OnabotulinumtoxinA for Treatment of Forehead and Glabellar Lines: Subject-Reported Satisfaction and Impact From a Phase 3 Double-Blind Study

Patricia Ogilvie, MD, PhD,* Alexander Z. Rivkin, MD,† Steven Dayan, MD,‡ Steven G. Yoelin, MD,§ Barry M. Weichman, PhD,‖ and Julie K. Garcia, MS, PhD¶

BACKGROUND Patient-reported outcomes are important measures of treatment benefit in facial aesthetic medicine.

OBJECTIVE Evaluate prespecified subject-reported satisfaction and impact outcomes with onabotulinumtoxinA treatment of forehead lines (FHL) and glabellar lines (GL).

METHODS The study randomized (3:1) 391 adults with moderate to severe FHL and GL to onabotulinumtoxinA (FHL, 20 U; GL, 20 U) or placebo in double-blind period 1 (days 0–180); subjects could receive up to 2 additional onabotulinumtoxinA treatments in open-label period 2. Patient-reported outcomes were assessed using the validated Facial Line Satisfaction Questionnaire (FLSQ) and the 11-item Facial Line Outcomes (FLO-11) Questionnaire.

RESULTS The proportion of subjects mostly or very satisfied with treatment was significantly greater with onabotulinumtoxinA than with placebo (90.3% vs 1.0%; $p < .0001$). Responder rates on FLSQ Impact Domain (73.9% vs 18.9%), FLO-11 Item 1 (85.4% vs 3.6%), Item 4 (77.2% vs 11.2%), Item 5 (83.5% vs 7.8%), and total score (86.0% vs 6.9%) were significantly greater with onabotulinumtoxinA than with placebo on Day 30 ($p < .0001$). Responder rates favoring onabotulinumtoxinA in Period 1 were generally maintained with repeated treatment during Period 2.

CONCLUSION Subjects were highly satisfied with onabotulinumtoxinA treatment and reported significant improvements in appearance-related psychological and emotional impacts of their facial lines.

This study was funded by Allergan plc, Dublin, Ireland. Editorial support for this article was provided by Peloton Advantage, Parsippany, New Jersey, and was funded by Allergan plc. P. Ogilvie has received research support or speaking/consultant fees from Allergan plc, Evolus, Inc., Galderma, Merz Aesthetics, and Revance. A.Z. Rivkin serves as a consultant and investigator for Allergan plc and Merz Aesthetics. S. Dayan has received research support or speaking/consultant fees from Allergan plc, Galderma, Merz Aesthetics, and Valeant. S.G. Yoelin serves as a consultant and investigator for Allergan plc. B.M. Weichman was employed by Peloton Advantage, which received funding from Allergan plc for medical editing and editorial support. J.K. Garcia is an employee of Allergan plc and owns stock/options in the company. The opinions expressed in this article are those of the authors. The authors received no honoraria/fee or other form of financial support related to the development of this article.

Upper facial lines can negatively influence self-perception, alter perception of others about age and emotional status, and have adverse psychological impacts.[1–3] Successful treatment of facial lines is associated with subject satisfaction and may lead to improved self-esteem.[1,2] OnabotulinumtoxinA has been used effectively and safely to treat facial lines since the early 1990s.[4] Controlled clinical studies have confirmed the effectiveness and safety of onabotulinumtoxinA for treating multiple types of facial lines, including glabellar lines (GL), lateral canthal lines (crow's feet lines), and forehead lines

*Skin Concept, Munich, Germany; †David Geffen School of Medicine, UCLA, Los Angeles, California; ‡DeNova Research, Chicago, Illinois; §Medical Associates Inc., Newport Beach, California; ‖Peloton Advantage, Parsippany, New Jersey; ¶Allergan plc, Irvine, California

ISSN: 1076-0512 • Dermatol Surg 2019;45:689–699 • DOI: 10.1097/DSS.0000000000001779

(FHL).[5–8] When treating FHL, concomitant treatment of GL is recommended to reduce the risk of eyebrow ptosis by maintaining a balance between eyebrow elevator muscles, primarily the frontalis muscle, and depressor muscles, including the procerus and corrugator muscles that are included in the glabellar complex.[9]

The safety and efficacy of onabotulinumtoxinA for the treatment of FHL, with 20 U to the frontalis muscle and 20 U to the glabellar complex, was evaluated in a 12-month phase 3 study.[10] The primary end point was the proportion of subjects who achieved at least a 2-grade improvement from baseline on Day 30 in FHL severity, as assessed by both the investigator and the subject using the Facial Wrinkle Scale (FWS) with photonumeric guide. This end point was achieved by 61.4% of subjects treated with onabotulinumtoxinA compared with 0% of those who received placebo ($p < .0001$); statistical significance of response versus placebo was maintained through Day 120 ($p = .259$).

Similarly, subject assessment of FHL severity was statistically significant for onabotulinumtoxinA versus placebo at Day 30 ($p < .0001$), reaching 95.4% versus 9.9% for ≥1-grade improvement and 88.7% versus 0% for achievement of none or mild, respectively. Significance of response versus placebo was maintained at all time points through Day 180 ($p \leq .025$). In the study, subject-reported satisfaction and impact of treatment from the subject's perspective were prespecified secondary end points. On the basis of these findings, the US Food and Drug Administration (FDA) approved the addition of subject satisfaction data to the product labeling for onabotulinumtoxinA (Botox Cosmetic; Allergan plc, Dublin, Ireland) for treatment of FHL.[11] The current study reports results for these patient-reported outcome (PRO) end points.

