Efficacy and Safety of OnabotulinumtoxinA for Moderate to Severe Forehead Lines in Subjects With Upper Facial Lines

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INTRODUCTION

- Recent data demonstrated the efficacy and safety of onabotulinumtoxinA for treatment of forehead lines (FHL) with 20 U to the frontalis muscle and 20 U to the glabellar complex[1]
- Resting eyebrow position results from a balance between eyebrow elevator muscles (primarily frontalis) and eyebrow depressor muscles, including the procerus and corrugator muscles, which make up the glabellar complex[2]
  - Because of the muscular anatomy, concurrent treatment of glabellar lines (GL) is recommended when treating FHL to reduce the risk of eyebrow ptosis[2]
- Additional studies further support the use of onabotulinumtoxinA for managing upper facial lines, consisting of FHL treatment with simultaneous treatment of GL and crow's feet lines (CFL) (**Figure 1**)[3,4]

Figure 1. Forehead, Glabellar, and Crow's Feet Lines

- The objective of this 12-month multicenter, phase 3 study was to evaluate the safety and efficacy of onabotulinumtoxinA versus placebo for treatment of moderate to severe FHL and GL (40 U total), or FHL and GL with simultaneous treatment of CFL (64 U total)

METHODS

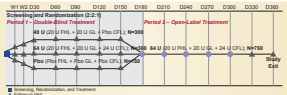
Patients

- Eligible subjects included neurotoxin-naive males and females aged ≥18 years who had the following:
  - Moderate to severe FHL at maximum eyebrow elevation, as assessed by both the investigator and the subject using the Facial Wrinkle Scale with Photonumeric Guide (FWS) on study day 1 prior to study treatment
  - Moderate to severe GL at maximum frown, as assessed by the investigator on the FWS on study day 1
  - Moderate to severe bilaterally symmetrical CFL at maximum smile, as assessed by the investigator on the FWS on day 1

Study Design and Treatments

- This 12-month study, conducted across 24 sites in the US (10 sites) and European Union (14 sites), included a 6-month double-blind, parallel-group treatment period (days 1–180) followed by a 6-month open-label treatment period (days 180–360) (**Figure 2**)
- Subjects were randomized in a 2:2:1 ratio to receive one of the following treatments at 16 injection sites:
  - OnabotulinumtoxinA 64 U (20 U in FHL, 20 U in GL, 24 U in CFL)
  - OnabotulinumtoxinA 40 U (20 U in FHL, 20 U in GL, 0 U in CFL)
  - Placebo
- During the double-blind period, follow-up assessments were conducted at weeks 1 and 2 and on days 30, 60, 90, 120, 150, and 180
- Following the double-blind period, subjects entered an open-label treatment period where they could receive up to 2 onabotulinumtoxinA 64 U treatments (with ≥84 days between treatment cycles) administered using the same 16-injection paradigm as in the double-blind period
  - Follow-up assessments for treated subjects were conducted at 1 and 2 weeks after each treatment, and all subjects had follow-up visits on study days 210, 240, 270, 300, 330, and 360

Figure 2. Study Design



CFL, crow's feet lines; D, day; FHL, forehead lines; GL, glabellar lines; Pbo, placebo; W, week.

Analysis Populations

- The efficacy analyses were based on the intent-to-treat (ITT) population, which included all randomized subjects, or the modified ITT (mITT) population, which included all randomized subjects with a baseline score ≥5 for Items 1, 4, and 5 (psychological impact) on the 11-item Facial Lines Outcomes questionnaire (FLO-11)
- The safety analyses were based on the safety population, which included all subjects who received ≥1 injection of study treatment

