OnabotulinumtoxinA for Simultaneous Treatment of Upper Facial Lines: Subject-Reported Satisfaction and Impact From a Phase 3 Study

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BACKGROUND Patient-reported outcomes are increasingly recognized as important measures of treatment benefit.

OBJECTIVE To evaluate subject-reported satisfaction and impact outcomes with onabotulinumtoxinA treatment in neurotoxin-naive adults with forehead lines (FHL), glabellar lines (GL), and crow's feet lines (CFL).

METHODS This Phase 3 study randomized 787 subjects to onabotulinumtoxinA 64 U (FHL 20 U, GL 20 U, and CFL 24 U), 40 U (FHL 20 U, GL 20 U, and CFL placebo), or placebo in double-blind Period 1. Subjects could receive up to 2 additional 64 U treatments in open-label Period 2. Patient-reported outcomes were assessed using the validated Facial Line Satisfaction Questionnaire (FLSQ) and 11-item Facial Line Outcomes (FLO-11) Questionnaire.

RESULTS The proportion of subjects mostly or very satisfied was significantly greater with onabotulinumtoxinA 64 U and 40 U versus placebo (87.9% and 81.4% vs 3.2%; $p < .0001$). Responder rates on FLSQ Impact Domain, FLO-11 Items 1, 4, 5, and total score were significantly greater with onabotulinumtoxinA versus placebo on Day 30 ($p < .0001$). Responder rates favoring onabotulinumtoxinA in Period 1 were maintained with repeated onabotulinumtoxinA 64 U treatment in Period 2.

CONCLUSION OnabotulinumtoxinA treatment was associated with high subject satisfaction and significant improvements in appearance-related psychological and emotional impacts.

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Aesthetic treatment of facial lines offers the potential to counter negative appearance-related psychosocial impacts associated with facial lines.[1,2] Since the early 1990s, onabotulinumtoxinA has been used effectively and safely to treat facial lines.[3] When treating forehead lines (FHL), concomitant treatment of glabellar lines (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 comprise the glabellar complex).[4] Clinical studies investigating onabotulinumtoxinA treatment of upper facial lines support treatment of FHL concurrently with GL and lateral canthal lines (crow's feet lines [CFL]).[5,6]

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The safety and efficacy of onabotulinumtoxinA in treating FHL and GL (40 U total dose [20 U to frontalis muscle, 20 U to glabellar complex]) or FHL and GL with simultaneous CFL treatment (64 U total dose, with additional 24 U to CFL) was evaluated in a 12-month, Phase 3 study. The primary outcome measure was the proportion of subjects achieving at least a 2-grade improvement from baseline on Day 30 in FHL severity at maximum eyebrow elevation, per investigator and subject assessment using the Facial Wrinkle Scale (FWS) with photonumeric guide. This end point was achieved by 53.0% of subjects treated with onabotulinumtoxinA 64 U and by 45.6% treated with onabotulinumtoxinA 40 U versus 0.6% who received placebo (both, $p < .0001$). Statistically significant response versus placebo was maintained through Day 120 (64 U, $p = .002$; 40 U, $p = .01$).[7] Subject-reported satisfaction and the effect of treatment in appearance-related psychological and emotional impacts from the subject's perspective were also prespecified secondary end points. This article reports results for these patient-reported outcome (PRO) end points, collected through 2 validated PRO measures: the Facial Line Satisfaction Questionnaire (FLSQ) and the 11-item Facial Line Outcomes (FLO-11) Questionnaire. Of note, the US Food and Drug Administration approved the addition of subject satisfaction data from this study to the product labeling for onabotulinumtoxinA in treating FHL.[8]

Methods

Subjects

Eligible subjects included botulinum toxin–naive men and women aged at least 18 years with moderate to severe horizontal symmetrical FHL at maximum eyebrow elevation, per investigator and subject evaluation, moderate to severe GL at maximum frown, per investigator evaluation, and moderate to severe bilaterally symmetrical CFL at maximum smile, per investigator evaluation, each assessed using the FWS before treatment on study Day 1. The FWS includes descriptors of none, mild, moderate, and severe. Baseline assessment of FHL severity by investigator and subject had to be identical. Women of childbearing potential had to have a negative urine pregnancy test.

Subjects with 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, any uncontrolled disease, infection or skin disease at the injection sites, or anticipated need for botulinum toxin treatment for another indication during the study were excluded. Subjects were also excluded if they underwent previous 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; had received any facial nonablative resurfacing laser or light treatment, microdermabrasion, or superficial peel within 3 months before enrollment; had any medium- or deep-depth facial chemical peel, resurfacing, or permanent makeup in the study treatment area within 6 months before enrollment; or received treatment with non-permanent soft-tissue fillers or oral retinoids in the study treatment area within 12 months before enrollment.

Study Design

This 12-month, Phase 3 study (clinicaltrials.gov identifier NCT02261493) was conducted at 10 US and 14 European sites (6 in Germany, 5 in the United Kingdom, and 3 in Belgium) from October 2014 to April 2016. The study was conducted in accordance with Good Clinical Practice guidelines, national and local regulations, and the ethical principles of the Declaration of Helsinki. An institutional review board or independent ethics committee approved the study protocol before subjects were enrolled. All subjects provided written informed consent.

