Pooled Subject-Reported Outcomes From 2 Phase 3 Studies of OnabotulinumtoxinA for Simultaneous Treatment of Forehead and Glabellar Lines

Patricia Ogilvie, MD,* Alexander Z. Rivkin, MD,† Steven Dayan, MD,‡ Steven G. Yoelin, MD,§ Kristin E. Larsen, PhD,‖ Sepideh Varon, PhD,¶ and Julie K. Garcia, MS, PhD¶

BACKGROUND Understanding the subjects' perspective is critical for successfully treating upper facial lines.

OBJECTIVE To understand subjects' self-perception and overall satisfaction after onabotulinumtoxinA treatment for forehead and glabellar lines.

METHODS This analysis pooled data from two 12-month, pivotal phase 3 studies in which toxin-naive subjects received onabotulinumtoxinA 40 U or placebo for treatment of upper facial lines. OnabotulinumtoxinA was administered as 0.1-mL injections at 10 prespecified sites (frontalis: 20 U; glabellar complex: 20 U). Each study used 3 reliable and validated patient-reported outcome instruments to evaluate subject satisfaction and appearance-related psychological effects: the Facial Line Satisfaction Questionnaire (FLSQ), the Facial Line Outcomes (FLO-11) Questionnaire, and the Self-Perception of Age (SPA) Questionnaire. In total, data for 865 subjects (608, onabotulinumtoxinA 40 U; 257, placebo) were analyzed.

RESULTS Treatment with onabotulinumtoxinA 40 U resulted in significant and sustained improvements across all pooled FLO-11 items and FLSQ items compared with placebo. SPA results demonstrated that a significant proportion of subjects in the pooled analysis felt they looked younger after treatment than at baseline (all, $p < .0001$ vs placebo).

CONCLUSION This study demonstrates a high level of treatment satisfaction and significantly improved appearance-related psychological outcomes among toxin-naive subjects after onabotulinumtoxinA 40 U treatment.

This study was funded by Allergan plc, Dublin, Ireland. Editorial support for this article was provided by Peloton Advantage, LLC, an OPEN Health company, 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, and served as a study investigator, trainer, and consultant for Allergan plc. 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. K.E. Larsen is an employee of Peloton Advantage, which received funding for medical writing and editorial support for this manuscript. S. Varon and J.K. Garcia are employees of Allergan plc and may own stock/options in the company.

In clinical practice, treatment satisfaction determines the success of facial aesthetic treatments and is influenced by improvements in self-confidence and quality of life (QOL). Because self-esteem is a crucial component of QOL,[1] improvements in self-esteem may contribute to better QOL. Enhanced psychological benefits are goals of facial aesthetic treatments[2] and may be what drive a patient to seek ongoing treatment and to recommend treatment to others.

Development of upper facial lines is associated with negative psychological impacts that reduce self-esteem, interfere with social interactions, negatively

*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; ¶Health Economics and Outcomes Research, Allergan plc, Irvine, California

ISSN: 1076-0512 • Dermatol Surg 2020;46:950–957 • DOI: 10.1097/DSS.0000000000002153

influence self-perception and mood,[3] and alter perceptions by others about age and emotional status.[4–6] Facial areas of highest treatment priority for aesthetically oriented women and men include glabellar lines (GL), crow's feet lines (CFL), and forehead lines (FHL).[7,8]

OnabotulinumtoxinA, indicated for treatment of GL, CFL, and FHL, is the only botulinum toxin approved in the United States for treatment of FHL,[9–13] based on results from 2 pivotal studies (142 and 143) that demonstrated its efficacy and safety for treating moderate to severe FHL.[12,13] OnabotulinumtoxinA treatment (20 U in frontalis and 20 U in glabellar complex) was associated with significantly higher response rates versus placebo ($p < .0001$) on investigator- and participant-assessed measures of FHL severity.[12,13]

This analysis pooled results from Studies 142[14] and 143[15] for patient-reported outcomes (PROs) using 3 reliable, validated measures: the Facial Line Satisfaction Questionnaire (FLSQ), Facial Line Outcomes (FLO-11) Questionnaire,[12] and Self-Perception of Age (SPA) Questionnaire. Based on these PRO data, the US FDA approved the addition of subject satisfaction data to the product labeling for onabotulinumtoxinA (Botox; Allergan plc, Dublin, Ireland) for treating FHL.[9] The purpose of this analysis was to gain insight into subject self-perception and overall satisfaction with onabotulinumtoxinA treatment outcomes, including concepts related to self-confidence and self-esteem.