Efficacy and Safety Outcome Measures

- Primary efficacy endpoints—day 30 of double-blind period
  - US-specific: proportion of subjects (ITT population) who achieved ≥2-grade improvement from baseline on a composite of investigator and subject FWS ratings of FHL severity (0=none; 3=severe) at maximum eyebrow elevation
  - EU-specific: coprimary efficacy endpoints were the proportion of subjects (mITT population) who achieved an investigator and subject FWS rating of none or mild for FHL severity at maximum eyebrow elevation
- Key secondary efficacy endpoints
  - Investigator FWS rating of none or mild in FHL severity at maximum eyebrow elevation (ITT population) at day 30
  - ≥1-grade improvement from baseline in investigator FWS rating of FHL severity at rest (ITT population) at day 30
  - ≥3-point improvement from baseline on FLO-11 Items 1, 4, and 5 (mITT population) at day 30
  - Proportion of subjects reporting mostly or very satisfied ratings on the Facial Line Satisfaction Questionnaire (FLSQ) Item 5 (ITT population) at day 60
- Safety
  - Treatment-emergent adverse events (TEAEs), vital signs, urine pregnancy test

Statistical Analysis

- Active treatment vs placebo comparisons were conducted using the Cochran-Mantel-Haenszel tests, stratified by study site (statistical significance, *P*≤0.05)

RESULTS

Subject Demographics and Baseline Characteristics

- The ITT population comprised 787 subjects: 568 were included in the mITT population and 787 were included in the safety population
  - The majority of subjects completed the 6-month double-blind period; most of the discontinuations were for subjects being lost to follow-up or for personal reasons
- At baseline, demographics, FWS ratings of FHL severity at maximum eyebrow elevation, and FLO-11 ratings were similar between the two treatment groups (**Table 1**)

Table 1. Subject Demographics and Baseline Facial Line Severity

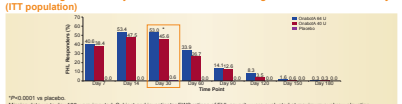
Parameter	ITT Population			mITT Population		
	OnabotA 64 U (n=313)	OnabotA 40 U (n=318)	Placebo (n=194)	OnabotA 64 U (n=194)	OnabotA 40 U (n=222)	Placebo (n=111)
Completed double-blind period, %	95.2	93.1	89.1	95.7	91.9	89.2
Mean age, years	45.5	47.6	48.1	46.3	47.7	48.9
Range	21–76	22–75	22–73	21–72	22–75	26–73
Female, %	90.7	87.4	89.7	91.5	88.7	89.2
Caucasian, %	91.1	90.3	92.9	90.2	90.5	92.8
Investigator FWS rating of FHL severity at maximum eyebrow elevation, %						
Moderate	51.8	54.1	51.9	53.2	55.9	45.9
Severe	48.2	45.9	48.1	46.8	44.1	54.1
FLO-11 scores,* mean (range)						
Item 1: Bothered by facial lines	7.3 (0–10)	7.0 (0 –10)	7.1 (0–10)	8.0 (5–10)	8.0 (5–10)	7.9 (5–10)
Item 4: Looking older than actual age	6.4 (0–10)	6.2 (0–10)	6.1 (0–10)	7.4 (5–10)	7.6 (5–10)	7.3 (5–10)
Item 5: Looking less attractive	6.9 (0–10)	6.7 (0–10)	7.0 (0–10)	7.9 (5–10)	7.9 (5–10)	7.9 (5–10)

*Individual FLO-11 items were scored on a scale from 0=not at all to 10=very much.
FHL, forehead lines; FLO-11, 11-item Facial Lines Outcomes questionnaire; FWS, Facial Wrinkle Scale; ITT, intent-to-treat; mITT, modified intent-to-treat; OnabotA, onabotulinumtoxinA.

Efficacy

- OnabotulinumtoxinA significantly improved the appearance of FHL severity when treated with GL versus placebo, based on the investigator/subject composite FWS assessment in the ITT population (primary US endpoint; **Figure 3**)

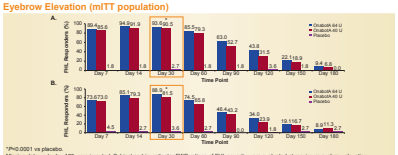
Figure 3. Proportion of Subjects Achieving ≥2-Grade Improvement From Baseline on Both Investigator and Subject Facial Wrinkle Scale Ratings of Forehead Line Severity (ITT population)



*P<0.0001 vs placebo.
Missing data up to day 180 were imputed. Subject and investigator FWS ratings of FHL severity were evaluated at maximum eyebrow elevation.
FHL, forehead lines; FWS, Facial Wrinkle Scale; ITT, intent-to-treat; OnabotA, onabotulinumtoxinA.