This study included 2 periods: a 6-month double-blind, placebo-controlled, parallel-group treatment period (Days 1–180) followed by a 6-month, open-label treatment period (Days 180–360). Eligible subjects were randomized (2:2:1) to receive a single treatment of onabotulinumtoxinA 64 U (20 U in FHL, 20 U in GL, and 24 U in CFL), onabotulinumtoxinA 40 U (20 U in FHL, 20 U in GL, and placebo in CFL), or placebo. Treatment was administered at 16 injection sites: 5 sites in the frontalis muscle, 5 in the glabellar complex, and 3 in each lateral canthal area (Figure 1). For each site,

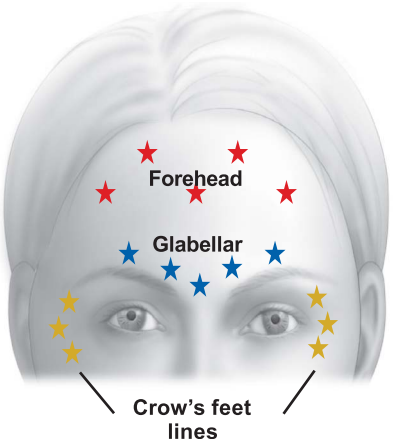

Figure 1. Injection sites for treatment of FHL, GL, and CFL. Reprinted with permission from Allergan plc. CFL, crow's feet lines; FHL, forehead lines; GL, glabellar lines.

onabotulinumtoxinA 4 U or placebo was administered in a volume of 0.1-mL bolus injection using a 30-gauge, half-inch needle; the use of topical anesthetic was not permitted. Randomization assignments were obtained from an interactive voice/web response system based on a randomization scheme prepared by Allergan Biostatistics. Randomization was stratified at each site by baseline FHL severity, with enrollment to include at least 40% of subjects with moderate FHL, at least 40% with severe FHL, and at least 60% with a baseline score of at least 5 for each of FLO-11 Items 1, 4, and 5. During the open-label period, subjects were eligible to receive up to 2 additional treatments with onabotulinumtoxinA 64 U (treatment cycles 2 and 3) between Days 180 and 300, if they had at least moderate FHL severity at maximum eyebrow elevation, at least moderate GL severity at maximum frown, and at least moderate CFL severity at maximum smile based on the investigator FWS ratings, with treatment cycles separated by at least 84 days. Follow-up assessments were made at Weeks 1 and 2 after each study treatment, and all subjects had follow-up visits every 30 days from study Day 30 through Day 360.

Prespecified Patient-Reported Outcome Measures

Facial Line Satisfaction Questionnaire Follow-up Item 5 and Impact Domain and FLO-11 Items 1, 4, 5, and total score were prespecified secondary end points, as they reflect each subject's perception of treatment effects and drive retreatment decisions. Subjects completed the FLSQ and FLO-11 at baseline, Days 7, 14, and 30, then every 30 days through Day 360. Both PRO instruments were developed, validated, and implemented in accordance with US Food and Drug Administration guidance.[9,10] The FLSQ, comprising 11 questions at baseline and 13 at follow-up, was designed to assess treatment satisfaction and appearance-related emotional impacts associated with facial lines in the FHL, GL, and/CFL areas from the subject's perspective.[9] Facial Line Satisfaction Questionnaire Follow-up Item 5 (subjects' satisfaction with treatment of facial lines) was rated on a 5-point Likert scale (very dissatisfied, mostly dissatisfied, neither satisfied nor dissatisfied, mostly satisfied, and very satisfied). The FLSQ Impact Domain comprises 5 items: 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 a greater negative emotional impact of facial lines.

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

Statistical Analysis

The PROs were evaluated in the intent-to-treat (ITT) population, which comprised all randomized subjects. Facial Line Satisfaction Questionnaire Follow-up Item 5 was evaluated as the proportion of subjects who 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. Only subjects with baseline scores of at least 20 were included in this analysis. 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 a baseline score of 80 points or less 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.[11] Comparisons between each onabotulinumtoxinA group and the placebo group 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 787 subjects, 313 in the onabotulinumtoxinA 64 U group, 318 in the onabotulinumtoxinA 40 U group, and 156 in the placebo group. The majority completed the study (n = 684; 86.9%); early discontinuations were mostly due to being lost to follow-up or for personal reasons (Figure 2). Overall, 295 subjects (94.2%) received onabotulinumtoxinA 64 U in treatment cycle 2 and 197 subjects (62.9%) received onabotulinumtoxinA 64 U in treatment cycle 3. The 3 treatment groups were well matched for demographics, baseline facial line severity, and baseline PRO scores (Table 1). Median age in the ITT cohort was 47 years (range, 21–76); most subjects were women (89.2%) and Caucasian (91.1%). All subjects had baseline severity scores of moderate or severe for FHL at maximum eyebrow elevation, GL at maximum frown (except for 1 subject with a rating of mild), and CFL at maximum smile. Baseline FLSQ Impact Domain and FLO-11 scores demonstrated the appearance-related emotional and psychological impacts of facial lines on study subjects.

