

# A Multicenter Study to Evaluate Subject Satisfaction With Two Treatments of AbobotulinumtoxinA a Year in the Glabellar Lines

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**BACKGROUND** Real-world re-treatment intervals for botulinum toxins vary, but most subjects receive treatment less frequently than the manufacturer-recommended minimum intervals. In subjects receiving treatment with AbobotulinumtoxinA (ABO) less frequently, high levels of satisfaction and psychosocial improvements in well-being, self-confidence, and quality of life are observed.

**OBJECTIVE** To evaluate subject satisfaction with a twice yearly re-treatment schedule.

**METHODS AND MATERIALS** This open-label, multicenter, interventional study evaluated subject satisfaction following injections of ABO 50 U in the glabellar lines at baseline and 6 months. The primary end point was subject satisfaction at 12 months. Secondary endpoints included subject satisfaction, FACE-Q scales, and glabellar line severity scale (GLSS).

**RESULTS** Ninety-five percent of the 120 subjects were “highly satisfied” or “satisfied” with their treatment outcomes at 12 months. FACE-Q total scores suggested that subjects were less bothered by glabellar lines and felt better about their facial appearance with each treatment versus baseline. Approximately half of subjects had  $\geq 1$ -grade improvement from baseline in GLSS at 12 months. Median onset of effect was 2 days.

**CONCLUSION** The majority of subjects (95%) were satisfied with ABO treatment every 6 months; results were supported by high subject satisfaction, long duration, rapid onset, natural-looking results, and overall psychological wellness and safety.

AbobotulinumtoxinA (ABO) is approved in more than 70 countries worldwide for temporary aesthetic improvement in the appearance of moderate-to-severe glabellar lines seen at maximum frown (Dysport, Galderma SA, Lausanne, Switzerland).<sup>1–3</sup>

The efficacy and safety of ABO in the treatment of glabellar lines has been demonstrated in several, randomized, double-blind, controlled trials.<sup>1,4–9</sup> The average time to onset of action is reported at 2 to 4 days after treatment,<sup>10,11</sup> with real-world re-treatment intervals frequently longer than the manufacturer-recommended minimum of 3 months,<sup>2,3,12,13</sup> and efficacy reported up to 5 months posttreatment.<sup>1,14</sup> In observational studies, subjects returned for treatment after a median of 5 to 6.5 months.<sup>12,13</sup> There is increasingly a focus

on both longer-lasting and higher-dose botulinum toxins that attempt to more closely match effect to real-world treatment frequency.<sup>15,16</sup>

Use of standard doses and a twice yearly injection frequency is associated with high subject satisfaction, maintained over repeated treatments, and without increase in frequency of ptosis.<sup>12</sup> There is also a significant and positive psychosocial impact associated with the treatment of glabellar lines,<sup>17</sup> including improvements in well-being, self-confidence, and quality of life,<sup>18–21</sup> which are reported to outlast the actual clinical improvements.<sup>11,22</sup>

When injecting the recommended doses for glabellar lines (50 Speywood Units), greater amounts of active neurotoxin are delivered with ABO ([0.27 ng]) than other botulinumtoxinA formulations (onabotulinumtoxinA: 20 units [0.18 ng]; incobotulinumtoxinA: 20 units [0.08 ng]).<sup>23</sup> Larger doses, which deliver greater amounts of active neurotoxin, have been associated with a longer duration of treatment effect.<sup>16,23,24</sup> Well-controlled clinical trials comparing on-label glabellar dosing have not been conducted, so the clinical significance of more active botulinumtoxinA protein is unknown at this point.

In this study, twice yearly ABO injections in the glabellar region were used to closely reflect real-world treatment frequency and evaluate for subject satisfaction, efficacy, and safety.<sup>12</sup>

## Materials and Methods

This open-label, multicenter, interventional, Phase-IV study was conducted between 02 October 2018 and 04 December

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2019 across 6 investigational sites in the United States (NCT03687736). The study was performed in compliance with the ethical principles of the Declaration of Helsinki, the clinical trial agreement, the clinical study protocol, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice.

## Subjects

Subjects met inclusion criteria if they were 18- to 65-year old with moderate-to-severe glabellar lines on the glabellar lines severity scale (GLSS) and provided written informed consent.

Main exclusion criteria included subjects receiving facial botulinum toxin treatment within 9 months prior to the baseline visit or those with signs and symptoms of eyelid or brow ptosis.

