Efficacy and Safety of OnabotulinumtoxinA for Treatment of Moderate to Severe Forehead Lines

Steve Fagien, MD[1]; Joel L. Cohen, MD[2]; William Coleman, MD[3]; Gary Monheit, MD[4]; Jean Carruthers, MD[5]; Cheri Mao, MS[6]; Domenico Vitarella, PhD[6]; Xiaofang Lei, PhD[6]; Bhushan Hardas, MD, MBA[6]

[1]Aesthetic Eyelid Plastic Surgery, Boca Raton, FL; [2]AboutSkin Dermatology and DermSurgery, Greenwood Village, CO; [3]Coleman Center for Cosmetic Dermatologic Surgery, Metairie, LA; [4]Total Skin and Beauty Dermatology Center, Birmingham, AL; [5]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada; [6]Allergan plc, Irvine, CA

INTRODUCTION

- Since the early 1990s, onabotulinumtoxinA has been effectively and safely used to treat facial lines[1,2]
- Recent data demonstrated the efficacy of onabotulinumtoxinA for treatment of forehead lines (FHL) with 20 U to the frontalis muscle and 20 U to the glabellar complex[3]
- 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[4]
  - Because of the muscular anatomy, concurrent treatment of glabellar lines (GL) is recommended when treating FHL (**Figure 1**) to reduce the risk of eyebrow ptosis[4]

Figure 1. Forehead and Glabellar Lines

OBJECTIVE

- This 12-month, multicenter, phase 3 study aimed to evaluate the safety and efficacy of onabotulinumtoxinA versus placebo for treatment of moderate to severe FHL, with simultaneous treatment of GL

METHODS

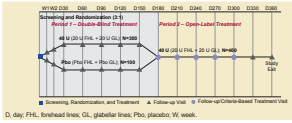
Patients

- Eligible subjects included neurotoxin-naive males and females aged ≥18 years with both:
  - Moderate to severe FHL at maximum eyebrow elevation as assessed by both the investigator and 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 using the FWS on study day 1

Study Design and Treatment

- This 12-month study was conducted across 16 sites in the United States (9), Canada (5), and the European Union (2)
- The study 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 3:1 ratio to receive a single treatment with onabotulinumtoxinA 40 U (20 U in FHL and 20 U in GL) or placebo administered at 10 injection sites (onabotulinumtoxinA: 4 U/0.1 mL at each injection site)
  - 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 could receive up to 2 open-label treatments with onabotulinumtoxinA 40 U (with ≥84 days between treatment cycles), administered using the same 10-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 days 210, 240, 270, 300, 330, and 360

Figure 2. Study Design



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 score 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 mostly or very satisfied 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

- Between-group comparisons were conducted using the Cochran-Mantel-Haenszel test, stratified by study site (statistical significance, P≤0.05)

RESULTS

Subject Disposition and Baseline Characteristics

- The ITT population comprised 391 subjects
  - 254 were included in the mITT population
  - 390 were included in the safety population
  - The majority of subjects completed the double-blind period; discontinuations were primarily for personal reasons
- At baseline, demographics, FWS ratings of FHL severity at maximum eyebrow elevation, and FLO-11 ratings were similar between treatment groups (**Table 1**)

Table 1. Subject Demographics and Baseline Facial Line Severity

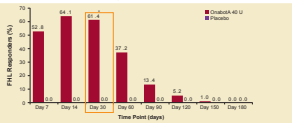
	ITT Population		mITT Population	
Parameter	**OnabotA (n=290)**	**Placebo (n=101)**	**OnabotA (n=194)**	**Placebo (n=60)**
Completed double-blind period, %	93.1	84.2	91.8	83.3
Age, mean, years	44.5	42.4	46.0	44.9
Range	18-77	22-64	23-75	26-64
Female, %	85.9	86.1	86.6	91.7
Caucasian, %	89.7	86.1	90.2	81.7
Investigator FWS rating of FHL severity at maximum eyebrow elevation				
Moderate, %	47.5	47.6	40.0	41.8
Severe, %	52.5	53.4	60.0	58.2
FLO-11 scores,* mean (range)				
Item 1: Bothered by facial lines	6.9 (0-10)	6.5 (0-10)	8.0 (5-10)	7.9 (5-10)
Item 4: Looking older than actual age	5.9 (0-10)	5.6 (0-10)	7.5 (5-10)	7.1 (5-10)
Item 5: Looking less attractive	6.8 (0-10)	6.1 (0-10)	8.2 (5-10)	8.0 (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**)

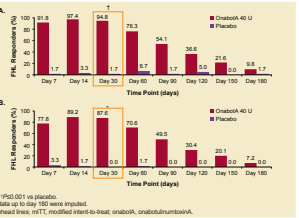
Figure 3. Proportion of Subjects Achieving ≥2-Grade Improvement From Baseline on Both Investigator and Subject Facial Wrinkle Scale Ratings of Forehead Line Severity (ITT population)



*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; 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**)

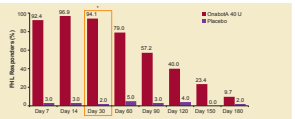
Figure 4. Proportion of Subjects Achieving a Rating of None or Mild on the Investigator-Assessed (A) and Subject-Assessed (B) Facial Wrinkle Scale for Forehead Line Severity at Maximum Eyebrow Elevation (mITT population)