Methods

Subjects

Botulinum toxin–naive men and women aged at least 18 years with both moderate to severe FHL at maximum eyebrow elevation, as evaluated by the investigator and the subject using the FWS, and moderate to severe GL at maximum frown, as assessed by the investigator using the FWS, were eligible. Both measures were performed before treatment on study Day 1. For each assessment, the FWS used descriptors of none, mild, moderate, and severe. Females of childbearing potential were required to have a negative urine pregnancy test before receiving treatment.

Subjects were excluded for any uncontrolled systemic disease, marked periocular or eyebrow asymmetry, marked dermatochalasis, deep dermal scarring, excessively thick sebaceous skin, eyebrow or eyelid ptosis, eyelid folds reaching the pupil or touching the upper lash line, known immunization to any botulinum toxin serotype, or anticipated need for botulinum toxin treatment for another indication during the study. Subjects were also excluded if they had ever undergone prior periorbital, midfacial, or upper facial treatment with permanent soft-tissue fillers, synthetic implant placement, autologous fat transplantation, periorbital surgery, or face- or brow-lifting surgery. Also, subjects who had received any facial nonablative resurfacing laser or light treatment, microdermabrasion, or superficial peel within 3 months of enrollment, any medium- or deep-depth facial chemical peel, or resurfacing or permanent makeup in the study treatment area within 6 months of enrollment, or treatment with nonpermanent soft-tissue fillers or oral retinoids in the study treatment area within 12 months before enrollment were ineligible.

Study Design

This 12-month, phase 3 study (clinicaltrials.gov identifier NCT02261467) was conducted at 9 sites in the United States, 5 in Canada, and 2 in Europe (Ireland) from October 2014 to April 2016. The study was conducted in accordance with ethical principles originating in the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines and national and local regulations. An institutional review board or independent ethics committee approved the study protocol before subjects were enrolled. All subjects provided written informed consent and signed privacy-related documents.

The study comprised a 6-month, double-blind, placebo-controlled, parallel-group treatment period (Period 1, days 1–180) followed by a 6-month open-label treatment period (Period 2, days 180–360). Eligible subjects were randomized (3:1) to receive a single treatment consisting of onabotulinumtoxinA 40 U (20 U in FHL and 20 U in GL) or placebo administered at 10 injection sites (Figure 1). For each site, onabotulinumtoxinA 4 U or placebo was administered in a volume of 0.1-mL bolus injections using a 30-gauge, half-inch needle. The randomization assignment was obtained from an interactive voice/web response system, which was based on a randomization scheme prepared by Allergan Biostatistics. The randomization was stratified at each site by FHL severity at baseline, with enrollment specified to include at least 40% of subjects with moderate FHL and at least 40% with severe FHL, and with at least 60% having a baseline score of at least 5 on each of the 11-item Facial Line Outcomes (FLO-11) Questionnaire Items 1, 4, and 5. After the double-blind period, those subjects with FHL severity at maximum eyebrow elevation and GL severity at maximum frown of at least moderate severity based on the investigator's evaluation using the FWS could receive up to 2 open-label treatments with onabotulinumtoxinA at the same 10 injection sites, with treatment cycles separated by at least 84 days. Follow-up assessments were made at Weeks 1 and 2 after each study treatment. In addition, all subjects had follow-up visits every 30 days from study Day 30 through Day 360.

Prespecified Patient-Reported Outcome Measures

Subjects completed the Facial Line Satisfaction Questionnaire (FLSQ) and FLO-11 at baseline, on Days 7, 14, and 30, then every 30 days through Day 360. Both PRO instruments were developed, validated, and implemented in accordance with US FDA guidance.[12,13] The FLSQ, comprising 11 questions at baseline and 13 questions at follow-up, was designed to assess treatment satisfaction and appearance-related emotional impacts associated with FHL and GL from the subject's perspective.[12] Facial Line Satisfaction Questionnaire Follow-up Item 5 assesses subjects' satisfaction with treatment of their facial lines; it was rated on a 5-point Likert scale, with responses including very satisfied, mostly satisfied, neither satisfied nor dissatisfied, mostly dissatisfied, or very dissatisfied. The FLSQ Impact Domain comprises 5 separate items that measure appearance-related impacts of treatment, including appearance-related age, anger, tiredness, emotional unhappiness, and negative self-esteem. The FLSQ Impact Domain scores range from 0 to 100, with higher scores representing facial lines having a greater negative impact on the subject.

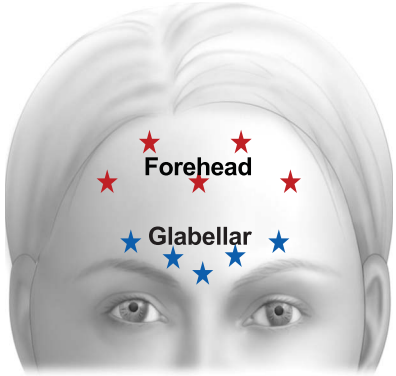

Figure 1. Injection sites for treatment of forehead lines and glabellar lines.

The FLO-11 assesses appearance-related psychological impacts associated with FHL and GL from the subject's perspective.[13] Item 1 evaluates whether subjects are bothered by their facial lines when looking in the mirror, Item 4 evaluates whether subjects feel that they look older than their actual age, and Item 5 evaluates whether subjects feel less attractive than they would like because of their facial lines. Individual FLO-11 Items were rated on a scale from 0 (not at all) to 10 (very much). The total score for all 11 items was transformed to a scale from 0 (worst) to 100 (best).