Methods

Subjects

Subjects in Studies 142 and 143 were toxin-naive men and women aged 18 years or older with moderate to severe FHL at maximum eyebrow elevation and moderate to severe GL at maximum frown.[12,13] Using the Facial Wrinkle Scale with a photonumeric guide (FWS), subjects and investigators assessed FHL at baseline; investigators also assessed GL using the FWS before treatment commenced. Subjects were excluded if they had marked periocular and eyebrow asymmetry, eyebrow ptosis, excessive forehead and eyebrow skin laxity, or eyelids reaching the pupil or touching the upper lash line.

Study Design

This analysis evaluated data pooled from the 12-month, phase 3, double-blind, placebo-controlled, parallel-group Studies 142 (NCT02261467) and 143 (NCT02261493), which measured the safety and efficacy of onabotulinumtoxinA for treatment for FHL and GL.[12,13] Efficacy data were pooled from the 6-month double-blind periods of both studies, whereas safety assessments included the double-blind and open-label periods. Study 143 also included a cohort who received simultaneous CFL treatment (not included in this analysis).

Subjects were randomized to receive 0.1-mL injections at 10 sites of onabotulinumtoxinA 40 U (20 U, frontalis and 20 U, glabellar complex) or placebo.[12,13] Subjects were randomized 3:1 in Study 142 and 2:1 in Study 143, and returned for assessments on Days 7, 14, 30, 60, 90, 120, 150, and 180. Both studies were conducted following Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All subjects provided written informed consent.

Analysis Populations

The PRO analyses were based on the observed cases (OCs) subgroup of the pooled intent-to-treat (ITT) population, as defined for each efficacy measure for those who had analysis values for both baseline and postbaseline visits of interest.

Efficacy Outcome Measures

The PRO measures of interest were efficacy measures prespecified in the pivotal studies, with Day 30 defined as the primary time point for all except FLSQ Follow-up Item 5. These measures were developed and validated following FDA guidance.[16,17]

The FLO-11 was designed to assess appearance-related psychological impacts of FHL and GL from the subjects' perspective.[17] Each question was scored from 0 (not at all) to 10 (very much). Items 1 (bothered by

facial lines), 4 (looking older than actual age), and 5 (looking less attractive) were specified as secondary efficacy measures. Responders were subjects who achieved at least a 3-point improvement in FLO-11 scores. The remaining FLO-11 items were exploratory end points: Item 2 (looking older than they want to look), 3 (feeling unattractive), 6 (looking not well rested), 7 (skin not looking smooth), 8 (looking tired), 9 (looking stressed), 10 (looking angry), and 11 (feeling good about facial appearance). Pooled change from baseline scores for FLO-11 items and Total Score were assessed. The OC populations included all FLO-11 subjects with baseline scores of 3 or higher.

The FLO-11 Total Score was also a secondary efficacy end point. The first 10 questions were phrased negatively, whereas the last was positively phrased. Subjects recorded responses on an 11-grade Likert scale, as done for individual items, and these scores were transformed to a 0- to 100-point scale. A response was considered a 20-point or greater improvement. The OC population for FLO-11 Total Score comprised subjects with a score of 80 or less at baseline.

