A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Phase III, Non-Inferiority Study Comparing PrabotulinumtoxinA and OnabotulinumtoxinA for the Treatment of Moderate to Severe Glabellar Lines in Adult Patients

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Abstract

Background: PrabotulinumtoxinA is a 900-kDa botulinum toxin type A produced by *Clostridium botulinum*.

Objectives: The authors sought to investigate the efficacy and safety of prabotulinumtoxinA compared to onabotulinumtoxinA and placebo for the treatment of glabellar lines.

Methods: This was a 150-day, multicenter, double-blind, controlled, single-dose Phase III study. Adult patients (n = 540) with moderate to severe glabellar lines at maximum frown as assessed by the investigator on the validated 4-point Glabellar Line Scale (0 = no lines, 1 = mild, 2 = moderate, 3 = severe), who also felt that their glabellar lines had an important psychological impact, were enrolled. Patients were randomized 5:5:1 to receive a single treatment (0.1 mL injected into each of 5 glabellar sites) of 20 U prabotulinumtoxinA (n = 245), 20 U onabotulinumtoxinA (n = 246), or placebo (n = 49). The primary efficacy endpoint was the proportion of responders (patients with a Glabellar Line Scale score of 0 or 1 at maximum frown by investigator assessment) on day 30.

Results: Responder rates for the primary efficacy endpoint were 87.2%, 82.8%, and 4.2% in the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups, respectively. The absolute difference between prabotulinumtoxinA and onabotulinumtoxinA groups was 4.4% (95% confidence interval [−1.9, 10.8]). Given that the lower bound of the 95% confidence interval for the difference was less than −10.0%, noninferiority of prabotulinumtoxinA vs onabotulinumtoxinA was concluded. Five patients (3 prabotulinumtoxinA, 1.2%; 1 onabotulinumtoxinA, 0.4%; 1 placebo, 2.0%) experienced serious adverse events, none of which were study drug related.

Conclusions: A single treatment of 20 U prabotulinumtoxinA was safe and effective and noninferior to 20 U onabotulinumtoxinA for the treatment of moderate to severe glabellar lines.

Level of Evidence: 1

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PrabotulinumtoxinA is a new 900-kDa botulinum toxin type A preparation produced by *Clostridium botulinum* that was originally developed by Daewoong Pharmaceutical Co., Ltd. of Seoul, South Korea. It was licensed to Evolus, Inc. of Newport Beach, CA for clinical development and distribution in several regions including the United States, Europe, and Canada. Evidence that 20 U of the original formulation of prabotulinumtoxinA was both safe and effective for the treatment of moderate to severe glabellar lines in adult patients was first established in a 268-patient, randomized, double-blind, Phase III comparator study conducted in South Korea.[1] The final prabotulinumtoxinA formulation, which was investigated in this study, is different from the original Daewoong formulation in that it is vacuum-dried and uses a different source for the excipient human serum albumin: excipients include 0.5 mg human serum albumin and 0.9 mg NaCl per 100-U vial. Results from 2 identical placebo-controlled Phase III clinical trials (EV-001, n = 330; EV-002, n = 324) conducted in the United States confirmed the efficacy and safety of a single treatment of 20 U of this prabotulinumtoxinA formulation for the treatment of glabellar lines in adult patients.[2]

The current study, EVB-003, was undertaken to investigate the efficacy and safety of 20 U of prabotulinumtoxinA compared with 20 U onabotulinumtoxinA and placebo in a European and Canadian population. Efficacy outcomes were based on investigator and patient assessments performed employing the 4-point Glabellar Line Scale (GLS) at maximum frown as well as measures of patient satisfaction and psychological well-being.