Statistical Analysis

The PROs were evaluated in the intent-to-treat (ITT) population, which comprised all randomized subjects. The FLSQ Impact Domain, FLSQ Follow-up Item 5, and FLO-11 Items 1, 4, and 5 were prespecified as important secondary efficacy end points because they reflect each subject's perception of treatment effects and drive retreatment decisions. FLSQ Follow-up Item 5 was evaluated as the proportion of subjects who

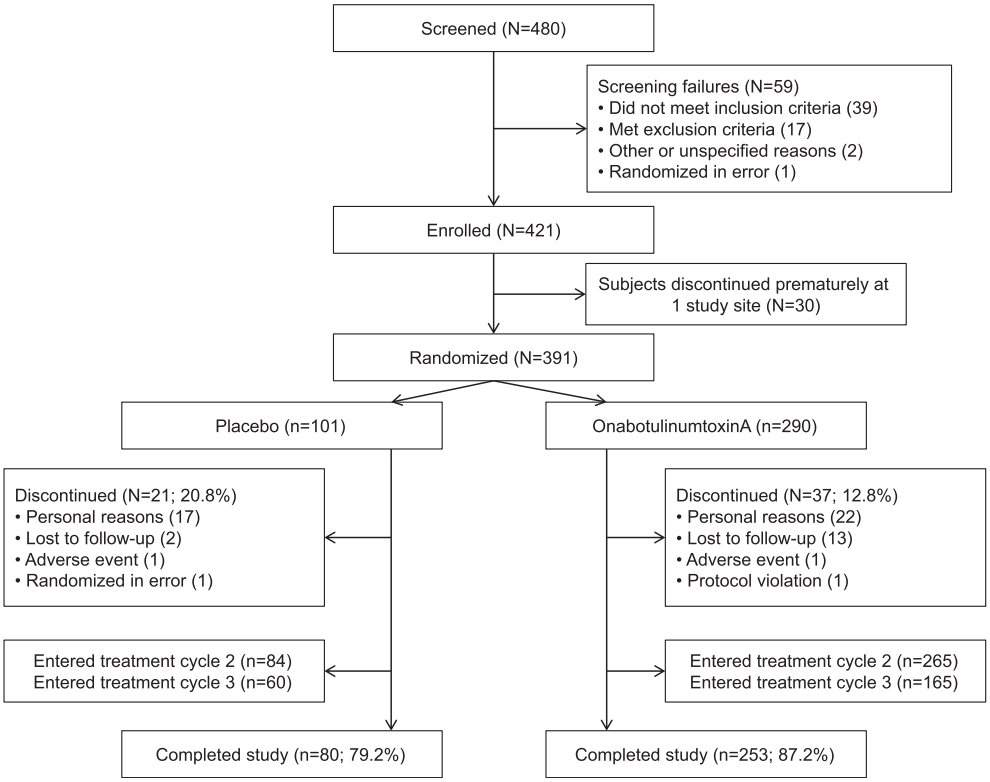

Figure 2. Subject disposition.

were mostly or very satisfied. The FLSQ Impact Domain was evaluated as the proportion of responders defined by at least a 20-point improvement from baseline. This analysis included only those subjects with baseline scores of at least 20. FLO-11 Items 1, 4, and 5 were evaluated as the proportion of responders defined by at least a 3-point improvement from baseline. Only subjects with baseline scores of at least 3 were included. Finally, the FLO-11 total score was evaluated as the proportion of responders defined by at least a 20-point improvement from baseline. Only subjects with 80 points or less at baseline were included. Analyses of these end points were performed at each study visit, with the primary time point prespecified as Day 30 for the FLSQ Impact Domain and FLO-11 Items, and as Day 60 for FLSQ Follow-up Item 5. The choice of Day 60 for subject satisfaction was based on an earlier study showing that peak satisfaction was achieved after peak clinical efficacy.[14] Comparisons between the onabotulinumtoxinA and placebo groups were conducted using the Cochran–Mantel–Haenszel test, stratified by study site, with statistical significance achieved at $p \leq .05$.

Results

Subjects

The ITT population comprised 391 subjects, including 290 randomized to onabotulinumtoxinA and 101 randomized to placebo. The majority completed the 12-month study (n = 333; 85.2%); early discontinuations were mostly attributable to personal reasons or being lost to follow-up (Figure 2). Overall, 349 subjects (89.3%) received onabotulinumtoxinA in treatment cycle 2 and 225 subjects (57.5%) received onabotulinumtoxinA in treatment cycle 3. The treatment groups were well balanced with respect to demographics, baseline facial line severity, and baseline PRO scores (Table 1). The ITT cohort had a median age of 45 years (range, 18–77); the majority of subjects were women (85.9%) and Caucasian (88.7%). All subjects had baseline severity scores of moderate or severe FHL at maximum eyebrow elevation, as assessed by the investigator and subjects, and all except for 1 subject had moderate or severe GL at maximum frown, as assessed by the investigator. Baseline FLSQ Impact Domain and FLO-11 scores

TABLE 1. Subject Demographics and Baseline Characteristics (ITT Population)