## Treatment

Subjects were treated with ABO 50 U at baseline and again at 6 months, with an optional re-treatment (50 U) at 12 months. Subject were followed for up to 13 months after the initial treatment at baseline.

AbobotulinumtoxinA contains a neurotoxin complex produced by fermentation of *Clostridium botulinum* bacteria toxin type A, Hall strain. AbobotulinumtoxinA is labeled for a 50-U dose injected intramuscularly in 5 equal aliquots into each of 5 sites in the glabellar region: 2 in each corrugator muscle and 1 in the procerus muscle. In this study, investigators used 1.5-mL reconstitution volumes of preservative-free 0.9% sodium chloride (10 U per 0.05 mL).

## Assessments

The primary objective was to evaluate subject satisfaction with treatment every 6 months by direct questioning of the subject at 12 months (“Overall, how satisfied are you with the aesthetic results of treating the lines between your eyebrows every 6 months?”). Secondary objectives included onset of treatment response, subject’s level of satisfaction, and clinical efficacy.

Treatment efficacy was assessed using the subject satisfaction questionnaire, FACE-Q Scales (psychological function and appraisal of lines), and the GLSS (scale ranging from 0 [none] to 3 [severe], assessed by both subject [Static 4-point categorical scale] and investigator [4-point photographic scale] at maximum frown) at baseline, 1, 3, 6, 7, 9, and 12 months. The subject satisfaction questionnaires included general questions such as “How satisfied are you with the aesthetic outcome in the treated area?” and subjects were asked the same questions at each time point, whereas the FACE-Q questionnaires specifically ask the subject to think about how they have felt in the last week. Onset of effect was assessed using diary cards for the first 7 days after each treatment.

The sum of the subject’s FACE-Q scores was converted to a Rasch-transformed total score; a higher total score indicated greater subject satisfaction. Higher total scores reflect a better outcome ranging from 0 (worst) to 100

(best). Safety was evaluated throughout the study by adverse event (AE) reporting and physical examination.

## Statistical Analysis

To demonstrate that the majority of subjects were satisfied with the treatment regimen with a power of 90% and account for 15% dropouts or nonevaluable subjects, 120 subjects were required.

The primary efficacy variable was analyzed based on the modified intention-to-treat population: subjects treated both at baseline and 6 months. A 2-sided 95% confidence interval was calculated using the Clopper–Pearson method. Secondary effectiveness analyses were performed based on observed cases in the intention-to-treat population: all subjects treated with ABO. Time to onset of treatment response was analyzed using Kaplan–Meier estimates.

A post hoc statistical analysis was performed on the GLSS data. A McNemar’s test for paired nominal data was applied to proportional change in outcomes at both 3 and 6 months in each treatment period and for each GLSS assessment. All other data were summarized using descriptive statistics. Safety data were summarized descriptively based on the safety population (all subjects administered ABO).

## Results

In total, 120 subjects were entered into the study; 39 were naive to toxin therapy. The majority of subjects were women (90%) and of white race (89%); mean age at baseline was 43.8 years (range, 21–64 years). At 6 months, 113 subjects were re-treated; at the optional 12-month time point, 101 subjects received further treatment (See **Supplemental Digital Content 1**, Table S1, <http://links.lww.com/DSS/A601>, which shows subject baseline demographics).