METHODS

Study Design and Conduct

EVB-003 was a prospectively designed, multicenter, randomized, double-blind, active- and placebo-controlled, single-dose study. This study was conducted between June 2015 and April 2016 at 19 study centers in France (5 sites), Germany (7 sites), Sweden (2 sites), the United Kingdom (1 site), and Canada (4 sites). The EVB-003 study protocol and its amendments were approved in each country by an independent ethics committee or institutional review board as follows: Comité de Protection des Personnes Ile de France 5 (all sites in France), Landesamt für Gesundheit und Soziales Berlin Ethik (all sites in Germany), Regionala etikprövningsnämnden i Stockholm (both sites in Sweden), NRES Committee London-Central (the UK site), and Quorum Review IRB (all sites in Canada). The study was conducted in accordance with the ethical principles that have their origin in the 1975 Declaration of Helsinki and in compliance with International Conference on Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP). EU Clinical Trials Register Identifier: 2014-001063-12.

Patients

Study patients were selected from a population of healthy adults, at least 18 years of age, who had moderate (GLS score = 2) to severe (GLS score = 3) glabellar lines at maximum frown, as assessed by the investigator employing the validated 4-point photonumeric GLS (refer to Figure 1 of Beer et al[2] for photonumeric images of the GLS). In addition, patients must have answered yes to the question: "Do you find that your glabellar lines have an important psychological impact, for example, on mood, anxiety or depressive symptoms?" The main exclusion criteria included previous treatment with botulinum toxin of any serotype in the forehead within the last 6 months or any planned treatment during the study period, previous treatment with any facial aesthetic procedure in the glabellar area within the last 12 months, previous insertion of permanent material in the glabellar area, any surgery in the glabellar area or any

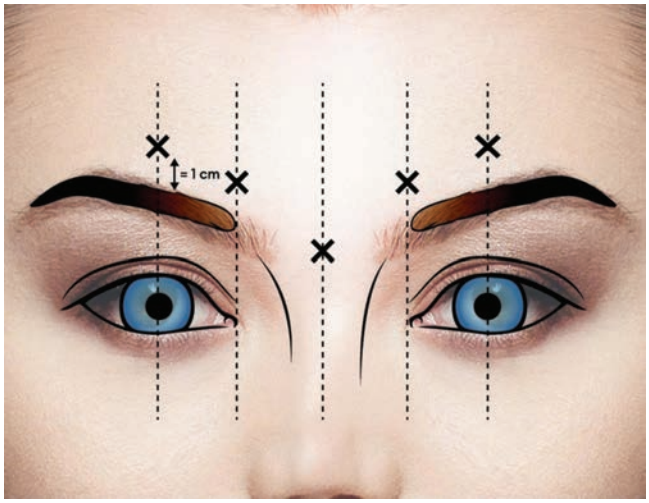

Figure 1. Target injection sites. The 5 target injection sites were the midline of the procerus, the inferomedial aspect of each corrugator muscle, and the superior middle aspect of each corrugator, at least 1 cm above the bony orbital rim. Adapted from Beer et al.[2]

other planned facial aesthetic procedure during the study, marked facial asymmetry, and presence or history of eyelid and/or eyebrow ptosis. Female patients of childbearing potential were required to have a negative pregnancy test and must have been willing to utilize an acceptable form of contraception. All patients provided written informed consent prior to entering the study.

Treatments and Follow-Up

On day 0, eligible patients were randomly assigned in a 5:5:1 ratio to receive a single treatment (0.1 mL injected into each of 5 sites) of prabotulinumtoxinA (total of 20 U, administered as 4 U/0.1 mL) or onabotulinumtoxinA (Botox Cosmetic, Allergan, Irvine, CA; total of 20 U, administered as 4 U/0.1 mL) or placebo (0.9% saline). Random numbers were generated utilizing SAS PROC PLAN (SAS Institute, Inc., Cary NC); a block randomization scheme with no stratification was employed where each block contained assignments for 5 prabotulinumtoxinA patients, 5 onabotulinumtoxinA patients, and 1 placebo patient. Study vials contained 100 U of prabotulinumtoxinA, 100 U of onabotulinumtoxinA, or placebo according to the randomization schedule. Trained individuals were responsible for reconstituting the vial with 2.5 mL of saline and filling the injection syringe. The loaded syringe was then provided to the investigator while maintaining appropriate spatial separation to ensure blinding. The investigator administered the study treatment by intramuscular injection (Figure 1). Patients were subsequently followed-up for 150 days with site visits on days 2, 14, 30, 90, 120, and 150.