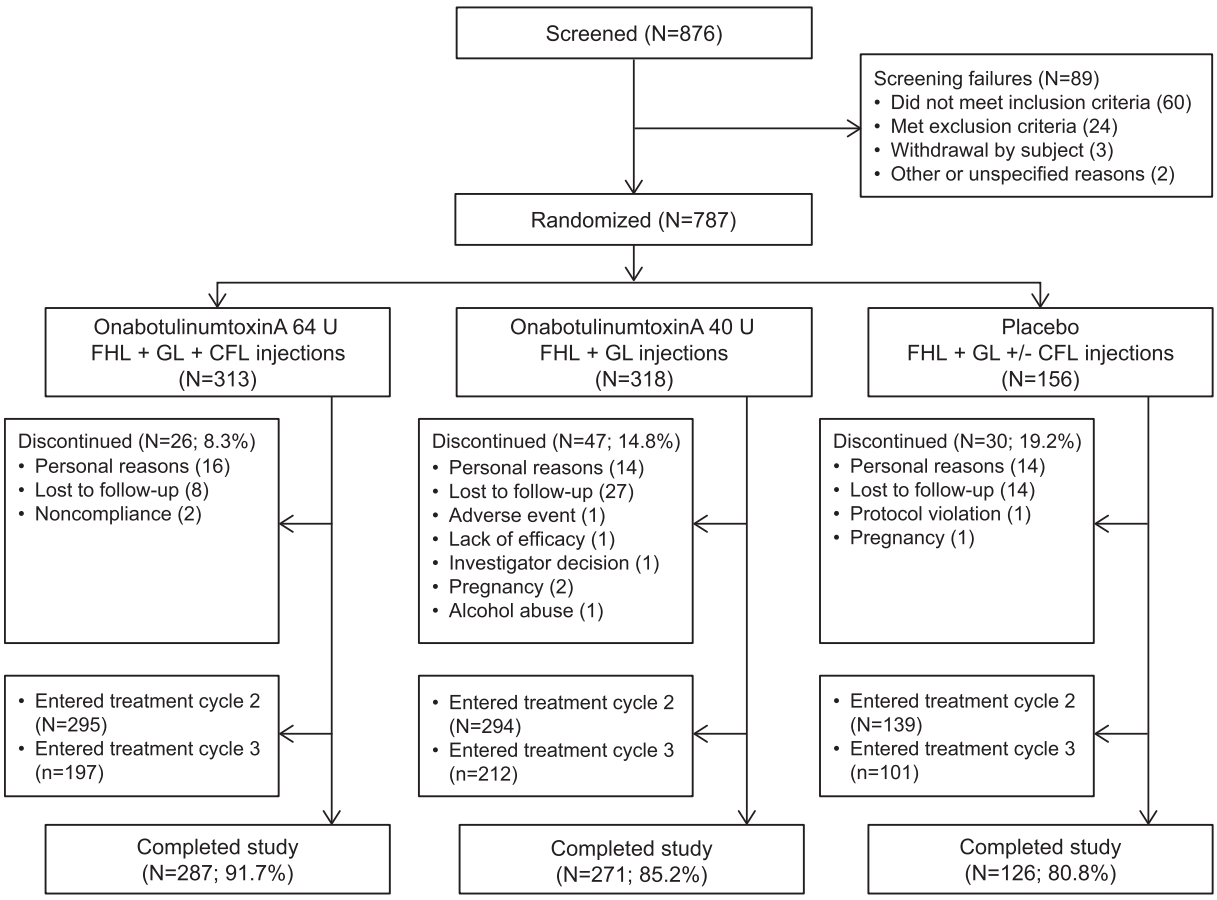

Figure 2. Subject disposition. CFL, crow's feet lines; FHL, forehead lines; GL, glabellar lines.

TABLE 1. Demographics and Baseline Characteristics (Intent-to-Treat Population)

Parameter	*OnabotulinumtoxinA 64 U* (n = *313*)	*OnabotulinumtoxinA 40 U* (n = *318*)	*Placebo* (n = *156*)
Age, yr			
Mean (SD)	45.5 (9.6)	47.6 (10.3)	48.1 (9.7)
Median (range)	45 (21–76)	48 (22–75)	48 (22–73)
Sex, *n* (%)			
Female	284 (90.7)	278 (87.4)	140 (89.7)
Male	29 (9.3)	40 (12.6)	16 (10.3)
Race, *n* (%)			
Caucasian	285 (91.1)	287 (90.3)	145 (92.9)
Black	2 (0.6)	7 (2.2)	3 (1.9)
Asian	2 (0.6)	3 (0.9)	1 (0.6)
Other	24 (7.7)	21 (6.6)	7 (4.5)
FHL severity at maximum eyebrow elevation, subject FWS rating, *n* (%)			
Moderate	162 (51.8)	171 (53.8)	82 (52.6)
Severe	151 (48.2)	147 (46.2)	74 (47.4)
FHL severity at maximum eyebrow elevation, investigator FWS rating, *n* (%)			
Moderate	162 (51.8)	172 (54.1)	81 (51.9)
Severe	151 (48.2)	146 (45.9)	75 (48.1)
GL severity at maximum frown, investigator FWS rating*, *n* (%)			
Moderate	119 (38.0)	101 (31.8)	49 (31.4)
Severe	194 (62.0)	217 (68.2)	106 (67.9)
CFL severity at maximum smile, investigator FWS rating, *n* (%)			
Moderate	140 (45.0)	123 (38.8)	66 (42.9)
Severe	171 (55.0)	194 (61.2)	88 (57.1)
FLSQ Impact Domain score,† mean (SD)	60.7 (22.2)	58.9 (22.0)	59.1 (20.2)
FLO-11 Item 1 score,‡ mean (SD)	7.3 (2.1)	7.0 (2.3)	7.1 (2.2)
FLO-11 Item 4 score,‡ mean (SD)	6.4 (2.5)	6.2 (2.7)	6.1 (2.6)
FLO-11 Item 5 score,‡ mean (SD)	6.9 (2.5)	6.7 (2.6)	6.9 (2.5)
FLO-11 total score,§ mean (SD)	28.6 (18.9)	30.1 (19.6)	29.1 (18.8)

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

†Scored from 0 to 100; higher scores indicate facial lines having greater negative impact; FLSQ Follow-up Item 5 did not have a baseline value.