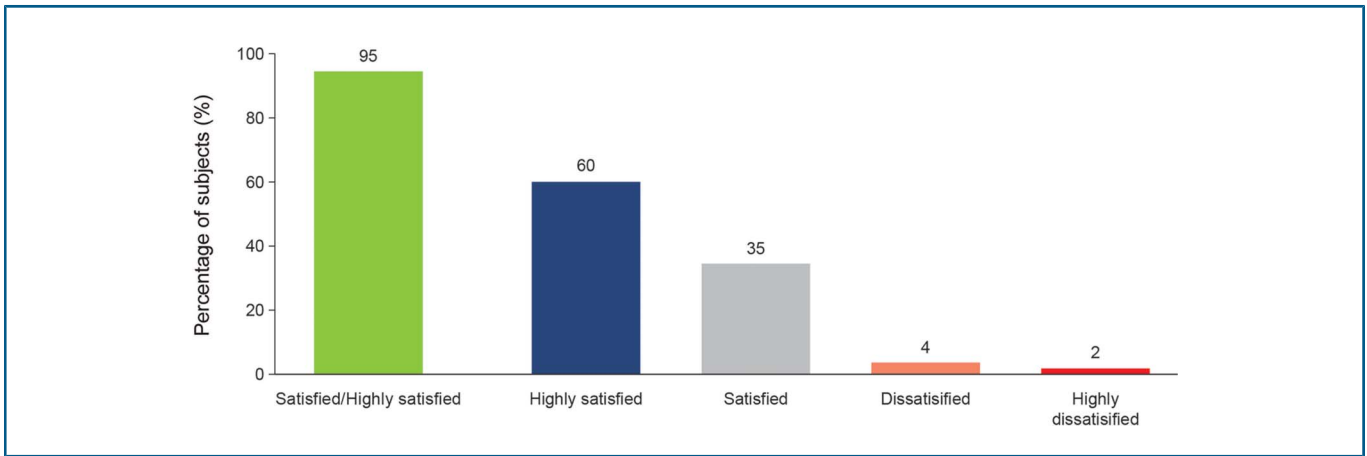
Glabellar lines assessment at baseline was considered severe at maximum frown by 65% of subjects and 68% of investigators (See **Supplemental Digital Content 1**, Table S1, <http://links.lww.com/DSS/A601>).

## Subject Satisfaction

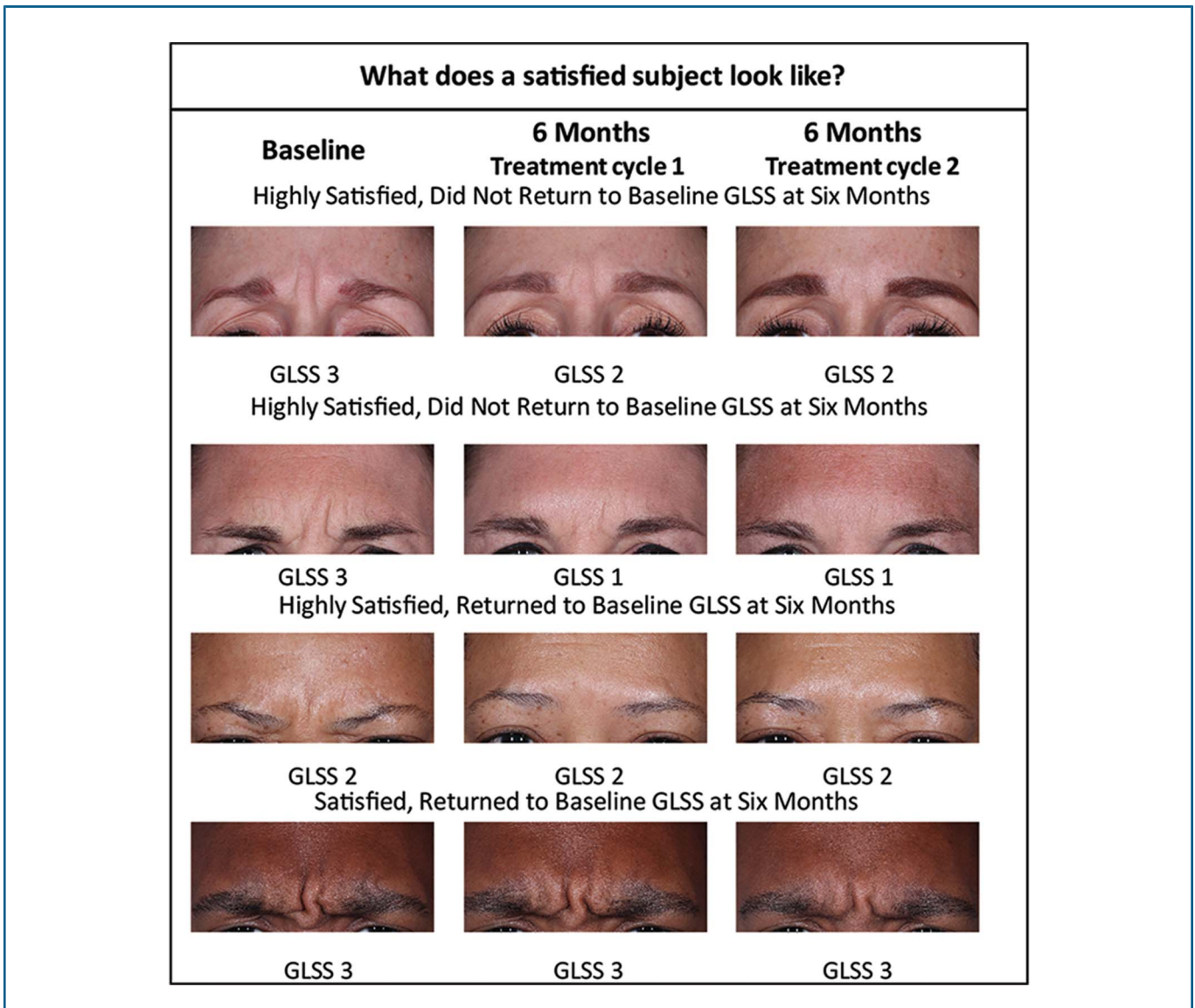
Ninety-five percent of subjects ( $n = 104/110$ ; confidence interval: 88.5 to 98.0) expressed satisfaction with the aesthetic results following treatment of glabellar lines with ABO 50 U every 6 months (primary end point) (Figures 1 and 2). Toxin-naive subjects reported similar overall satisfaction to those with previous treatment experience (97% vs 93%, respectively).