The FLSQ Questionnaire comprises Baseline and Follow-up versions; the 13-item Follow-up version measured satisfaction and appearance-related psychological impacts associated with FHL and GL treatment from the subjects' perspective.[16] The domains covered in the FLSQ Follow-Up Questionnaire were treatment satisfaction (Items 1 through 5), impact (Items 6 through 8, 12, and 13), continue treatment (Item 9), recommend to others (Item 10), and met expectations (Item 11). The items in the Treatment Satisfaction Domain were: "improved facial appearance" (Item 1), "treatment onset" (Item 2), "treatment duration" (Item 3), "receiving a natural look" (Item 4), and "treatment effect on facial lines" (Item 5). For this analysis, Follow-up Item 5 (treatment effect on facial lines) and Impact Domain Items 6 (feeling older), 7 (negatively affecting self-esteem), 8 (looking tired), 12 (feeling unhappy about facial lines), and 13 (looking angry) were secondary outcomes.[16] Facial Line Satisfaction Questionnaire Follow-up Items 1 (satisfaction with facial appearance), 4 (satisfaction with natural effect of treatment), 9 (likelihood of continuing treatment), 10 (likelihood of recommending treatment), and 11 (treatment expectations) were included as stand-alone items. Although not validated as stand-alone items, Follow-up Items 2 (satisfaction with treatment onset) and 3 (satisfaction with treatment duration) were also evaluated.

Response options for all FLSQ Follow-up Items except for Item 11 were measured using a 5-point response scale, with 5 being very satisfied and 0 being very dissatisfied; Item 11 used a 3-point scale. For Follow-up Items 1 through 5, responders indicated that they were very or mostly satisfied. Day 60 was selected as the primary time point for Follow-up Item 5 because, although peak efficacy results from onabotulinumtoxinA treatment were evident on Day 30 in studies,[18–20] the greatest treatment satisfaction for this item was evident on Day 60.[20] Responders indicated "quite" or "extremely" for Follow-up Items 8 through 10, 12, and 13, "quite a bit" or "a lot" for Follow-up Items 6 and 7, and "met" or "exceeded" expectations for Follow-up Item 11. Scores for the Impact Domain ranged from 0 (worst) to 100 (best), using a transformed scale; responders were those with a baseline score of at least 20 points who achieved at least a 20-point improvement.

The SPA assessed how old subjects thought they looked in relation to their actual age, using one item with 3 choices: (1) I look my current age, (2) I look (number) years younger, and (3) I look (number) years older.[21] After treatment, responders rated themselves as either looking younger or older than their age at baseline, or as looking their current age. The OC population comprised those who rated themselves as looking their current age or older at baseline.

Statistical Analyses

Analyses were conducted using the Cochran–Mantel–Haenszel (CMH) test, adjusted for the pooled population. The CMH odds ratio, corresponding 95% confidence intervals, and associated *p*-values were calculated. For each comparison performed using the CMH test, homogeneity of effectiveness across the pooled studies was assessed using the Breslow–Day test. Further examinations were explored if the

Breslow–Day test suggested heterogeneity in the odds ratios (indicated by $p < .10$).

Results

Subjects

The pooled ITT population comprised 608 subjects randomized to onabotulinumtoxinA 40 U and 257 to placebo ($N = 865$). Full details of subject disposition for each study were previously published.[12,13] Treatment groups (Table 1) were well balanced for baseline characteristics.

FLO-11 Questionnaire

A significantly greater proportion of subjects in the onabotulinumtoxinA versus the placebo group ($p < .001$) were responders on Day 30 for all FLO-11 items and Total Score (Figure 1). According to most individual item measures, more than 75% of those who received onabotulinumtoxinA were responders. The difference in responses between the onabotulinumtoxinA and placebo groups on the FLO-11 Total Score was significant at all study visits ($p = .0001$; Figure 2), as were results for all individual items (data not shown).

Facial Line Satisfaction Questionnaire

Satisfaction with onabotulinumtoxinA treatment was reported for all FLSQ Follow-up Items (Figure 3). Treatment response versus placebo was significant at Day 30 (or Day 60 for FLSQ Follow-up Item 5; $p < .001$).

