OnabotulinumtoxinA for Treatment of Moderate to Severe Horizontal Frontalis Lines and Glabellar Lines From the Subject's Perspective: Patient-Reported Satisfaction and Impact Outcomes From a Phase 3 Double-Blind Study

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INTRODUCTION

- The development of upper facial lines can negatively influence self-perception and may have adverse psychological impacts[1-3]
- Subject satisfaction with aesthetic treatment reflects successful treatment outcomes, which consequently may be associated with improved self-esteem and body image[1,2]
- OnabotulinumtoxinA has been used effectively and safely to treat facial lines since the early 1990s[4,5]
- When treating forehead lines (FHL), concurrent 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 making up the glabellar complex)[6]
- The safety and efficacy of onabotulinumtoxinA for treating FHL with 20 U to the frontalis muscle and 20 U to the glabellar complex was evaluated in a 12-month, phase 3 study[7]
  - The primary endpoint—proportion of subjects achieving ≥2-grade improvement from baseline on day 30 in investigator and subject Facial Wrinkle Scale with photonumeric guide (FWS) scores of FHL severity at maximum eyebrow elevation—was met (61.4% with onabotulinumtoxinA vs 0% with placebo; *P*<0.0001)

OBJECTIVE

- To present results from a 12-month, phase 3 study on the effects of onabotulinumtoxinA on patient-reported satisfaction and to assess impacts of treatment

METHODS

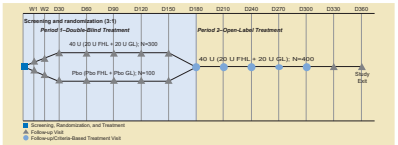
Patients

- Neurotoxin-naive males and females aged ≥18 years with both:
  - Moderate to severe FHL at maximum eyebrow elevation (as assessed by both investigator and subject using the FWS on study day 1, before treatment)
  - Moderate to severe GL at maximum frown (as assessed by the investigator using the FWS on study day 1, before treatment)

Study Design

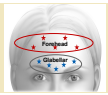
- This 12-month, phase 3 study was conducted at 9 sites in the United States, 5 in Canada, and 2 in Europe (Ireland) from October 2014 to April 2016
- The study comprised a 6-month double-blind, placebo-controlled, parallel-group treatment period (days 1–180) followed by a 6-month open-label treatment period (days 180–360) (**Figure 1**)
- Eligible subjects were randomized (3:1) to receive a single treatment consisting of onabotulinumtoxinA 40 U (20 U in FHL and 20 U in GL) or placebo administered at 10 injection sites (**Figure 2**)
  - OnabotulinumtoxinA 4U or placebo was given in 0.1 mL at each injection site
- Following the double-blind period, subjects could receive up to 2 open-label treatments with onabotulinumtoxinA using the same 10 injection sites, with ≥84 days between 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 from study day 30 through day 360

Figure 1. Study Design



D, day; FHL, forehead lines; GL, glabellar lines; Pbo, placebo; W, week.

Figure 2. Injection Sites for OnabotulinumtoxinA Treatment of FHL and GL



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[8,9]
- The FLSQ (comprising 11 questions at baseline and 13 questions at follow-up) was designed to assess treatment satisfaction and appearance-related impacts associated with FHL and GL from the subject's perspective
  - FLSQ Item 5 assesses subjects' satisfaction with treatment of their facial lines
  - The Impact Domain measures appearance-related and emotional impacts of treatment, including appearance-related age, anger, tiredness, emotional unhappiness, and negative self-esteem
- The FLO-11 assesses psychological and appearance-related impacts associated with FHL and GL from the subjects' perspective
  - Item 4 evaluates whether subjects feel that they look older than their actual age

Statistical Analysis

- FLSQ Item 5 and Impact Domain and FLO-11 Item 4 were included as key secondary efficacy endpoints as they reflect each subject's perception of treatment effects and drive retreatment decisions
  - Proportion of subjects mostly or very satisfied on FLSQ Item 5 (primary time point: day 60)
  - Proportion of responders on FLSQ Impact Domain, defined by ≥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)
- These PROs were evaluated in the intent-to-treat (ITT) population, comprising all randomized subjects
- Between-group comparisons 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 391 subjects, including 290 in the onabotulinumtoxinA group and 101 in the placebo group
- The majority of subjects completed the study (n=333; 85.2%); discontinuations were mostly for personal reasons (n=39; 10.0%) or being lost to follow-up (n=15; 3.8%)
  - Overall, 349 subjects (89.3%) received a second treatment cycle and 225 subjects (57.5%) received a third treatment cycle during the open-label period
- Demographics and baseline characteristics were similar between treatment groups (**Table 1**)