Parameter	*OnabotulinumtoxinA* (n = *290*)	*Placebo* (n = *101*)
Age, yrs		
Mean (SD)	44.5 (11.2)	42.4 (10.6)
Median (range)	46 (18–77)	43 (22–64)
Sex, n (%)		
Female	249 (85.9)	87 (86.1)
Male	41 (14.1)	14 (13.9)
Race, n (%)		
Caucasian	260 (89.7)	87 (86.1)
Asian	9 (3.1)	5 (5.0)
Other	21 (7.2)	9 (8.9)
FHL severity at maximum eyebrow elevation, subject FWS rating, n (%)		
Moderate	138 (47.6)	48 (47.5)
Severe	152 (52.4)	53 (52.5)
FHL severity at maximum eyebrow elevation, investigator FWS rating, n (%)		
Moderate	135 (46.6)	48 (47.5)
Severe	155 (53.4)	53 (52.5)
GL severity at maximum frown, investigator FWS rating,* n (%)		
Moderate	85 (29.3)	39 (38.6)
Severe	205 (70.7)	61 (60.4)
FLSQ Impact Domain score,† mean (SD)	55.3 (23.9)	52.0 (23.2)
FLO-11 Item 1 score,‡ mean (SD)	6.9 (2.5)	6.5 (2.4)
FLO-11 Item 4 score,‡ mean (SD)	5.9 (3.0)	5.6 (2.6)
FLO-11 Item 5 score,‡ mean (SD)	6.8 (2.8)	6.1 (3.0)
FLO-11 total score,§ mean (SD)	30.8 (22.6)	34.2 (22.2)

*One subject in the placebo group had a rating of mild.

†Scored from 0 to 100, with higher scores indicating facial lines that have a greater negative impact on the subject; FLSQ Follow-up Item 5 does not have a baseline value.

‡FLO-11 Items 1, 4, and 5 were scored on a scale from 0 (not at all) to 10 (very much).

§Transformed to a scale from 0 (worst) to 100 (best).

FHL, forehead lines; FLO-11, 11-item Facial Line Outcome questionnaire; FLSQ, Facial Line Satisfaction Questionnaire; FWS, Facial Wrinkle Scale with photonumeric guide; GL, glabellar lines; ITT, intent-to-treat.

indicated that facial lines had a negative impact on study subjects.

Facial Line Satisfaction Questionnaire

The proportion of subjects who were mostly or very satisfied with study treatment was significantly greater with onabotulinumtoxinA than with placebo on Day 30 (88.9% vs 3.0%; $p < .0001$) and at the primary time point for this measure on Day 60 (90.3% vs 1.0%; $p < .0001$). On the FLSQ Impact Domain, the responder rate was significantly greater with onabotulinumtoxinA than with placebo on Day 30 (73.9% vs 18.9%; $p < .0001$). Figure 3 shows the proportion of subjects mostly or very satisfied on Day 60 and the Impact Domain responder rate on Day 30.

Subject satisfaction with treatment remained significantly higher with onabotulinumtoxinA than with placebo at all time points through the end of the double-blind treatment period (all $p \leq .0001$; 86.9% vs 2.0% at Day 180; Figure 4). During the open-label period, subject satisfaction was maintained with repeated onabotulinumtoxinA treatment. The FLSQ Impact Domain responder rate also remained significantly higher with onabotulinumtoxinA than with

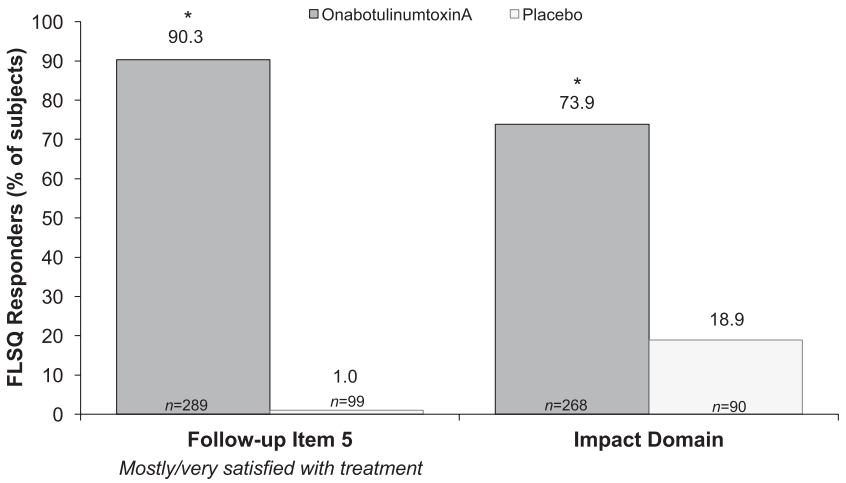

Figure 3. Responder rates for FLSQ Follow-up Item 5 (Day 60) and FLSQ Impact Domain (Day 30). Responders on the Impact Domain were those with at least a 20-point improvement from baseline. *$p < .0001$ for onabotulinumtoxinA versus placebo. FLSQ, Facial Line Satisfaction Questionnaire.

placebo at all time points through the end of the double-blind period (all, $p \leq .0007$), and was generally maintained with repeated onabotulinumtoxinA treatments (Figure 5).

FLO-11

At Day 30, the primary assessment time point, the proportion of responders defined by at least a 3-point improvement from baseline was significantly greater in the onabotulinumtoxinA group than in the placebo group for FLO-11 Item 1 (bothered by facial lines), Item 4 (looking older than actual age), and Item 5 (looking less attractive) (all, $p < .0001$; Figure 6). Differences in responder rates with onabotulinumtoxinA on all 3 FLO-11 items were significant versus placebo at 1 week post-treatment (all, $p < .0001$) and remained significant through Day 180 of treatment cycle 1 (all, $p \leq .0002$; Figure 7). The profile for the FLO-11 total score was similar; the proportion of responders defined by at least a 20-point improvement from baseline was significantly greater with onabotulinumtoxinA than with placebo at the Day 30 primary time point (86.0% vs 6.9%), with significant between-treatment differences seen at all visits from Day 7 through Day 180 (all, $p < .0001$;