Satisfaction with onabotulinumtoxinA treatment, measured by Item 5, was robust and stable in the pooled population, as shown by the high proportion of responders who were mostly or very satisfied with treatment (range: 80.4%–86.8%; Figure 4). The proportion of onabotulinumtoxinA-treated subjects at each visit who felt that treatment met or exceeded their expectations highlighted this finding, with 91.7% to 93.6% of the onabotulinumtoxinA cohort responding positively to Item 11 (Figure 5).

Satisfaction with treatment, as measured by the FLSQ Impact Domain, was significantly greater in the onabotulinumtoxinA group than in the placebo group ($p < .001$) at all visits (data not shown). The proportion of Impact Domain responders peaked at Day 30 but remained significantly different through Day 180. This finding was similar to that of the FLO-11 Total Score response over time (Figure 2), as were results for all individual items (data not shown).

Self-Perception of Age Questionnaire

Subjects in the onabotulinumtoxinA group were significantly more likely than placebo to feel that they looked younger at every study visit compared with baseline ($p < .0001$; Figure 6). The percentage of SPA responders peaked at Day 30 but remained

TABLE 1. Demographics and Baseline Facial Line Severity

Parameter	*OnabotulinumtoxinA 40 U (n = 608)*	*Placebo (n = 257)*
Age, mean, yrs	46.1	45.8
Range	18–77	22–73
<65 yrs, *n* (%)	581 (95.6)	248 (96.5)
Female, *n* (%)	527 (86.7)	227 (88.3)
Race, *n* (%)		
White	547 (90.0)	232 (90.3)
Black	7 (1.2)	5 (1.9)
Asian	12 (2.0)	6 (2.3)
Other	42 (6.9)	14 (5.4)
Participant FWS rating of severe for FHL at max eyebrow elevation, %	49.2	49.4

FHL, forehead lines; FWS, facial wrinkle scale.

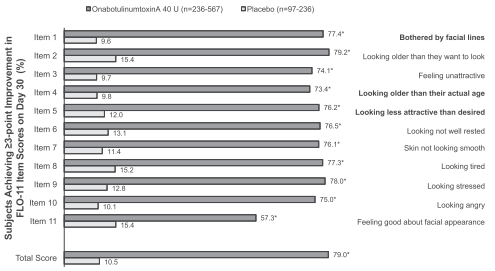

Figure 1. Proportions of pooled subjects in observed case populations who were FLO-11 responders at Day 30. Responders had improvements from baseline of at least 3 points for individual items and at least 20 points for Total Score. Bold items were prespecified end points in the studies. FLO-11 Item 11 is reverse-scored. *$p < .0001$. FLO-11, Facial Line Outcomes Questionnaire.

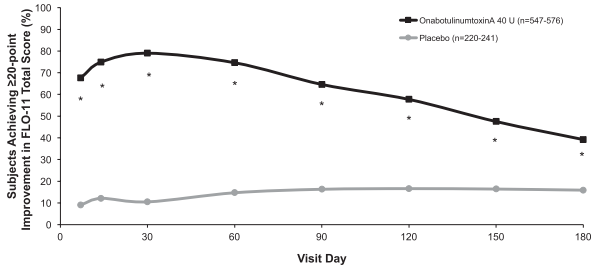

Figure 2. Proportions of pooled subjects in the observed case population who were FLO-11 Total Score responders, by study visit. Responders had improvements from baseline of at least 20 points. *$p < .001$. FLO-11, Facial Line Outcomes Questionnaire.

significantly different ($p < .0001$) through Day 180. Responses for the FLO-11 Total Score (Figure 3) and FLSQ Impact Domain were similar.

Discussion

This pooled study used 3 validated PRO instruments (FLSQ, FLO-11, and SPA) to evaluate subject satisfaction and appearance-related psychological effects of onabotulinumtoxinA treatment of both FHL and GL. The pooled data showed that onabotulinumtoxinA 40 U treatment of upper facial lines resulted in significant improvements as early as Day 7 (first study visit) across all FLO-11 and FLSQ Follow-up items. A significant proportion of the pooled population felt they looked younger after treatment than at baseline (SPA).