Assessments

Efficacy was evaluated at site visits by investigator and patient assessment of:

- Glabellar lines at maximum frown and at rest on the 4-point GLS (0 = no lines, 1 = mild, 2 = moderate, 3 = severe); and
- Aesthetic outcomes on the 5-point Global Aesthetic Improvement Scale (GAIS, 2 = much improved, 1 = improved, 0 = no change, −1 = worse, −2 = much worse).

At each visit, patients also assessed their:

- Level of overall satisfaction on the 5-point Subject Satisfaction Scale (SSS, 2 = very satisfied, 1 = satisfied, 0 = indifferent, −1 = unsatisfied, −2 = very unsatisfied); and
- Psychological well-being on the 14-item, 4-point/item Hospital Anxiety and Depression Scale (HADS), with points of 3, 2, 1, or 0 assigned to responses for each of 7 anxiety-related and 7 depression-related questions.[3] The maximum total score for each of the HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) subscales = 21; within each subscale, a score of 0-7 = normal, 8-10 = mild, 11-14 = moderate, 15-21 = severe.

Safety was evaluated by assessing adverse events (AEs), medical histories, physical examination results, vital signs, and concomitant medications. A directed questionnaire and directed review of body systems were performed as part of the medical history taken at each clinic visit; findings based on these assessments were utilized to help guide the physical examination and ensure that the reporting of AEs—particularly those of special interest—was comprehensive. AEs of special interest (AESIs) were those 50 events listed in the guidance document for industry developed by the US Food and Drug Administration for developing botulinum toxin products for the treatment of upper facial lines.[4] Examples of AESIs include blurred vision, dysphonia, eyelid ptosis, facial palsy, muscular weakness, and speech disorder.

Outcomes and Statistical Analysis

The primary efficacy endpoint was defined as the proportion of patients classified as responders on day 30. For this endpoint, a responder was a patient with a GLS score of 0 or 1, as assessed by the investigator at maximum frown on day 30. The primary population for this analysis was the Per Protocol (PP) population, defined as all patients who were randomized, received the protocol-required treatment, and had the primary outcome measure assessed on day 30, without a major protocol deviation. To confirm the stability

of the conclusion, a sensitivity analysis of the primary efficacy endpoint was repeated using the intent-to-treat (ITT) population, defined as all patients who were randomized to treatment. The tests of superiority for prabotulinumtoxinA vs placebo and for onabotulinumtoxinA vs placebo were performed employing the unconditional exact test by inversion of 2 one-sided tests utilizing standardized statistics.[5] A *P* value < 0.025 was required for each test to conclude that prabotulinumtoxinA and onabotulinumtoxinA were each superior to placebo. The primary hypothesis tested if the proportion of responders in the prabotulinumtoxinA group was no more than 0.10 lower than the proportion of responders in the onabotulinumtoxinA group. The evaluation of noninferiority was based on the two-sided 95% confidence interval (CI) of the difference between the proportions of responders in each group. If the lower bound of the 95% CI of the difference was greater than −0.10 (ie, greater than −10.0%), noninferiority of prabotulinumtoxinA vs onabotulinumtoxinA was concluded. Wald asymptotic CIs for risk difference were provided by SAS PROC FREQ.

Secondary efficacy endpoints, in the order that they were tested, included the:

- Proportion of patients with a GLS score of 0 or 1 on day 30 at maximum frown by patient assessment
- Proportion of patients with at least a 1-point improvement on the SSS at day 30 (ie, a score of 1 [satisfied] or 2 [very satisfied] on day 30)
- Change from baseline to day 90 in mean HADS Anxiety (HADS-A) score
- Change from baseline to day 90 in mean HADS Depression (HADS-D) score
- Proportion of patients with at least a 1-point improvement on the GLS from day 0 to day 2 at maximum frown by investigator assessment
- Proportion of patients with at least a 1-point improvement on the GLS from day 0 to day 150 at maximum frown by investigator assessment.