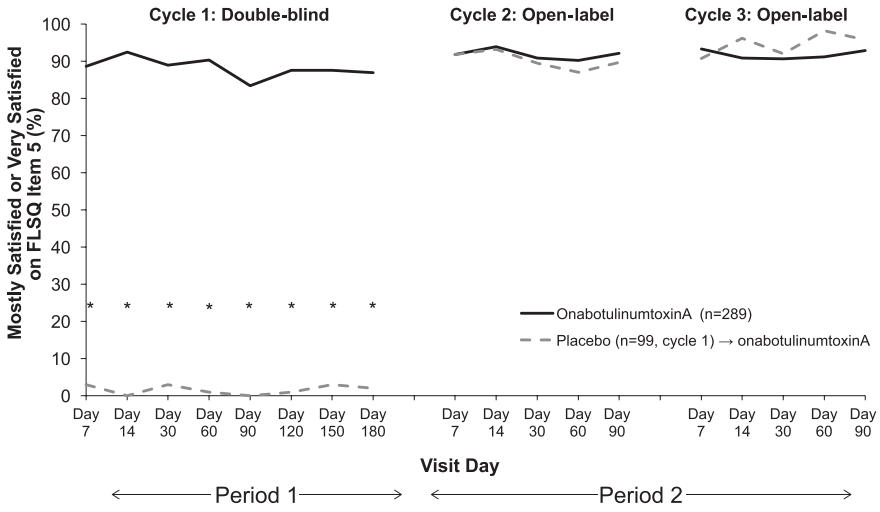

Figure 4. Proportion of subjects mostly or very satisfied on FLSQ Follow-up Item 5 over the 12-month study (intent-to-treat population). Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p \leq .0001$ for onabotulinumtoxinA versus placebo. FLSQ, Facial Line Satisfaction Questionnaire.

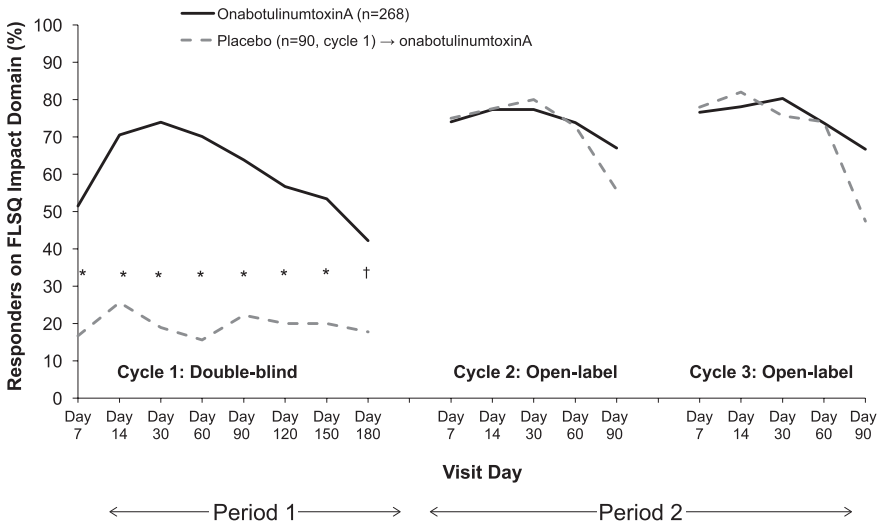

Figure 5. Responder rate for FLSQ Impact Domain over the 12-month study (intent-to-treat population). Responders are subjects with at least a 20-point improvement from baseline; only subjects with baseline scores of 20 or lower are included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p < .0001$; †$p = .0007$ for onabotulinumtoxinA versus placebo. FLSQ, Facial Line Satisfaction Questionnaire.

Figure 8). Responder rates for each of the FLO-11 Items 1, 4, and 5 and for the FLO-11 total score remained higher than 60% for at least 90 days after treatment, and higher than 40% at Day 150.

From Days 180 to 360 during the open-label period, responder rates for FLO-11 Items 1, 4, and 5, as well as for the FLO-11 total score, were generally maintained with repeated onabotulinumtoxinA treatments (Figures 7 and 8). Subjects initially allocated to placebo who received onabotulinumtoxinA during the open-label period achieved responder rates similar to those of the onabotulinumtoxinA group.

Discussion

This randomized controlled study used 2 validated PRO instruments, the FLSQ and the FLO-11,[12,13] to evaluate subject satisfaction with onabotulinumtoxinA treatment of both FHL and GL, and the effect of

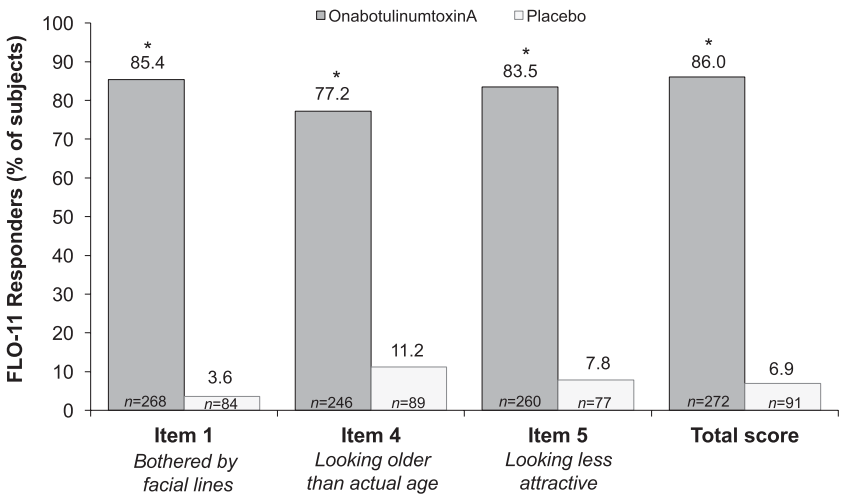

Figure 6. Responder rates for FLO-11 Items 1, 4, and 5 and FLO-11 total score on Day 30 (intent-to-treat population). Responders on FLO-11 Items 1, 4, and 5 are subjects with at least a 3-point improvement from baseline; only subjects with baseline scores of at least 3 are included in this analysis. Responders on the total score are those with at least a 20-point improvement from baseline; only subjects with baseline scores of 80 or lower are included in this analysis. *$p < .0001$ for onabotulinumtoxinA versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