Results of this pooled analysis of PRO measures indicate that the majority of subjects who receive onabotulinumtoxinA treatment for FHL and GL are pleased with the outcomes. Subjects reported a substantial, long-lasting, positive impact on concepts related to confidence and self-esteem beginning 7 days after treatment and continuing for up to 6 months. Based on the FLO-11 Total Score, in which subjects assessed the impact of upper facial line treatment on their appearance, nearly 80% of subjects were responders on Day 30. Although all subjects had moderate to severe FHL and GL at maximum contraction, onabotulinumtoxinA treatment resulted in significant improvements in efficacy ($p < .001$), including the stringent 2-grade increase from baseline in the FWS score. Because aesthetic treatments have been shown to be strongly associated with self-esteem and self-image improvements, it stands to reason that the findings of robust and stable patient satisfaction rates in this analysis were attributable at least in part to the efficacy improvements.

In clinical practice, a decrease in response to PRO assessments over time is typical and may not be an indication of declining satisfaction with treatment. Although the differences between the onabotulinumtoxinA-treated and placebo groups remained significant on FLO-11 measures at all visits up to Day 180, the percentage of responders declined slowly, which may reflect the temporary nature of improvements associated with onabotulinumtoxinA injections.[9] Similar declines were observed on the FLSQ Impact Domain and SPA assessments, which included several questions related to the perception of appearance. It seems, however, that such declines align with participant expectations. Response at all study visits was 80% on FLSQ Follow-up Item 5 (satisfaction with treatment of facial lines) and 94% on Item 11 (treatment meeting or exceeding expectations),

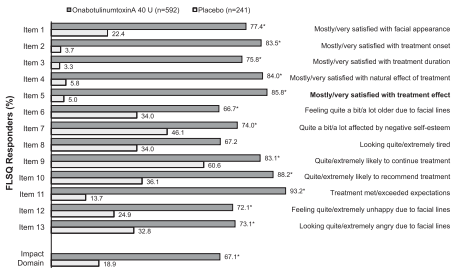

Figure 3. Proportions of pooled subjects in observed case populations who were FLSQ responders at Day 30. Responders are defined for each item along the right side of the graphic. *$p < .001$ at Day 30 (Day 60 for FLSQ Follow-up Item 5). Bold item was prespecified end point in the studies. FLSQ, Facial Line Satisfaction Questionnaire.

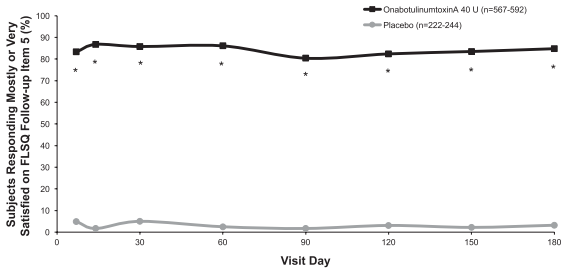

Figure 4. Proportions of pooled subjects in observed case populations who were FLSQ Follow-up Item 5 responders, by study visit. Responders were those very or mostly satisfied with the effect of treatment on facial lines. *$p < .0001$. FLSQ, Facial Line Satisfaction Questionnaire.

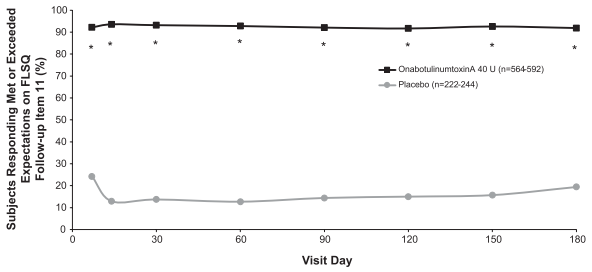

Figure 5. Proportions of pooled subjects in observed case populations who were FLSQ Follow-up Item 11 responders, by study visit. Responders were those whose treatment met or exceeded expectations. *$p < .0001$. FLSQ, Facial Line Satisfaction Questionnaire.

with no apparent decline. As noted earlier, the FDA approved the addition of subject satisfaction data to the product labeling for onabotulinumtoxinA for treatment of FHL based on the FLSQ Follow-up Item 5 findings from Studies 142 and 143.[9]

