects who were considered nonresponders may have had more severe CFL at baseline and thus were less likely to show the degree of improvement required to be counted as a responder using the FWS end point. One limitation of this study was that, in clinical practice, patients may require retreatment of 1 area before another, so retreatments may not necessarily always occur in multiple areas simultaneously. Second, this study was not designed specifically to assess the duration of effect because subjects could be retreated as early as 90 days after the last treatment without having to return to baseline severity before retreatment.

In conclusion, this study and the Phase 3 program in its entirety provide robust Level 1 evidence supporting the efficacy, safety, and tolerability of repeated injections of onabotulinumtoxinA to treat CFL alone or in combination with GL. OnabotulinumtoxinA treatments are associated with significant reductions in CFL FWS severity as assessed by both investigators and subjects. In addition, onabotulinumtoxinA treatment results in significant improvements in satisfaction with appearance and other PROs, including those related to the psychological impact of CFL. The safety profile was consistent with the approved GL indication, there was no evidence of distant spread of toxin, and no new safety concerns arose, even with up to 4 treatments over the course of a year.

Acknowledgments The authors thank Ms. Elisabeth Lee and Ms. Dawn Schiele, employees of Allergan, Inc., for contributing to the development of the manuscript.

References

1. Dessy LA, Fallico N, Mazzocchi M, Scuderi N. Botulinum toxin for glabellar lines: a review of the efficacy and safety of currently available products. Am J Clin Dermatol 2011;12:377–88.
2. Lowe NJ, Ascher B, Heckmann M, Kumar C, et al; On behalf of the Botox Facial Aesthetics Study Team. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. Dermatol Surg 2005; 31:257–62.
3. Botox Cosmetic [package insert]. Irvine, CA: Allergan, Inc.; 2013.
4. Carruthers A, Bruce S, de Coninck A, Connolly S, et al. Efficacy and safety of onabotulinumtoxinA for the treatment of crow's feet lines: a multicenter, randomized, controlled trial. Dermatol Surg; 40: 1181–90.
5. Moers-Carpi M, Carruthers J, Fagien S, Lupo M, et al. Efficacy and safety of onabotulinumtoxinA for treating crow's feet lines alone or in combination with glabellar lines: a multicenter, randomized, controlled trial. Dermatol Surg 2015;41:102–12.

Address correspondence and reprint requests to: Jean Carruthers Cosmetic Surgery Inc, 943 West Broadway, Suite 820, Vancouver, BC, Canada V5Z4E1;
E-mail: drjean@carruthers.net