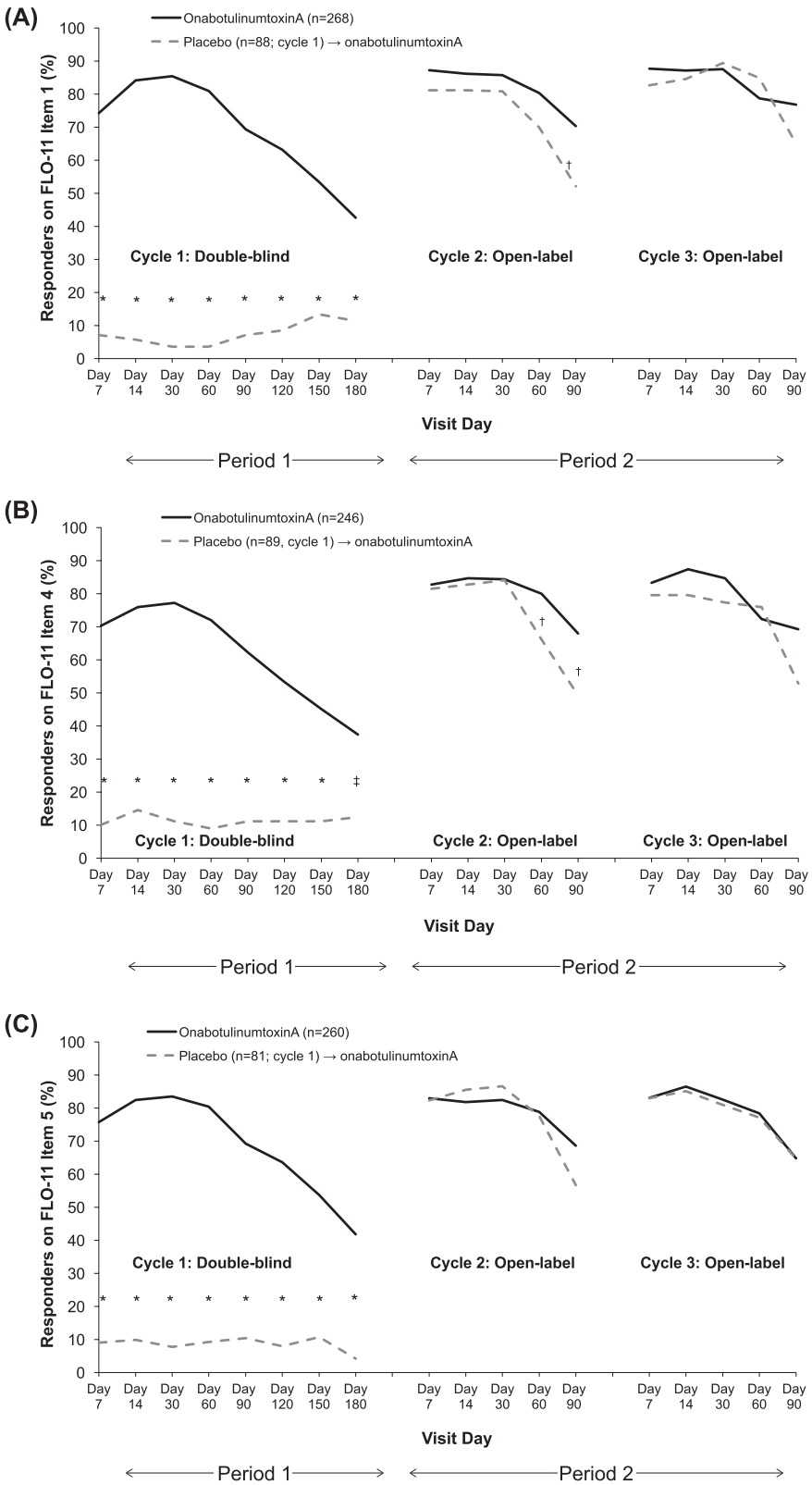

Figure 7. Responder rates for FLO-11 Item 1 (A), Item 4 (B), and Item 5 (C) over the 12-month study (intent-to-treat population). Responders are subjects with at least 3-point improvement from baseline; only subjects with baseline scores of at least 3 are included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p < .0001$; †$p < .05$; ‡$p = .0002$, for onabotulinumtoxinA versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