At Day 30, 60.6% of subjects who received placebo indicated that they were quite likely or extremely likely to continue treatment (FLSQ Item 9), in contrast to the much lower placebo response rate (5.0%) for satisfaction with treatment on the FLSQ Item 5. This incongruity may be attributable to the fact that subjects who were botulinum toxin–naive may have mistaken placebo for active treatment because they could not have anticipated the effects of onabotulinumtoxinA. Another potential explanation is that both studies offered subjects the opportunity to enroll in the open-label treatment period at the conclusion of the double-blind period, and subjects may have considered the prospect of receiving active treatment in the upcoming treatment cycle.

The outcomes in this pooled analysis ($N = 865$) are comparable with results from other onabotulinumtoxinA studies using similar treatments. In Study 142 ($N = 391$), FLO-11 response rates were higher for onabotulinumtoxinA 40 U versus placebo for Items 1 (85.4% vs 3.6%), 4 (77.2% vs 11.2%), and 5 (83.5% vs 7.8%).[14] Study 143 ($N = 474$) had similar response rates for onabotulinumtoxinA 40 U versus placebo for Items 1 (70.2% vs 13.0%), 4 (66.7% vs 9.9%), and 5 (69.5% vs 14.4%).[15] Among studies that assessed response to FLO-11 items 2, 5, and 8 ($N = 1,362$), an evaluation of onabotulinumtoxinA 44 U (CFL: 24 U; GL: 20 U)[22] found that on Day 30, response rates were generally higher for subjects aged 50 years or younger versus those older than 50 years; 75% versus 64% for Item 2, 68% versus 54% for Item 5, and 62% versus 54%, respectively. A small study ($N = 175$)[23] comparing onabotulinumtoxinA 30 U or 40 U injected to the frontalis and glabellar complex showed response rates at Day 30 of approximately 90% for Item 8 and more than 90% for Items 2 and 5.

In a study ($N = 125$) comparing subjects receiving onabotulinumtoxinA 44 U (CFL 24 U; GL 20 U) or placebo, satisfaction with treatment was assessed using FLSQ Follow-up Item 5.[20] The proportion of subjects mostly or very satisfied was 82% at Day 60 and at least 75% up to Day 120. In Study 142, 90.3% versus 1.0% of subjects receiving onabotulinumtoxinA 40 U versus placebo were mostly or very satisfied with treatment at Day 60[14]; for Study 143, 81.4% versus 3.2% of subjects were mostly or very satisfied with onabotulinumtoxinA 40 U or placebo treatment at Day 60, respectively.[15] In addition, the proportion of onabotulinumtoxinA-treated subjects who were responders on FLSQ Follow-up Item 11 (treatment

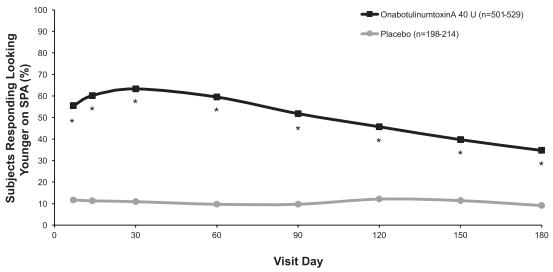

Figure 6. Proportions of pooled subjects in observed case populations who were SPA responders, by study visit. Responders were those who felt they looked younger than they did at baseline. *$p < .0001$. SPA, Self-perception of Age Questionnaire.

met expectations) ranged from 87% to 92% up to Day 120. A chart review of 207 subjects receiving onabotulinumtoxinA at varying doses and concomitant procedures (e.g., injectable filler) for at least 5 years found that 86% of those who did not have concomitant filler treatments were mostly or very satisfied based on FLSQ Follow-up Item 5 at 4 to 28 weeks after the last treatment.[24]

Of the studies assessing the proportion of SPA responders, one trial[22] found that 51% of subjects treated with onabotulinumtoxinA 44 U (24 U to CFL; 20 U to GL) felt that they looked younger at Day 30 than they did at baseline. Another study comparing onabotulinumtoxinA 30 U injected to the frontalis and glabellar complexes reported that 74% of subjects were SPA responders.[23] With a dose of 40 U, the same study reported that 72% were SPA responders. Although there are many indicators of aging (e.g., skin laxity, volume loss, and skin quality), it is a testament to the importance of FHL and GL in the hierarchy that the simple, quick, and noninvasive reduction of these lines using onabotulinumtoxinA injections resulted in more than 50% of subjects feeling that they looked younger within a week of treatment.