*Ps0.01; †Ps0.001 vs placebo.
Missing data up to day 180 were imputed.
FHL, forehead lines; 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 versus placebo (**Figure 5**)

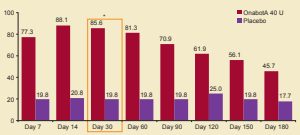
Figure 5. Responders Achieving Investigator Facial Wrinkle Scale Rating of None/Mild for Forehead Line Severity at Maximum Eyebrow Elevation (ITT population)



*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)



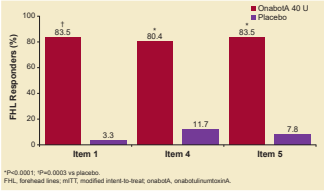
*P<0.0001 vs placebo.
Missing data up to day 180 were imputed.
FHL, forehead lines; ITT, intent-to-treat; onabotA, onabotulinumtoxinA.

- Patient images before and after treatment with onabotulinumtoxinA 40 U show the improvement achieved with simultaneous treatment of FHL and GL (**Figure 7**)

Figure 7. Patient Images at Maximum Eyebrow Elevation (A) and at Rest (B) Are Shown 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**)

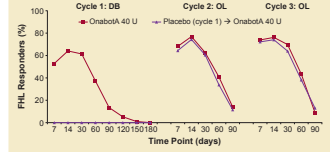
Figure 8. Responders Reporting ≥3-Point Improvement From Baseline for FLO-11 Items 1, 4, and 5 at Day 30 (mITT population)



*P<0.0001; †P=0.0003 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**

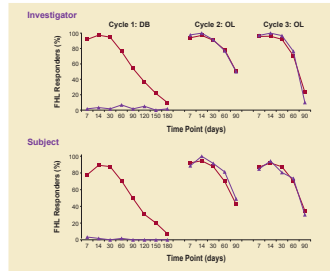
Figure 9. Proportion of Subjects With ≥2-Grade Improvement in Composite Facial Wrinkle Scale Forehead Line Ratings (ITT population)



All subjects received open-label onabotulinumtoxinA 40 U in cycles 2 and 3. Subjects in the onabotulinumtoxinA group received up to 3 treatment cycles of onabotulinumtoxinA; subjects in the placebo group received only 1–2 treatment cycles of onabotulinumtoxinA.
DB, double-blind; FHL, forehead lines; ITT, intent-to-treat; OL, open-label; onabotA, onabotulinumtoxinA.

- The proportion of responders who achieved 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 40 U in cycles 2 and 3. Subjects in the onabotulinumtoxinA group received up to 3 treatment cycles of onabotulinumtoxinA; subjects in the placebo group received only 1–2 treatment cycles of onabotulinumtoxinA.
DB, double-blind; FHL, forehead lines; mITT, modified intent-to-treat; OL, open-label; onabotA, onabotulinumtoxinA.

Safety

- Overall, TEAEs were reported by 46.5% of subjects (174/374) in the onabotulinumtoxinA group compared with 32.0% in the placebo group (32/100)
- The most frequently reported treatment-related AEs are summarized in **Table 2**; all TEAEs were mild or moderate in severity
- Serious AEs were reported by 5 subjects, all treated with onabotulinumtoxinA; 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)

TEAE, n (%)	OnabotA (n=374)*	Placebo(n=100)†
Overall	85 (22.7)	10 (10.0)
Brow ptosis	15 (4.0)	0
Eyelid ptosis	10 (2.7)	0
Headache	33 (8.8)	5 (5.0)
Injection site bruising	19 (5.1)	2 (2.0)
Injection site pain	6 (1.6)	3 (3.0)
Skin tightness	9 (2.4)	0

*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 40 U; subjects in the placebo group received only 1 to 2 treatment cycles of onabotA 40 U. TEAEs that occurred during the open-label phase of the study are captured in the onabotA column. OnabotA, onabotulinumtoxinA; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- For both primary efficacy endpoints, onabotulinumtoxinA 40 U (20 U in FHL and 20 U in GL) demonstrated significantly greater efficacy than placebo in the treatment of moderate to severe FHL
  - The primary efficacy results with onabotulinumtoxinA 40 U are 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
- OnabotulinumtoxinA administered as 20 U in FHL and 20 U in GL was well tolerated, with a low incidence of treatment-related AEs, all mild or moderate in severity

REFERENCES

1. Carruthers JD, Carruthers JA. *J Dermatol Surg Oncol*. 1992;18(1):17-21.
2. Carruthers J, et al. *Dermatol Surg*. 2015;41(6):702-11.
3. Solish N, et al. *Dermatol Surg*. 2016;42(3):410-9.
4. Lorenc ZP, et al. *Aesthetic Plast Surg*. 2013;37(5):975-83.

ACKNOWLEDGMENTS

This study was sponsored by Allergan plc, Dublin, Ireland. Medical writing and editorial assistance was provided 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 Fagien, JL Cohen, W Coleman, G Monheit, and J Carruthers serve as investigators for Allergan plc. C Mao, D Vitarella, X Lei, and B Hardas are employees of Allergan plc and may own stock/stock options in that company.