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

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

CFL, crow's feet lines; FHL, forehead lines; FLO-11, 11-item Facial Lines Outcome Questionnaire; FLSQ, Facial Line Satisfaction Questionnaire; FWS, Facial Wrinkle Scale; GL, glabellar lines; ITT, intent-to-treat.

Facial Line Satisfaction Questionnaire

The proportion of subjects mostly or very satisfied with study treatment was significantly greater with onabotulinumtoxinA 64 U and 40 U than placebo on Day 30 (89.8% and 82.0% vs 5.8%; both $p < .0001$) and on Day 60 ($p < .0001$; Figure 3). On the FLSQ Impact Domain, the responder rate on Day 30 was significantly greater with onabotulinumtoxinA 64 U and 40 U versus placebo (both, $p < .0001$; Figure 3).

Treatment satisfaction was significantly higher in both onabotulinumtoxinA groups versus placebo starting on Day 7 and remained significantly higher at all visits through the end of the double-blind treatment period (all, $p < .0001$; Figure 4). During the open-label

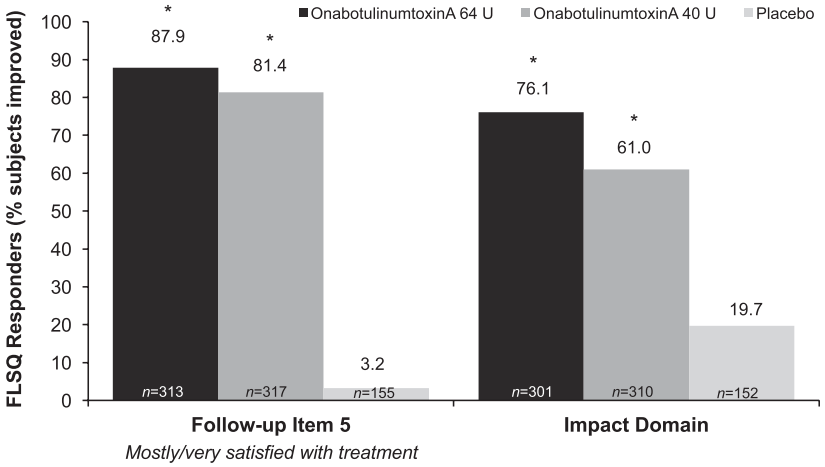

Figure 3. Responder rates for FLSQ Follow-up Item 5 (Day 60) and FLSQ Impact Domain (Day 30). Responders on the Impact Domain were those with at least a 20-point improvement from baseline. *$p < .0001$ versus placebo. FLSQ, Facial Line Satisfaction Questionnaire.

period, high subject satisfaction was maintained with repeated onabotulinumtoxinA 64 U treatment. The FLSQ Impact Domain responder rate in both onabotulinumtoxinA groups was also significantly higher than placebo starting on Day 7, remaining significantly higher at all time points through Day 180 (all, $p < .0001$, except $p = .0009$ for the 40 U group on Day 180; Figure 5). Improvement on the FLSQ Impact Domain was maintained with repeated onabotulinumtoxinA 64 U treatment during the open-label period.

FLO-11

The proportion of responders, defined by at least a 3-point improvement from baseline at Day 30 (primary time point), was significantly greater with onabotulinumtoxinA 64 U and 40 U than placebo for FLO-11