These findings should be interpreted in the context of potential study limitations of this pooled analysis. In both studies, the subjects were naive to onabotulinumtoxinA treatment, which may limit the extrapolation of conclusions to those with ongoing aesthetic treatment experience. However, in the authors' experience, subjects do not always experience the toxin effects of ongoing injections the same way they did when they were first treated. Thus, with respect to the PRO measures evaluated, the fact that the subjects were neurotoxin-naive may have been advantageous rather than limiting because they were not prejudiced by past experience and had no treatment–effect expectations. Any comparisons between these pooled results with PRO data from other studies involving different treatments and subject populations should be interpreted with caution. Another limitation of this study was the relatively high fixed dose of onabotulinumtoxinA (20 U) used to treat FHL. Although higher than what some investigators may use in their practices, the simultaneous treatment of GL with FHL may avert a "frozen" appearance by achieving a more natural, balanced treatment effect. Moreover, the rationale behind treating FHL with GL stems from the desire to reduce the risk of eyebrow ptosis because it has been recommended to include GL treatment when treating horizontal FHL to counterbalance the elevation and depression of the brow through the frontalis muscle and glabellar complex, respectively. In fact, the safety findings from Studies 142 and 143 demonstrated that the simultaneous treatment of FHL and GL with onabotulinumtoxinA resulted in a much lower incidence of eyebrow ptosis (1.7% and 1.9%, respectively) than what earlier studies of FHL treatment alone reported (8% to 25%).

Conclusions

In clinical practice, patients commonly report an increase in satisfaction with their appearance after onabotulinumtoxinA treatment, and frequently mention improved mood, self-esteem, and QOL.[3,25] Although published reports have linked aesthetic treatments to positive emotions[26] and more favorable first impressions,[27] assessments were often considered anecdotal rather than having research-based outcome measures.

Smaller early studies of treatments for facial rhytids on self-perceived QOL, self-esteem, and depression linked onabotulinumtoxinA injections with improvements in these parameters, using an array of validated PRO tools designed for general use, not specifically to assess facial lines.[25,28] These positive results are consistent with the outcomes in the present robust pooled analysis using 3 PRO assessment tools in 2 phase 3 studies, which demonstrate that by using validated instruments, investigators can quantify the effects of onabotulinumtoxinA injections on psychological impact. The current analysis of PRO data not only indicates a high level of satisfaction with treatment outcomes among subjects who treated their FHL and GL with onabotulinumtoxinA injections for the first time, but also provides verifiable, quantifiable data to show the long-lasting impact of this treatment on self-esteem, self-confidence, and, ultimately, QOL in this subject population. Of note, the recently published HARMONY study demonstrated that the self-reported treatment benefits of onabotulinumtoxinA also positively

impacted social perception; that is, when unrelated observers were provided with subjects' paired before and after treatment images, the observers reported that the subjects looked nearly 5 years younger after treatment.[29] At the time of the HARMONY study, on-label treatment areas included CFL and GL; now that treatment of FHL is FDA approved, the self-reported benefits of onabotulinumtoxinA for upper facial lines may be even more impressive with this additional treatment site. Controlled trials demonstrating the benefits of treating FHL with simultaneous treatment of GL are a welcome contribution to the body of evidence guiding treatment decisions.