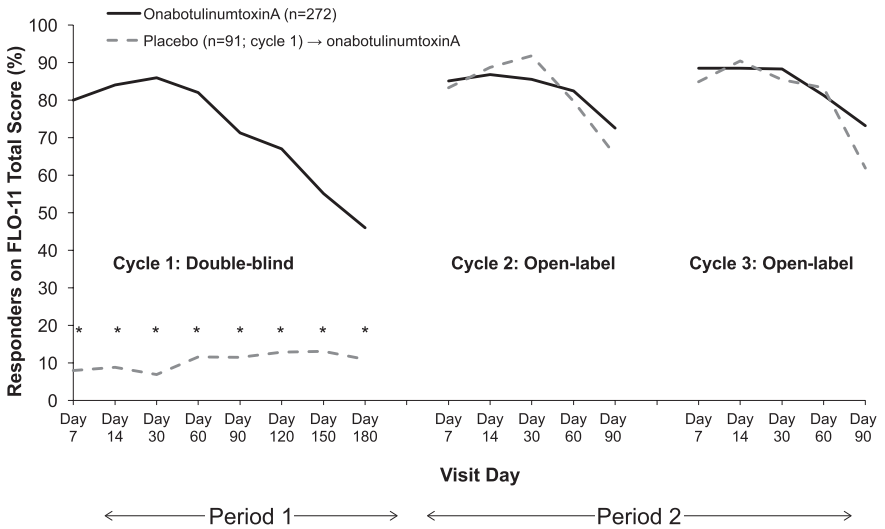

Figure 8. Responder rate for FLO-11 total score over the 12-month study (intent-to-treat population). Responders are subjects with at least a 20-point improvement from baseline; only subjects with baseline scores of 80 or less are included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p < .0001$ for onabotulinumtoxinA versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

treatment on the appearance-related psychological and emotional measures associated with their facial lines. Results presented in the current report show that onabotulinumtoxinA was associated with significantly greater subject satisfaction (FLSQ Follow-up Item 5) and with significantly greater improvements in appearance-related impacts (FLSQ Impact Domain) and psychological impacts (FLO-11) of the subjects' facial lines compared with placebo. The superiority of onabotulinumtoxinA over placebo was evident at the primary time points for each of these end points (Day 30 for each, except Day 60 for FLSQ Follow-up Item 5), as well as at each study visit from Days 7 through 180 of the double-blind treatment period. The improvements in these PROs are consistent with clinical improvements in FHL severity assessed by study investigators and reported previously.[10]

The high subject satisfaction and improvements in impact outcomes were maintained over the 3 cycles of onabotulinumtoxinA treatment. The responder rates observed in cycles 2 and 3 of onabotulinumtoxinA treatment during the open-label period were similar to or slightly higher than those observed during the double-blind treatment. Moreover, subjects initially allocated to placebo for cycle 1 achieved responder rates after onabotulinumtoxinA treatment in cycles 2 and 3, which were similar to those seen in the onabotulinumtoxinA group.

Throughout the double-blind treatment period, subject satisfaction remained consistently high, whereas responder rates for appearance-related impacts of facial lines started to decline between Days 60 and 90. Although assessment of treatment duration was not specifically addressed in this study, 2 general approaches may be taken to estimate the duration of the subject-reported benefits associated with onabotulinumtoxinA treatment, using time to re-treatment as proxy. First, the time to onabotulinumtoxinA re-treatment, based on the statistical comparison with placebo during the double-blind period, was 180 days for each subject-reported end point. For comparison, time to re-treatment for onabotulinumtoxinA versus placebo was estimated at 120 days by the most stringent responder analysis of a composite (investigator and subject) 2-grade improvement in FWS ratings at maximum contraction. Second, the duration can be estimated based on the time interval for which at least 50% of subjects remained as responders. Responder rates higher than 50% were maintained for 150 days for FLO-11 Items 1, 5, and total score, and FLSQ Impact Domain, and for 120 days for FLO-11 Item 4. In comparison, on FLSQ Follow-up Item 5, the proportion of subjects who were mostly

or very satisfied with onabotulinumtoxinA treatment was 86.9% at 180 days after treatment. Taken together, these observations suggest that subjects may perceive benefits lasting 4 to 6 months after onabotulinumtoxinA treatment. These findings support that a 40 U onabotulinumtoxinA dose may contribute to sustained treatment benefits.[8]

High subject satisfaction with onabotulinumtoxinA treatment, as indicated by the proportion of mostly or very satisfied subjects, was apparent from Day 7 after treatment. Responder rates for impact outcomes generally peaked about 14 days after treatment, indicating that improvement in psychological and emotional impacts may follow the ability to see and appreciate the effect of treatment on one's appearance.

The benefit of treatment is traditionally evaluated based on clinical safety and efficacy. For facial aesthetic treatments, the subject's perception of treatment benefits is also an important outcome measure. Importantly, subject satisfaction may help determine future behavior, such as returning for additional treatments to maintain improvements in impact outcomes.[15] The relationship between high satisfaction and re-treatment is illustrated by results from an international, multicenter study in which medical charts were reviewed retrospectively for 194 subjects who had received onabotulinumtoxinA treatment continuously for 5 years or more, with at least 2 treatments per year, including at least 1 for GL.[16] This cohort received onabotulinumtoxinA for a mean of 9.1 years and reported high satisfaction with treatment (92.3% were mostly or very satisfied, based on FLSQ Follow-up Item 5). Almost 90% of subjects reported looking younger than their actual age. In randomized controlled trials, high subject satisfaction based on the FLSQ and significant improvements in appearance-related impacts of facial lines based on FLO-11 have been reported previously with onabotulinumtoxinA treatment in subjects with GL and crow's feet lines.[14,17] In addition, satisfaction with onabotulinumtoxinA treatment of facial lines has been found to be consistently high when using a variety of other measures, most of which were based on Likert-type scales.[18]

Recognizing the importance of subject satisfaction as an outcome measure, the US product labeling now includes the FLSQ Follow-up Item 5 data from this study.[11] This distinguishes onabotulinumtoxinA from other treatments that have been approved to date for treatment of facial lines. Moreover, the dosing and results reported in this study are specific to onabotulinumtoxinA. The formulation used in this study is not interchangeable with other botulinum toxin–containing products, and the units administered cannot be converted to other products using a dose ratio. Therefore, the results with onabotulinumtoxinA on subject satisfaction and impact outcomes cannot be extrapolated to other botulinum toxin–containing formulations.