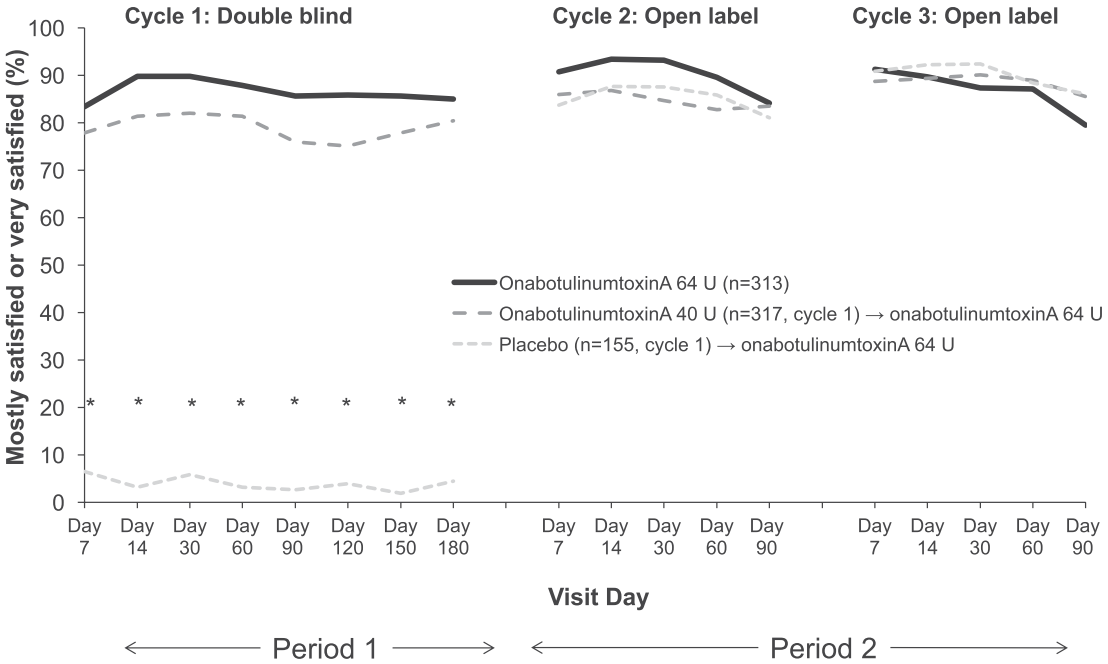

Figure 4. Proportion of subjects mostly or very satisfied on FLSQ Follow-up Item 5 over the 12-month study (intent-to-treat population). Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p < .0001$ for both onabotulinumtoxinA groups versus placebo. FLSQ,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

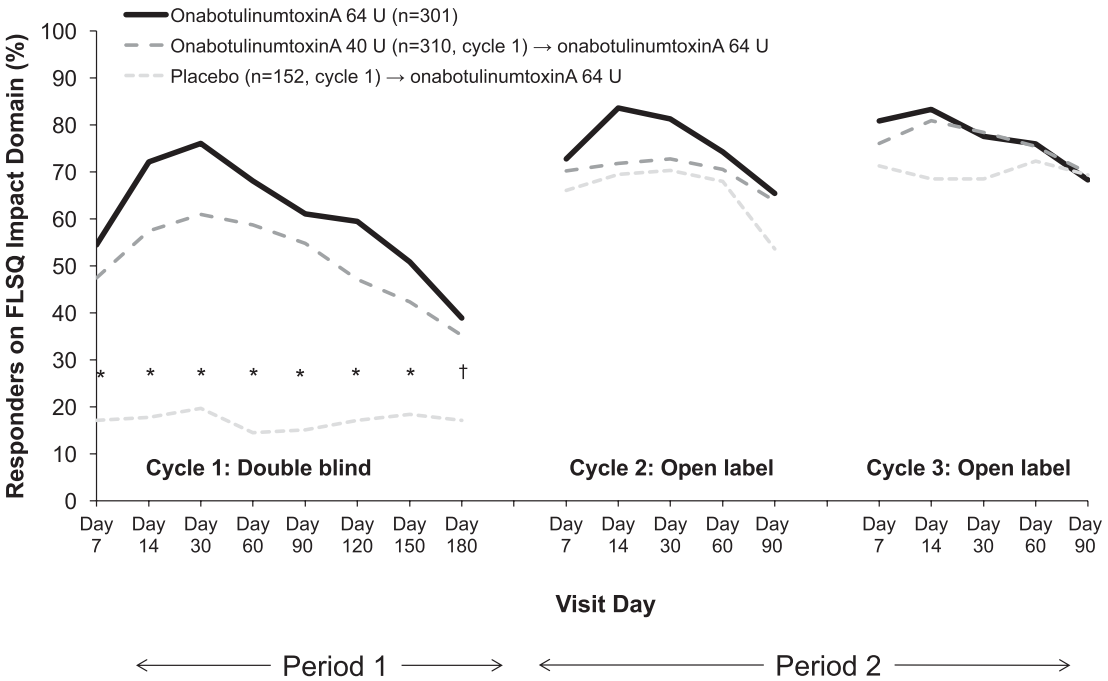

Figure 5. Responder rate for FLSQ Impact Domain over the 12-month study (intent-to-treat population). Responders were subjects with at least a 20-point improvement from baseline; only subjects with baseline scores of at least 20 were included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p < .0001$ for both onabotulinumtoxinA groups versus placebo. †$p \leq .0009$ for both onabotulinumtoxinA groups versus placebo. FLSQ, Facial Line Satisfaction Questionnaire.

Item 1, Item 4, and Item 5 (all, $p < .0001$; Figure 6). Responder rates were significantly higher with both onabotulinumtoxinA groups versus placebo for all 3 FLO-11 Items, starting on Day 7 after treatment (all, $p < .0001$) and remained significant at each visit through Day 180 of cycle 1 (all, $p \leq .0001$ through Day 150; $p \leq .0084$ on Day 180; Figure 7). Similar results were observed for the FLO-11 total score. The proportion of responders defined by at least a 20-point improvement from baseline in the FLO-11 total score was significantly greater with both onabotulinumtoxinA groups than with placebo on Day 30 (both $p < .0001$), with significant differences between each onabotulinumtoxinA group and placebo at all visits