When evaluated by age categories, a larger proportion of subjects aged 21 to 30 and 31 to 40 years were “highly satisfied” with the aesthetic results compared with older subjects (75% and 75% vs  $\leq 55\%$ , respectively) (See **Supplemental Digital Content 2**, Table S2, <http://links.lww.com/DSS/A602>, which shows overall satisfaction at 12 months by age category).

The proportion of subjects responding as satisfied or very satisfied with their appearance improved from baseline (increasing to 95% at Month 1) and remained high throughout each treatment (Figure 3). A majority of



**Figure 1.** Subject satisfaction after 2 treatments a year (+mITT ( $N = 113$ ), subjects assessed ( $n = 110$ ). Numbers may exceed 100% due to rounding).



**Figure 2.** Subject results at maximum frown at 6 months posttreatment. All patients have given permission for reproduction of photographs.

subjects agreed that they looked younger in the first month after each treatment. Overall,  $\geq 97\%$  of subjects thought that the results of treatment appeared “natural” (Figure 3) and  $\geq 90\%$  consistently reported appearing “refreshed” (Figure 3). Perception of self-attractiveness was also improved, with 95% of subjects reporting an increase in attractiveness from baseline (much more, more, or a little more) (Figure 3).

By Month 12, 88% of subjects reported feeling better (much better, better, or a little better) about themselves. A majority of subjects felt the treatment brought them “beauty,” “confidence,” a “youthful appearance,” and a “less tired appearance.” Ninety-eight percent of subjects agreed that they would like to receive treatment again, with 84% of subjects who had previously been treated with botulinum toxins at least as satisfied with ABO 50 U twice yearly as with prior treatment regimens. Ninety-seven percent of all subjects responded that they would recommend treatment with ABO 50 U to their friends or family.

### FACE-Q

Results from FACE-Q total scores suggest that subjects, compared with baseline, were less bothered by glabellar lines (appraisal of lines) and felt better with each treatment (psychological function). Subjects were happier with how they felt about the lines between their eyebrows following treatment at all postbaseline time points (mean baseline score: 31.6; mean increase from baseline range: 13.0–53.9). Subjects also reported improved overall psychological wellness with their facial appearance in mind at all postbaseline time points (mean baseline score: 72.2; mean increase from baseline range: 4.0–11.6).

### Onset of Effect

The median onset of effect was 2 days for both baseline and the 6-month treatment cycles. At approximately 24 hours

after treatment (day 1), up to 33% of subjects reported a treatment response across both cycles; by Day 4, the numbers increased to  $\geq 89\%$  (See **Supplemental Digital Content 3**, Figure S1, <http://links.lww.com/DSS/A600>, which shows subject-reported onset of effect).

### Glabellar Lines Severity Scale

At 1-month posttreatment for both treatment cycles, 99% to 100% of subjects were assessed by investigators as having a  $\geq 1$ -grade GLSS improvement from baseline (defined as responders). Subject self-assessment showed similar improvement. At 6 months, 37% were still assessed as improved by the investigator and 28% by subjects. At 12 months, 6 months after the second treatment, 50% and 49% were still responders (Figure 4).

