

Simultaneous Treatment of Moderate to Severe Horizontal Frontal Lines, Glabellar Lines, and Lateral Canthal Lines With OnabotulinumtoxinA From the Subject's Perspective: Patient-Reported Satisfaction and Impact Outcomes From a Phase 3 Double-Blind Study

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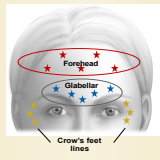
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INTRODUCTION

- Upper facial lines (UFL) can negatively influence self-perception and have adverse psychological impacts.¹⁻³
- Subject satisfaction with aesthetic treatment reflects successful treatment outcomes, which in turn may be associated with improved self-esteem and body image.^{4,5}
- OnabotulinumtoxinA has been used effectively and safely to treat facial lines since the early 1990s.⁶
- When treating forehead lines (FHL), concurrent treatment of glabellar lines (GL) is recommended to reduce 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 making up the glabellar complex).⁷
- Clinical studies further support the use of onabotulinumtoxinA for treatment of UFL, with FHL treatment administered concurrently with treatment for GL and crown's feet lines (CFL).^{8,9}
- The safety and efficacy of onabotulinumtoxinA for treating FHL and GL (40 U total) or FHL and GL with simultaneous treatment of CFL (64 U total) was evaluated in a 12-month phase 3 study.¹⁰
 - The primary endpoint was met (proportion of subjects achieving ≥2-grade improvement from baseline in investigator and subject Facial Wrinkle Scale with Photonic Guide [FWS] scores of FHL severity at maximum eyebrow elevation; 53.0% with onabotulinumtoxinA 64 U and 45.6% with onabotulinumtoxinA 40 U vs 0.6% with placebo on day 30; both P<0.0001).

- OnabotulinumtoxinA 4 U or placebo was given as 0.1 mL at 16 injection sites (Figure 2).
 - Following the double-blind period, subjects entered the open-label treatment period, during which they could receive up to 2 onabotulinumtoxinA 64 U treatments using the same 16-injection site paradigm, with at least 84 days separating treatment cycles.
 - Follow-up assessments were made at weeks 1 and 2 after each study treatment; all subjects also had follow-up visits every 30 days starting on study day 30 through day 360.
- Figure 2. Injection Sites for Treatment of Forehead Lines, Glabellar Lines, and Crown's Feet Lines**



Patient-Reported Outcome (PRO) Measures

- Subjects completed the Facial Line Satisfaction Questionnaire (FLSQ) and the 11-item Facial Line Outcomes Questionnaire (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 Food and Drug Administration guidance.^{11,12}
- FLSQ (11 questions at baseline and 13 questions at follow-up) is designed to assess treatment satisfaction and appearance-related impacts associated with facial lines in the FHL, GL, and/or CFL areas from the subject's perspective.
 - FLSQ Item 5 assesses the subjects' satisfaction with treatment of their facial lines.
 - FLSQ Impact Domain measures appearance-related and emotional impacts of treatment, including appearance-related age, anger, tiredness, emotional unhappiness, and negative self-esteem.
- FLO-11 assesses psychological and appearance-related impacts associated with facial lines in the forehead, glabellar, and crown's feet areas, from the subjects' perspective.
 - FLO-11 Item 4 evaluates whether subjects feel that they look older than their actual age.

Statistical Analysis

- FLSQ Item 5, FLSQ Impact Domain, and FLO-11 Item 4 were included as key secondary efficacy endpoints as they reflect the subject's perception of treatment effects and drive retreatment decisions.
 - Proportion of subjects mostly satisfied or very satisfied on FLSQ Item 5 (primary time point: day 60).
 - Proportion of responders on FLSQ Impact Domain, defined by a ≥20-point improvement from baseline (primary time point: day 30).
 - Proportion of responders on FLO-11 Item 4, defined by a ≥3-point improvement from baseline (primary time point: day 30) for subjects with baseline scores ≤80.
- These PRO measures were evaluated in the intent-to-treat (ITT) population, consisting of all randomized subjects.
- Comparisons between the onabotulinumtoxinA groups versus placebo were conducted using the Cochran-Mantel-Haenszel test, stratified by study site, with statistical significance achieved at P≤0.05.

RESULTS

Subjects

- The ITT population comprised 787 subjects, including 313 in the onabotulinumtoxinA 64 U group, 318 in the onabotulinumtoxinA 40 U group, and 156 in the placebo group.

- Overall, 728 subjects (92.5%) received a second treatment cycle and 510 subjects (64.8%) received a third treatment cycle during the open-label period.
- The majority of subjects completed the study (n=684; 86.9%); discontinuations were mostly due to being lost to follow-up (n=49; 6.2%) or personal reasons (n=44; 5.6%).
- Demographics and baseline characteristics were similar among treatment groups (Table 1).