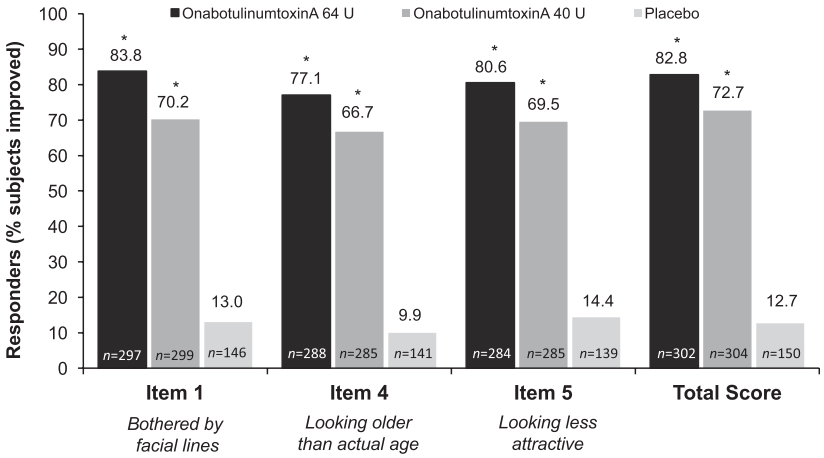

Figure 6. Responder rates for FLO-11 Items 1, 4, and 5 and FLO-11 total score on Day 30 (intent-to-treat population). Responders on Items 1, 4, and 5 were subjects with at least a 3-point improvement from baseline; only subjects with baseline scores of at least 3 were included in this analysis. All 11 individual items were transformed to scale from 0 (worst) to 100 (best) to obtain total score. *$p < .0001$ versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

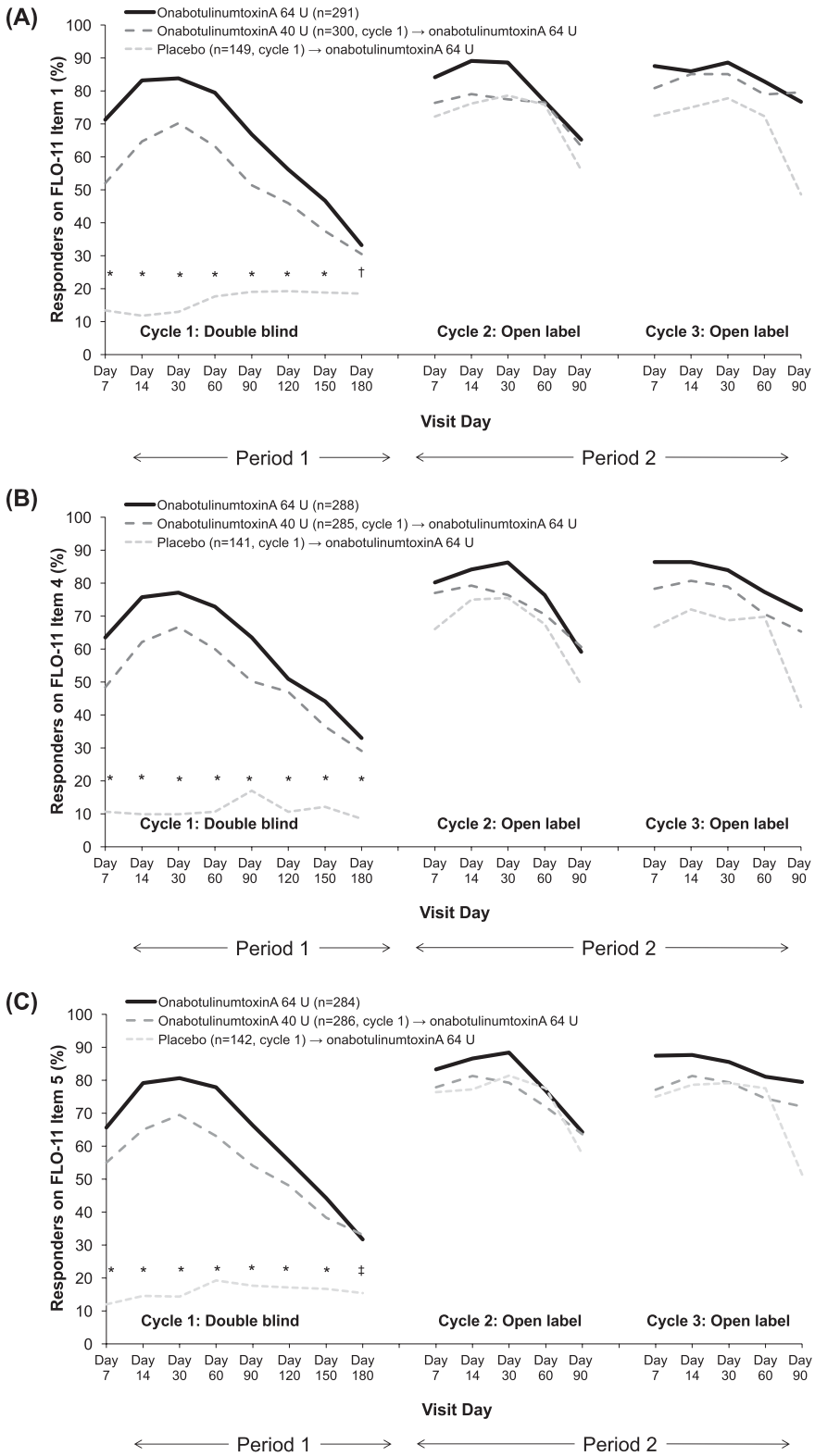

Figure 7. Responder rates for FLO-11 Item 1 (A), Item 4 (B), and Item 5 (C) over the 12-month study (intent-to-treat population). Responders were subjects with at least a 3-point improvement from baseline; only subjects with baseline scores of at least 3 were included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). *$p \leq .0001$ for both onabotulinumtoxinA groups versus placebo. †$p < .01$ for both onabotulinumtoxinA groups versus placebo. ‡$p < .001$ for both onabotulinumtoxinA groups versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