References

1. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999; 48:1507–15.
2. Singh C, Dulku A, Haq A, Bhatti T, et al. Why do females use botulinum toxin injections? J Cutan Aesthet Surg 2015;8:236–8.
3. Lewis MB, Bowler PJ. Botulinum toxin cosmetic therapy correlates with a more positive mood. J Cosmet Dermatol 2009;8:24–6.
4. Cox SE, Finn JC. Social implications of hyperdynamic facial lines and patient satisfaction outcomes. Int Ophthalmol Clin 2005;45:13–24.
5. Finn CJ, Cox SE, Earl ML. Social implications of hyperfunctional facial lines. Dermatol Surg 2003;29:450–5.
6. Gupta MA, Gilchrest BA. Psychosocial aspects of aging skin. Dermatol Clin 2005;23:643–8.
7. Jagdeo J, Keaney T, Narurkar V, Kolodziejczyk J, et al. Facial treatment preferences among aesthetically oriented men. Dermatol Surg 2016;42: 1155–63.
8. Narurkar V, Shamban A, Sissins P, Stonehouse A, et al. Facial treatment preferences in aesthetically aware women. Dermatol Surg 2015; 41(Suppl 1):S153–60.
9. *Botox Cosmetic [package insert]*. Dublin, Ireland: Allergan plc; 2017.
10. 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.
11. 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.
12. 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: S274–84.
13. de Boulle KL, Werschler WP, Gold MH, Bruce S, et al. Phase 3 study of onabotulinumtoxinA distributed between frontalis, glabellar complex, and lateral canthal areas for treatment of upper facial lines. Dermatol Surg 2018;44:1437–48.
14. Ogilvie P, Rivkin AZ, Dayan S, Yoelin SG, et al. OnabotulinumtoxinA for treatment of forehead and glabellar lines: subject-reported satisfaction and impact from a phase 3 double-blind study. Dermatol Surg 2019;45:689–99.
15. Rivkin AZ, Ogilvie P, Dayan S, Yoelin SG, et al. OnabotulinumtoxinA for simultaneous treatment of upper facial lines: subject-reported satisfaction and impact from a phase 3 study. Dermatol Surg 2020;46:50–60.
16. 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.
17. 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.
18. 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.
19. Carruthers JD, Lowe NJ, Menter MA, Gibson J, et al. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. Plast Reconstr Surg 2003;112: 1089–98.
20. 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.
21. Carruthers A, Carruthers J. A single-center dose-comparison study of botulinum neurotoxin type A in females with upper facial rhytids: assessing patients perception of treatment outcomes. J Drugs Dermatol 2009;8:924–9.
22. Dayan S, Coleman WP III, Dover JS, De Boulle K, et al. Effects of onabotulinumtoxinA treatment for crow's feet lines on patient-reported outcomes. Dermatol Surg 2015;41(Suppl 1):S67–74.
23. 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.
24. 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):S19–28.
25. Dayan SH, Arkins JP, Patel AB, Gal TJ. A double-blind, randomized, placebo-controlled health-outcomes survey of the effect of botulinum toxin type A injections on quality of life and self-esteem. Dermatol Surg 2010;36(Suppl 4):2088–97.
26. Foustanos A, Pantazi L, Zavrides H. Representations in plastic surgery: the impact of self-image and self-confidence in the work environment. Aesthet Plast Surg 2007;31:435–42. discussion 43–4.
27. Dayan SH, Lieberman ED, Thakkar NN, Larimer KA, et al. Botulinum toxin A can positively impact first impression. Dermatol Surg 2008; 34(Suppl 1):S40–7.
28. Wollmer MA, de Boer C, Kalak N, Beck J, et al. Facing depression with botulinum toxin: a randomized controlled trial. J Psychiatr Res 2012; 46:574–81.
29. Dayan S, Rivkin A, Sykes JM, Teller CF, et al. Aesthetic treatment positively impacts social perception: analysis of subjects from the HARMONY study. Aesthet Surg J 2019;39:1380–9.

Address correspondence and reprint requests to: Julie K. Garcia, MS, PhD, Health Economics Outcomes Research, Allergan plc, 2525 Dupont Drive, Irvine, CA 92612, or e-mail: Garcia_julia@allergan.com