- OnabotulinumtoxinA also significantly improved the appearance of FHL severity when treated with GL versus placebo, based on the investigator/subject composite FWS assessment in the mITT population (primary EU endpoint; **Figure 4**)

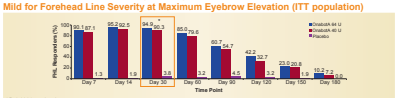
Figure 4. Proportion of Subjects Achieving a Rating of None or Mild on the Investigator (A) and Subject (B) Facial Wrinkle Scale for Forehead Line Severity at Maximum Eyebrow Elevation (mITT population)



*P<0.0001 vs placebo.
Missing data up to day 180 were imputed. Subject and investigator FWS ratings of FHL severity were evaluated at maximum eyebrow elevation.
FHL, forehead lines; FWS, Facial Wrinkle Scale; mITT, modified intent-to-treat; OnabotA, onabotulinumtoxinA.

- A significantly greater proportion of subjects in the ITT population treated with onabotulinumtoxinA achieved an investigator FWS rating of none or mild for FHL severity at maximum eyebrow elevation (**Figure 5**)

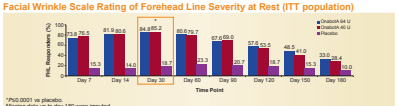
Figure 5. Responders Achieving Investigator Facial Wrinkle Scale Ratings of None/Mild for Forehead Line Severity at Maximum Eyebrow Elevation (ITT population)



*P≤0.0001 vs placebo.
Missing data up to day 180 were imputed.
FHL, forehead lines; ITT, intent-to-treat; OnabotA, onabotulinumtoxinA.

- The proportion of subjects in the ITT population who achieved ≥1-grade improvement from baseline on the investigator FWS rating of FHL severity at rest was also significantly greater in the onabotulinumtoxinA treatment group versus placebo (**Figure 6**)

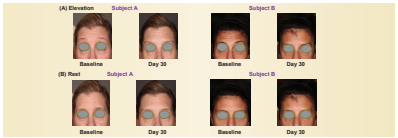
Figure 6. Responders Achieving ≥1-grade Improvement From Baseline on Investigator Facial Wrinkle Scale Rating of Forehead Line Severity at Rest (ITT population)



*P≤0.0001 vs placebo.
Missing data up to day 180 were imputed.
FHL, forehead lines; ITT, intent-to-treat; OnabotA, onabotulinumtoxinA.

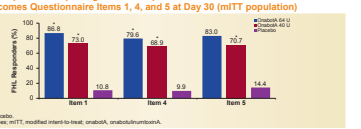
- To exemplify treatment outcomes, patient images before and after treatment at maximum eyebrow elevation and at rest show the improvement afforded by simultaneous onabotulinumtoxinA 64 U treatment of FHL and GL (**Figure 7**)

Figure 7. Patient Images at Maximum Eyebrow Elevation (A) and at Rest (B) Before and After Treatment With OnabotulinumtoxinA 40 U



- OnabotulinumtoxinA treatment was associated with significant improvement from baseline in mean subject ratings on FLO-11 Items 1, 4, and 5 (**Figure 8**)

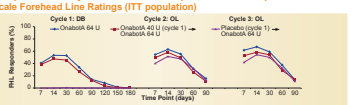
Figure 8. Responders Reporting ≥3-Point Improvement From Baseline for the Facial Lines Outcomes Questionnaire Items 1, 4, and 5 at Day 30 (mITT population)



*P<0.0001 vs placebo.
FHL, forehead lines; mITT, modified intent-to-treat; onabotA, onabotulinumtoxinA.