Table 1. Subject Demographics and Baseline Characteristics (ITT population)

Parameter	OnabotulinumtoxinA 64 U (n=313)	OnabotulinumtoxinA 40 U (n=318)	Placebo (n=156)
Age, mean, years	45.5	47.6	48.1
Range	21-76	22-75	22-73
Female, n (%)	284 (90.7)	278 (87.4)	140 (89.7)
Caucasian, n (%)	285 (91.1)	287 (90.3)	145 (92.9)
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)
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 (38.6)	66 (42.9)
Severe	171 (55.0)	194 (61.2)	88 (57.1)
mean (range)	6.4 (0-10)	6.2 (0-10)	6.1 (0-10)
FLSQ Impact Domain score, ¹ mean (range)	60.7 (5-100)	58.9 (0-100)	59.1 (15-100)

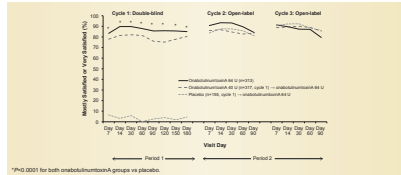
¹The subject in the placebo group had a rating of 100.
 FLSQ-11 Item 4 was scored on a scale from 0 ("not at all") to 10 ("very much").
 FLSQ Impact Domain score from 0 to 100, with higher scores indicating that facial lines had greater negative impact on the subject.
 CFL, crown's feet lines; FHL, forehead lines; FLO-11, 11-item facial line outcomes questionnaire; FLSQ, facial line satisfaction questionnaire; FWS, facial wrinkle scale; GL, glabellar lines; ITT, intent-to-treat.

FLSQ Item 5

- The proportion of subjects who were mostly or very satisfied with onabotulinumtoxinA 64 U and 40 U was significantly greater than with placebo, respectively, on day 30 (89.8% and 82.0% vs 5.8%, both P<0.0001) and on day 60, the primary time point (87.9% and 81.4% vs 3.2%, both P<0.0001).
- Subject satisfaction with treatment remained significantly higher in both onabotulinumtoxinA groups compared with placebo at all time points through the end of the double-blind treatment period (ie, day 180) (all, P<0.0001) (Figure 3).

- During the open-label period, subject satisfaction was maintained with repeated onabotulinumtoxinA 64 U treatment, including in subjects initially allocated to placebo.

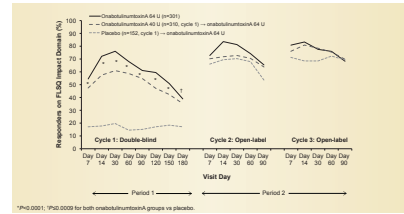
Figure 3. Subjects Mostly Satisfied or Very Satisfied on FLSQ Item 5 During the Entire 12-Month Study



FLSQ Impact Domain

- The responder rate on the FLSQ Impact Domain was significantly greater in the onabotulinumtoxinA 64 U and 40 U groups versus placebo on day 30 (76.1% and 61.0% vs 19.7%; both P<0.0001).
- The FLSQ Impact Domain responder rate remained significantly higher with onabotulinumtoxinA 64 U (all, P<0.0001) and 40 U (P≤0.0009) versus placebo at all time points through day 180 (Figure 4).
- During the open-label treatment period, FLSQ Impact Domain responder rates were generally maintained with repeated onabotulinumtoxinA 64 U treatment (Figure 4).

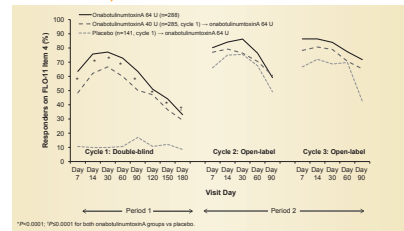
Figure 4. Responders Reporting ≥20-Point Improvement From Baseline on FLSQ Impact Domain During the Entire 12-Month Study (Subjects With Baseline Score ≥20)



FLO-11 Item 4

- The responder rate on FLO-11 Item 4 (looking older than actual age) was significantly greater in the onabotulinumtoxinA 64 U and 40 U groups versus placebo on day 30 (77.1% and 66.7% vs 9.9%; both P<0.0001).
- The FLO-11 Item 4 responder rate remained significantly higher with onabotulinumtoxinA 64 U and 40 U versus placebo at all time points through day 180 (P≤0.0001) (Figure 5).
- Like the other PRO measures, the FLO-11 responder rate was generally maintained with repeated onabotulinumtoxinA 64 U treatment during the open-label period (Figure 5).

Figure 5. Responders Reporting ≥3-Point Improvement From Baseline on FLO-11 Item 4 During the Entire 12-Month Study (Subjects With Baseline Score ≥3)



CONCLUSIONS

- Subjects were highly satisfied with onabotulinumtoxinA 64 U treatment of UFL (FHL, GL, and CFL) and with onabotulinumtoxinA 40 U treatment of FHL and GL.
- With both onabotulinumtoxinA regimens, subjects reported significant improvements in appearance-related and emotional impacts of their facial lines.
- The improvements in PROs were sustained for at least 6 months after a single treatment cycle, and were maintained thereafter with repeated onabotulinumtoxinA treatment.

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ACKNOWLEDGMENTS

This study was sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided to the authors by Cactus Communications and was funded by Allergan plc. All authors met the ICMJE authorship criteria. Neither honoraria nor other form of payments were made for authorship.

FINANCIAL DISCLOSURES

S Dayan has received research support or speaking/consultant fees from Allergan plc, Galderma, Merz Aesthetics, and Valent. P Ogilvie serves as an investigator for Allergan plc. AZ Rivkin serves as a consultant and investigator for Allergan plc and Merz Aesthetics. SG Yoelin serves as a consultant and investigator for Allergan plc. JK Garcia is an employee of Allergan plc and may own stock options in the company. IL Ferrusi was an employee of Allergan plc at the time of this study.

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