In terms of limitations, this study enrolled botulinum toxin–naive subjects; therefore, the impact of their facial lines and their expectations of treatment may differ from subjects in real-world clinical practice, many of whom may have been treated previously with onabotulinumtoxinA. However, in this study, high satisfaction and impact benefits were maintained during the second and third treatment cycles with repeated onabotulinumtoxinA treatment. In addition, the study protocol specified that a fixed dose of onabotulinumtoxinA be administered at each injection site, whereas doses of onabotulinumtoxinA may be individualized in clinical practice. The dose used in this study was shown to be safe, effective, and able to provide sustained benefit in a previous dose-ranging study.[8] By individualizing therapy, it should be possible to achieve outcomes that compare favorably with those observed in this study.

In summary, subjects were highly satisfied with onabotulinumtoxinA treatment of their FHL and GL, and reported significant improvements in appearance-related psychological and emotional impacts of their facial lines with onabotulinumtoxinA compared with placebo. Subject satisfaction remained high throughout the 6-month double-blind treatment period, and improvements in impact outcomes were sustained for at least 4 to 6 months after the initial onabotulinumtoxinA treatment. Thereafter, improvements on these PROs were maintained with repeated onabotulinumtoxinA treatment during the open-label period.

The high satisfaction rate and improvements in negative impacts associated with FHL and GL are consistent with clinical improvements in facial line severity, as previously assessed by both investigators and subjects.[10] Together, these outcomes demonstrate the effectiveness of onabotulinumtoxinA not only for aesthetic treatment of moderate to severe FHL and GL, but also for amelioration of the negative psychological impact of these facial lines.

References

1. Charles Finn J, Cox SE, Earl ML. Social implications of hyperfunctional facial lines. Dermatol Surg 2003;29:450–5.
2. Cox SE, Finn JC. Social implications of hyperdynamic facial lines and patient satisfaction outcomes. Int Ophthalmol Clin 2005;45:13–24.
3. Gupta MA, Gilchrest BA. Psychosocial aspects of aging skin. Dermatol Clin 2005;23:643–8.
4. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol 1992;18:17–21.
5. Carruthers JA, Lowe NJ, Menter MA, Gibson J, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. J Am Acad Dermatol 2002;46:840–9.
6. 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 2014;40:1181–90.
7. Carruthers J, Rivkin A, Donofrio L, Bertucci V, et al. 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. Dermatol Surg 2015; 41:702–11.
8. Solish N, Rivers JK, Humphrey S, Muhn C, et al. Efficacy and safety of onabotulinumtoxinA treatment of forehead lines: a multicenter, randomized, dose-ranging controlled trial. Dermatol Surg 2016;42:410–9.
9. Lorenc ZP, Kenkel JM, Fagien S, Hirmand H, et al. Consensus panel's assessment and recommendations on the use of 3 botulinum toxin type A products in facial aesthetics. Aesthet Surg J 2013;33:35S–40S.
10. Fagien S, Cohen JL, Coleman W, Monheit G, et al. Forehead line treatment with onabotulinumtoxinA in subjects with forehead and glabellar facial rhytids: a phase 3 study. Dermatol Surg 2017;43:S274–S84.
11. *Botox Cosmetic [package Insert]*. Dublin, Ireland: Allergan plc; 2017.
12. Pompilus F, Burgess S, Hudgens S, Banderas B, et al. Development and validation of a novel patient-reported treatment satisfaction measure for hyperfunctional facial lines: Facial Line Satisfaction Questionnaire. J Cosmet Dermatol 2015;14:274–85.
13. Yaworsky A, Daniels S, Tully S, Beddingfield F III, et al. The impact of upper facial lines and psychological impact of crow's feet lines: content validation of the Facial Line Outcomes (FLO-11) Questionnaire. J Cosmet Dermatol 2014;13:297–306.
14. Rivers JK, Bertucci V, McGillivray W, Muhn C, et al. Subject satisfaction with onabotulinumtoxinA treatment of glabellar and lateral canthal lines using a new patient-reported outcome measure. Dermatol Surg 2015;41:950–9.
15. Stotland MA, Kowalski JW, Ray BB. Patient-reported benefit and satisfaction with botulinum toxin type A treatment of moderate to severe glabellar rhytides: results from a prospective open-label study. Plast Reconstr Surg 2007;120:1386–93.
16. Trindade de Almeida A, Carruthers J, Cox SE, Goldman MP, et al. Patient satisfaction and safety with aesthetic onabotulinumtoxinA after at least 5 years: a retrospective cross-sectional analysis of 4,402 glabellar treatments. Dermatol Surg 2015;41(Suppl 1):S19–S28.
17. Dayan S, Coleman WP III, Dover JS, De Boulle K, et al. Effects of onabotulinumtoxinA treatment for crows feet lines on patient-reported outcomes. Dermatol Surg 2015;41(Suppl 1):S67–S74.
18. Fagien S, Carruthers JD. A comprehensive review of patient-reported satisfaction with botulinum toxin type a for aesthetic procedures. Plast Reconstr Surg 2008;122:1915–25.

Address correspondence and reprint requests to: Patricia Ogilvie, MD, PhD, Skin Concept, Theatinerstraße 46, Munich 80333, Germany, or e-mail: skin-concept@hotmail.de