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

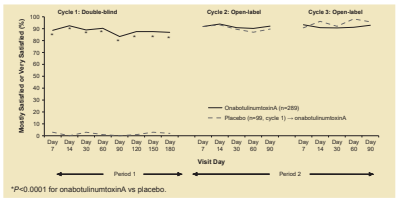
Parameter	Onabotulinum-toxinA (n=290)	Placebo (n=101)
Age, mean, years	44.5	42.4
Range	18–77	22–64
Female, n (%)	249 (85.9)	87 (86.1)
Caucasian, n (%)	260 (89.7)	87 (86.1)
FHL severity at maximum eyebrow elevation, subject FWS rating, n (%)		
Moderate	138 (47.6)	48 (47.5)
Severe	152 (52.4)	53 (52.5)
GL severity at maximum frown, investigator FWS rating,* n (%)		
Moderate	85 (29.3)	39 (38.6)
Severe	205 (70.7)	61 (60.4)
FLO-11 Item 4 score,† mean (range)	5.9 (0–10)	5.6 (0–10)
FLSQ Impact Domain score,‡ mean (range)	55.3 (0–100)	52.0 (0–100)

*One subject in the placebo group had a rating of mild.
†FLO-11 Item 4 scored on a scale from 0 ("not at all") to 10 ("very much").
‡FLSQ Impact Domain scored from 0–100, with higher scores indicating facial lines have greater negative impact on the subject.
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 study treatment was significantly greater with onabotulinumtoxinA than placebo on day 30 (88.9% vs 3.0%; *P*<0.0001) and at the primary time point for this measure on day 60 (90.3% vs 1.0%; *P*<0.0001)
- Subject satisfaction with treatment remained significantly higher with onabotulinumtoxinA than placebo at all time points through the end of the double-blind treatment period (ie, day 180; *P*<0.0001) (**Figure 3**)
- During the open-label period, subject satisfaction was maintained with repeated onabotulinumtoxinA treatment, including in subjects initially allocated to placebo

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

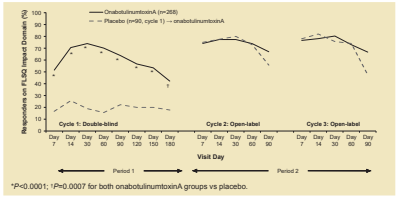


*P<0.0001 for onabotulinumtoxinA vs placebo.

FLSQ Impact Domain

- The responder rate on the FLSQ Impact Domain was significantly greater with onabotulinumtoxinA than placebo on day 30 (73.9% vs 18.9%; *P*<0.0001)
- The FLSQ Impact Domain responder rate remained significantly higher with onabotulinumtoxinA than placebo at all time points through day 180 (*P*≤0.0007) (**Figure 4**)
- During the open-label treatment period, FLSQ Impact Domain responder rates were generally maintained with repeated onabotulinumtoxinA treatment

Figure 4. Responders Achieving ≥20-Point Improvement From Baseline on FLSQ Impact Domain Over the 12-Month Study (subjects with baseline scores ≥20)

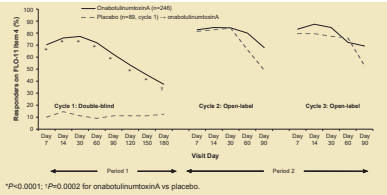


*P<0.0001; †P=0.0007 for both onabotulinumtoxinA groups vs placebo.

FLO-11 Item 4

- The responder rate on the FLO-11 Item 4 (looking older than actual age) was significantly greater with onabotulinumtoxinA than placebo on day 30 (77.2% vs 11.2%; *P*<0.0001)
- The FLO-11 Item 4 responder rate remained significantly higher with onabotulinumtoxinA than placebo at all time points through day 180 (*P*≤0.0002) (**Figure 5**)
- Like the other PRO measures, the FLO-11 responder rate was generally maintained with repeated onabotulinumtoxinA treatment during the open-label period

Figure 5. Responders Achieving ≥3-Point Improvement From Baseline on FLO-11 Item 4 Over the 12-Month Study (subjects with baseline score ≥3)



*P<0.0001; †P=0.0002 for onabotulinumtoxinA vs placebo.

CONCLUSIONS

- Subjects were highly satisfied with onabotulinumtoxinA treatment of FHL and GL, and reported significant improvements in appearance-related and emotional impacts of their facial lines
- These PRO improvements were sustained for ≥6 months after a single treatment cycle and, thereafter, were maintained with repeated onabotulinumtoxinA treatment

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