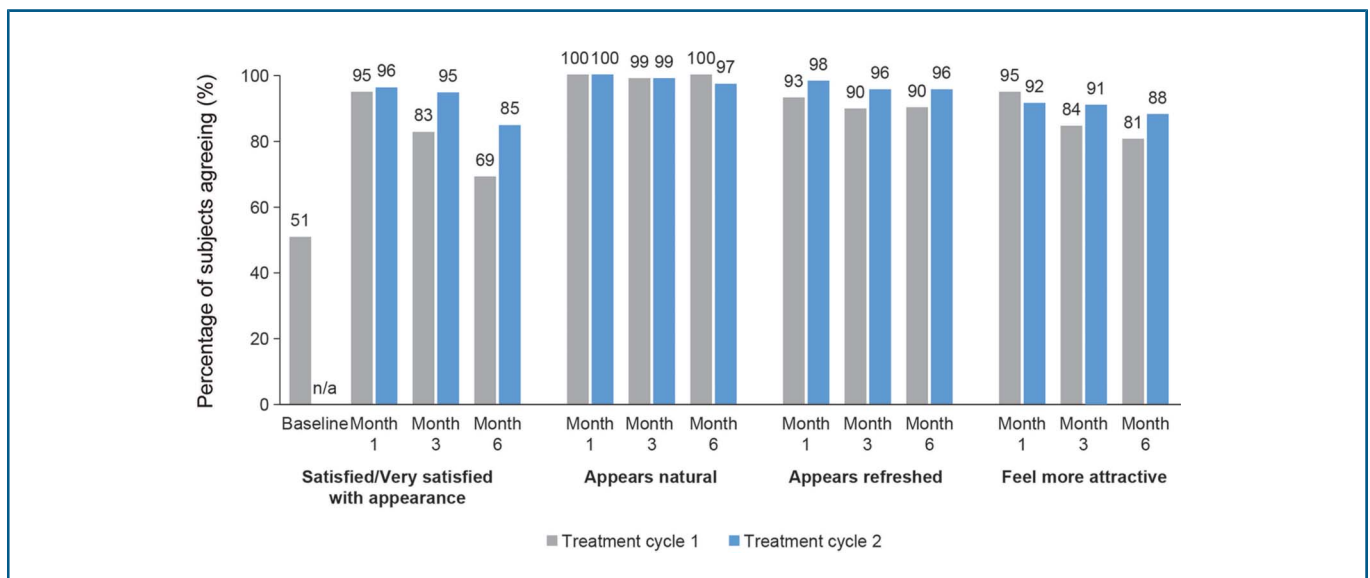
### Safety

In total, 27 subjects ( $n = 27/120$ , 23%) reported a total of 45 treatment-emergent AEs during the study. One subject had a treatment-emergent AE that was considered related to the study injection procedure (one event of mild injection site bruising). The most commonly reported unrelated, treatment-emergent AEs ( $\geq 5\%$ ) included infections and infestations (9.2%), and injury, poisoning, and procedural complications (5.0%). No cases of ptosis were reported.

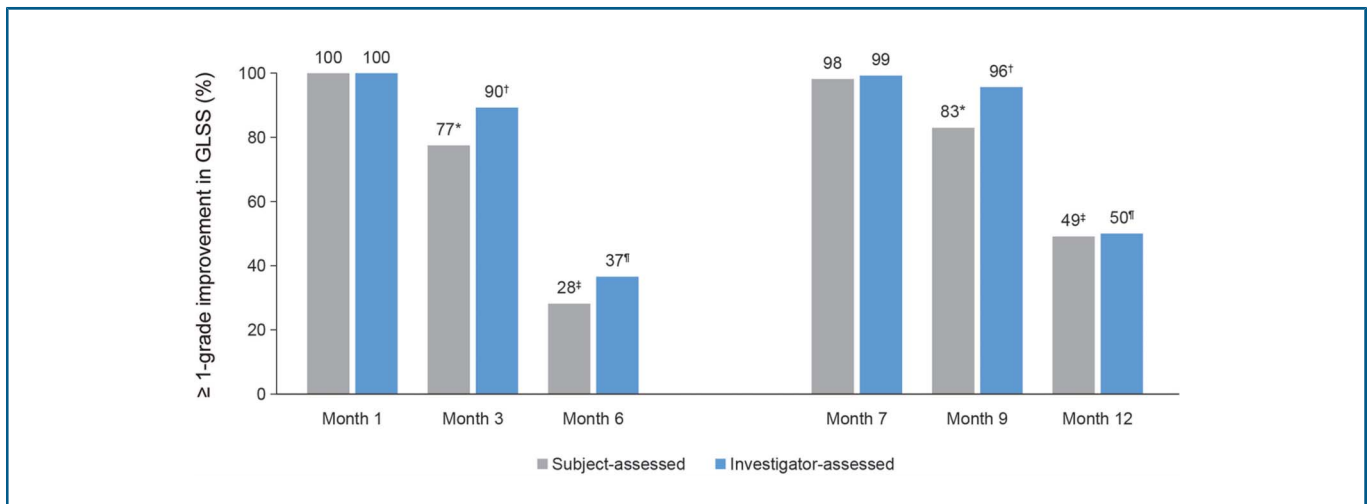
Three unrelated, serious treatment-emergent AEs were reported by 2 subjects: ureterolithiasis (1 subject) and abdominoplasty and subsequent internal abdominal bleeding following the abdominoplasty (1 subject).