- Treatment response was maintained across treatment cycles
- The proportion of subjects with ≥2-grade improvement on the FWS investigator/subject composite ratings of FHL at maximum eyebrow elevation is shown across cycles in **Figure 9**

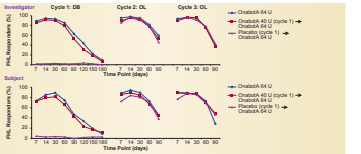
Figure 9. Proportion of Subjects With ≥2-Grade Improvement in Composite Facial Wrinkle Scale Forehead Line Ratings (ITT population)



All subjects received open-label onabotulinumtoxinA 64 U in cycles 2 and 3. Missing data up to the day 180 visit of treatment cycle 1 were imputed.
DB, double-blind; FHL, forehead lines; ITT, intent-to-treat; OL, open-label; onabotA, onabotulinumtoxinA.

- The proportion of responders achieving an investigator FWS rating of none/mild in FHL severity at maximum eyebrow elevation across treatment cycles is shown in **Figure 10**

Figure 10. Proportion of Subjects With Investigator and Subject Facial Wrinkle Scale Ratings of None or Mild in Forehead Lines (mITT population)



All subjects received open-label onabotulinumtoxinA 64 U in cycles 2 and 3. Missing data up to the day 180 visit of treatment cycle 1 were imputed.
DB, double-blind; FHL, forehead lines; mITT, modified intent-to-treat; OL, open-label; onabotA, onabotulinumtoxinA.

- A significantly greater proportion of subjects (ITT population) treated with onabotulinumtoxinA achieved an investigator rating of none or mild FHL severity for all 3 facial areas (FHL, GL, and CFL) at maximum eyebrow elevation (**Figure 11**)

Figure 11. Responders Achieving Investigator Facial Wrinkle Scale Rating of None/Mild in Forehead Line Severity for All 3 Facial Areas (forehead lines, glabellar lines, and crow's feet lines) at Maximum Eyebrow Elevation (mITT population)

*P≤0.0001 vs placebo.
All subjects received open-label onabotulinumtoxinA 64 U in cycles 2 and 3. Missing data up to the day 180 visit of treatment cycle 1 were imputed.
FHL, forehead lines; mITT, modified intent-to-treat; OnabotA, onabotulinumtoxinA.

Safety

- Overall, TEAEs were reported by 44.1% of subjects (329/746) in the onabotulinumtoxinA 64 U group compared with 48.4% (154/318) in the onabotulinumtoxinA 40 U group and 33.3% (52/156) in the placebo group
- The most frequently reported TEAEs are summarized in **Table 2**
- All treatment-related AEs were mild or moderate in severity
- Serious AEs were reported in 25 subjects; none were considered related to treatment
- No clinically meaningful changes in vital signs were noted during the study

Table 2. Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in Either Treatment Group (safety population)

	OnabotulinumtoxinA	OnabotulinumtoxinA	
TEAEs, n (%)	64 U* (n=746)	40 U† (n=318)	Placebo† (n=156)
Overall	160 (21.4)	79 (24.8)	16 (10.3)
Headache	46 (6.2)	16 (5.0)	4 (2.6)
Injection site bruising	46 (6.2)	24 (7.5)	5 (3.2)
Injection site hematoma	34 (4.6)	16 (5.0)	3 (1.9)

*Includes up to 365 days of safety data. †Includes up to 180 days of safety data. Subjects in the onabotA group received up to 3 treatment cycles of onabotA 64 U; subjects in the placebo group received only 1 to 2 treatment cycles of onabotA 64 U. TEAEs that occurred during the open-label phase of the study are captured in the onabotA 64 U column. OnabotA, onabotulinumtoxinA; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Overall, onabotulinumtoxinA significantly improved the appearance of FHL and upper facial lines, consisting of FHL, GL, and CFL
- OnabotulinumtoxinA 64 U (20 U in FHL, 20 U in GL, and 24 U in CFL) and onabotulinumtoxinA 40 U (20 U in FHL, 20 U in GL, and 0 in CFL) demonstrated significantly greater efficacy than placebo in the treatment of moderate to severe FHL for both primary efficacy endpoints
  - Primary efficacy results with onabotulinumtoxinA 64 U and 40 U were supported by statistically significant results for all secondary efficacy analyses, including a high rate of subject satisfaction with treatment outcomes
- Treatment response was maintained with repeated treatment cycles of onabotulinumtoxinA 64 U
- OnabotulinumtoxinA was well tolerated, with a low incidence of TEAEs, which were all mild or moderate in severity

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