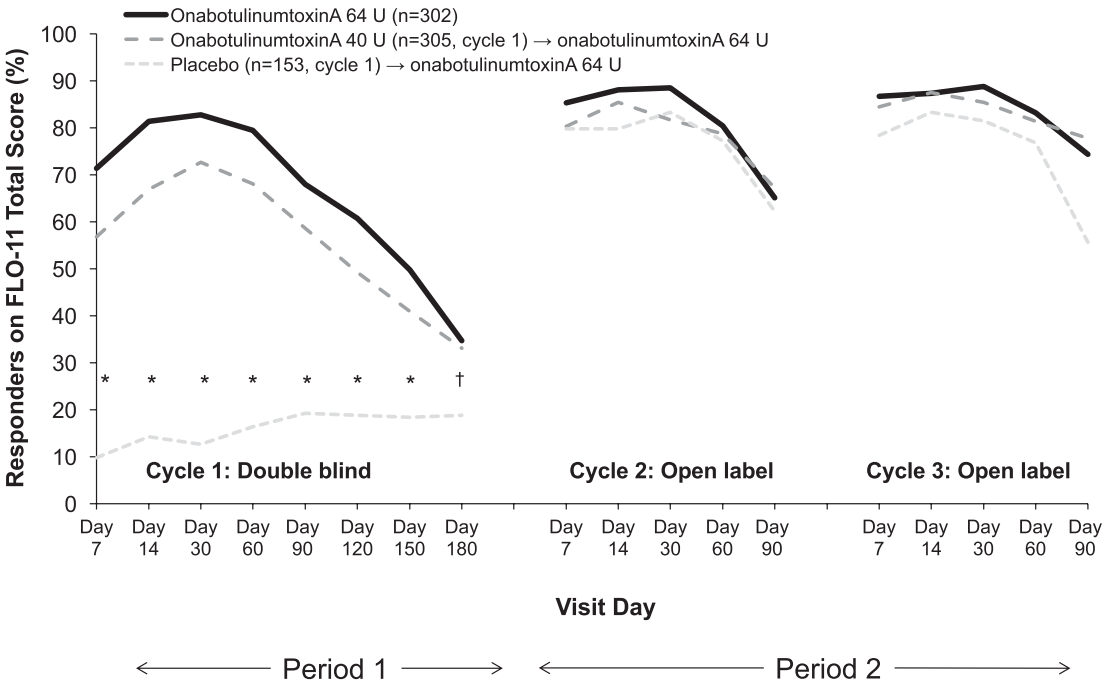

Figure 8. Responder rate for FLO-11 total score over the 12-month study (intent-to-treat population). Responders were subjects with at least a 20-point improvement from baseline; only subjects with baseline scores of at least 20 were included in this analysis. Each *n* value represents the number of subjects assessed at the primary time point (Day 30). All 11 individual items were transformed to scale from 0 (worst) to 100 (best) to obtain total score. *$p < .0001$ for both onabotulinumtoxinA groups versus placebo. †$p \leq .002$ for both onabotulinumtoxinA groups versus placebo. FLO-11, 11-item Facial Line Outcomes Questionnaire.

from Day 7 through Day 180 (all, $p < .0001$ through Day 150; $p \leq .002$ on Day 180; Figure 8). Responder rates for FLO-11 Items 1, 4, 5, and total score were consistently higher with onabotulinumtoxinA 64 U than 40 U through at least 150 days after treatment. At Day 120, responder rates in the onabotulinumtoxinA 64 U group remained greater than 50% for FLO-11 Items 1 (56.2%), 4 (51.0%), and 5 (55.4%), and for total score (60.7%).

Responder rates for FLO-11 Items 1, 4, and 5 and for the FLO-11 total score were generally maintained during the open-label period with repeated onabotulinumtoxinA 64 U treatment (Figures 7 and 8). Subjects from the placebo group who received onabotulinumtoxinA 64 U during the open-label period achieved responder rates similar to those seen with onabotulinumtoxinA 64 U during Period 1. Responder rates with onabotulinumtoxinA 64 U were generally higher in the group initially allocated to the 64 U dose than in the other 2 groups.