### Discussion

The current study evaluated subject satisfaction with twice-yearly injections of ABO 50 U for the correction of moderate to severe glabellar lines. Results demonstrate that 95% of subjects were “highly satisfied” or “satisfied” with the treatment outcomes at 12 months and the primary



**Figure 3.** Subject views of treatment impact by assessment time point.



**Figure 4.** Improvement from baseline in GLSS ( $\geq 1$ -grade). GLSS, glabellar line severity scores. McNemar's test, comparing Month 3 to Month 9; Month 6 to Month 12. \* $p = .2393$ ; † $p = .0348$ ; ‡ $p < .0001$ ; ¶ $p = .0053$ .

objective was thus met. Moreover, satisfaction was expressed across all age categories and regardless of prior toxin exposure.

Subject satisfaction scores were consistently high, with most subjects reporting satisfaction at all time points during the study. Such findings are consistent with previous studies highlighting subject satisfaction with standard ABO treatment schedules,<sup>13,17,25</sup> and supported by the fact that almost all subjects chose to have the optional treatment at study end (101/120 subjects). The prolonged duration of effect up to 6 months and rapid onset of action, reported within 1 to 2 days of injection for both treatment intervals, are consistent with previous pivotal clinical trials and numerous Phase-IV postmarketing studies.<sup>1,7,8,10,13,22,26,27</sup>

The long duration of ABO 50 U efficacy and associated subject satisfaction were consistent across both 6-month treatment intervals. However, an apparent elevation in subject satisfaction at 12 months may reflect a potential clinical effect not fully captured by the GLSS scale assessment. Although a definitive improvement cannot be claimed from such data, the concept of increased effect with subsequent treatments has been reported previously for botulinum toxins<sup>13,28</sup>; thus, a "carryover" effect from the previous injection may be possible. Many subjects return for reinjection before their symptoms return to baseline, potentially providing a subclinical additive or enhancing effect to the next injection. Such outcomes suggest that twice yearly treatments provide a robust level of subject satisfaction without the requirement for higher toxin dosages.

Subjects reported natural-looking results and a refreshed appearance throughout the study, similar to previous studies.<sup>13,17,22,25</sup> As one of the barriers to treatment is subject concern about treatment outcome, it may reassure physicians to note that treatment with ABO consistently produces outcomes that subjects are not only satisfied with but also agree look natural and refreshed. Previous studies suggest that the psychosocial impact of ABO treatment is

prolonged beyond the clinical effect and provides improved benefits to mood in subjects receiving multiple treatments.<sup>11,13,17,22</sup> Such ongoing psychological benefits may also play a role in subject-reported satisfaction results. The results suggest that future research into the psychological aspects of treatment with botulinum toxins may be warranted to further explore this relationship.

There were no unexpected reports of AEs and no cases of ptosis. As clinicians become more experienced with use and administration of ABO 50 U, there is an expectation that the incidence of treatment-related AEs (especially procedural events) would be minimized. The single AE of injection site bruising that was related to the study injection procedure, not study drug, was mild and resolved without treatment. Thus, applications of ABO 50 U every 6 months displayed a highly favorable benefit-risk profile, with almost all subjects (98%) responding that they would receive treatment again.

## Conclusion

Ninety-five percent of subjects were satisfied with receiving ABO 50 U every 6 months. These results were supported by a rapid onset and long duration of action, high levels of subject satisfaction and overall psychological wellness, and a highly favorable benefit-risk profile.

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