Discussion

In this randomized, controlled, Phase 3 study, the authors used 2 validated PRO instruments (FLSQ and FLO-11)[9,10] to assess subject satisfaction with onabotulinumtoxinA treatment of upper facial lines, and the effect of treatment on appearance-related emotional and psychological measures associated with their facial lines. Two onabotulinumtoxinA regimens were compared with placebo: the first included treatment of FHL, GL, and CFL (total dose: 64 U); the other included treatment of FHL and GL (total dose: 40 U), with placebo administered at CFL sites. Compared with placebo, both onabotulinumtoxinA regimens were associated with significantly greater subject satisfaction based on FLSQ Follow-up Item 5, significantly greater improvements in appearance-related emotional outcomes based on the FLSQ Impact Domain, and significantly greater improvements in appearance-related psychological outcomes based on the FLO-11. These improvements in PROs with onabotulinumtoxinA 64 U and 0 U versus placebo were

seen at the Day 30 primary time point for each end point (and at Day 60 primary time point for FLSQ Follow-up Item 5) and at each study visit from Days 7 through 180 of the double-blind period. These PRO improvements paralleled the reduction in FHL severity assessed by investigators using the FWS.[7]

The high subject satisfaction and improvements in impacts were maintained over 3 cycles of onabotulinumtoxinA treatment. Responder rates observed during cycles 2 and 3 of onabotulinumtoxinA 64 U treatment were similar to or somewhat higher than those seen in cycle 1. In subjects who received placebo in cycle 1, responder rates after treatment with onabotulinumtoxinA 64 U during cycles 2 and 3 were similar to those seen in the onabotulinumtoxinA 64 U group during cycle 1. During cycles 2 and 3, responder rates tended to be somewhat higher in the onabotulinumtoxinA 64 U group than in the other 2 groups, especially regarding improvements in appearance-related, psychological, and emotional impacts (Figures 5 and 7). These increases may be related to the enhanced efficacy afforded by repeated onabotulinumtoxinA treatment, as has been demonstrated previously. For example, subjects receiving repeated onabotulinumtoxinA treatment showed progressive improvement in GL severity, which helped achieve and sustain patient satisfaction.[12] In the authors' current study, repeated dosing of onabotulinumtoxinA 64 U also showed progressive improvements in FHL and GL severity across the cycles.[7]

This study was not designed to compare improvements in PRO measures between onabotulinumtoxinA dose levels. However, subject satisfaction, FLO-11 responder rates, and FLSQ Impact Domain responder rates were consistently higher with onabotulinumtoxinA 64 U versus onabotulinumtoxinA 40 U for each measure, suggesting that treatment of CFL in addition to FHL and GL may provide incrementally greater satisfaction and treatment outcomes from the subjects' perspective. Similarly, responder rates on FLO-11 items and the FLSQ Impact domain during cycles 2 and 3 with open-label treatment with onabotulinumtoxinA 64 U trended higher than those during cycle 1 in the group initially randomized to onabotulinumtoxinA 40 U.

Subjects' perception of treatment benefits is an important outcome measure in facial aesthetic medicine because, like efficacy and safety, it may contribute to future behavior, for example, returning for treatment to maintain improvements.[13] In a retrospective chart review of 194 subjects who received onabotulinumtoxinA for treatment of GL and other facial lines for a mean of 9.1 years, 92.3% of subjects reported being mostly or very satisfied with treatment on FLSQ Follow-up Item 5.[14] In addition, almost 90% of subjects reported looking younger than their actual age. Moreover, high subject satisfaction using the FLSQ and significant improvements in appearance-related impacts using FLO-11 were reported previously with onabotulinumtoxinA treatment in randomized controlled clinical trials in subjects with GL and CFL.[11,15]

The authors' findings are consistent with those from a similarly designed 12-month, Phase 3 study in which subjects with moderate to severe FHL at maximum eyebrow elevation and moderate to severe GL at maximum frown reported high satisfaction and significant improvements in appearance-related outcomes after treatment with onabotulinumtoxinA 40 U.[16] Unlike this study, the presence of moderate to severe CFL was not an eligibility criterion. Nevertheless, both studies illustrate that onabotulinumtoxinA treatment of FHL in conjunction with other facial lines leads to high subject satisfaction. Recognizing the importance of subject satisfaction as an outcome measure, the FLSQ Follow-up Item 5 data from both studies are now included in US product labeling for onabotulinumtoxinA.[8] In comparison, satisfaction data are not included in labeling for other facial line treatments. In addition, dosing and results in this study are specific to onabotulinumtoxinA and are not interchangeable with other botulinum toxin–containing products. Importantly, the units of onabotulinumtoxinA administered cannot be converted to other products using a dose ratio. Therefore, results with onabotulinumtoxinA on subject satisfaction and impact outcomes cannot be extrapolated to other botulinum toxin–containing formulations.

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.

Among several study limitations, neurotoxin-naive subjects may have had different treatment expectations and facial line impacts than subjects in clinical practice, many of whom may have been treated previously with onabotulinumtoxinA. This is likely of small consequence, however, as high satisfaction and impact benefits were maintained during the second and third treatment cycles with repeated treatment. In addition, onabotulinumtoxinA was administered at a fixed dose of 4 U per injection site, with the total number of injection sites specified in the protocol. In clinical practice, doses and injection sites are often individualized for each subject. Nevertheless, it should be possible to achieve outcomes similar to those reported here.

In summary, subjects were highly satisfied with concomitant treatment of their FHL, GL, and CFL with onabotulinumtoxinA and reported significant improvements in appearance-related emotional and psychological impacts of their upper facial lines compared with placebo. Subject satisfaction remained high throughout the 6-month double-blind treatment period, and improvements in PROs were maintained with repeated onabotulinumtoxinA treatment during the 6-month open-label period. The high satisfaction rate and improvements in the negative psychological impacts associated with upper facial lines are consistent with clinical improvement in facial line severity as assessed by both investigators and subjects.[7] 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 impacts of these facial lines.

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