The primary population for analysis of the secondary endpoints was the ITT population. The denominators for all secondary endpoints were all patients in the ITT population with nonmissing data at the visits of interest for that endpoint. The secondary efficacy endpoints were tested in a closed sequential process employing gatekeeping methods to maintain the overall study Type 1 error rate of 0.05 (ie, each endpoint was tested only if the *P* value for the previous test was <0.05). Secondary endpoints were tested as follows:

- In the case of secondary endpoints based on the GLS and SSS, the differences between groups in the proportions of responders were tested utilizing the same exact test as was employed for the primary analysis of the primary efficacy endpoint; sequential testing was limited to testing the superiority of prabotulinumtoxinA vs placebo utilizing the ITT population.
- In the case of secondary endpoints based on the HADS, the day 90 HADS scores were compared with baseline scores within each group utilizing the paired *t* test; for these endpoints only, sequential testing was limited to testing the improvement of HADS scores from baseline to day 90 for the prabotulinumtoxinA group utilizing the ITT population.

Note that the onabotulinumtoxinA group was not part of the sequential testing of secondary efficacy endpoints. GLS, GAIS, and SSS scores for all visits were considered exploratory efficacy endpoints and were evaluated employing descriptive statistics.

Safety outcomes were reported for the Safety population, defined as all patients who were randomized and received treatment. All AEs were coded according to the Medical Dictionary for Regulatory Activities (Version 17.0) and grouped by system organ class and preferred term. The incidences of AEs were summarized for each treatment group as frequencies and proportions. A two-sided 95% CI was calculated for the differences between prabotulinumtoxinA and onabotulinumtoxinA groups for the proportion of patients with any AE and for the most common AEs.

Sample Size

The sample size calculation was based on the primary noninferiority comparison between prabotulinumtoxinA and onabotulinumtoxinA, and the superiority comparisons between the active treatments and placebo, utilizing the following assumptions:

- The proportions of patients classified as responders on day 30 in each of the prabotulinumtoxinA and onabotulinumtoxinA groups were estimated to be 0.85, and the noninferiority margin was set as 0.10; a one-sided Type I error rate of 2.5% and a power of 80% were used for the noninferiority hypothesis
- The proportion of patients classified as responders on day 30 in the placebo group was estimated to be 0.15; a two-sided Type I error rate of 2.5% (to account for the multiple comparisons) and a power of 80% were employed for each of the 2 superiority tests
- A 10% dropout rate.

Based on these assumptions, the total study sample size was initially estimated to be 497. This estimate included 226 patients randomized to each of the prabotulinumtoxinA and onabotulinumtoxinA groups and 45 patients randomized to the placebo group to ensure that 203 patients in each active treatment group and 40 patients in the placebo group completed the day 30 visit. However, during

the ongoing monitoring of the study, it became evident that approximately 10% of patients had attended the day 30 visit—the visit of the primary efficacy endpoint assessment—outside the protocol-mandated ±3-day window. Accordingly, a decision was made to increase the total sample size from 497 to 540 (ie, an increase of slightly less than 10%).

RESULTS

Patient Disposition and Demographics

A total of 540 patients were randomized to treatment, received the treatment as allocated, and formed the ITT and Safety populations (Figure 2). These included 245 prabotulinumtoxinA, 246 onabotulinumtoxinA, and 49 placebo patients. Most patients (531/540, 98.3%) attended the day 150 visit and completed the study. Nine patients (6 prabotulinumtoxinA, 2 onabotulinumtoxinA, 1 placebo) did not finish the study. Most commonly (8/9), these patients were lost to follow-up: 2 after day 1, 1 after day 12, 1 after day 15, 2 after day 29, 1 after day 31, and 1 after day 126. In addition, one onabotulinumtoxinA patient left the study at day 118 due to surgery and hospitalization following a serious AE unrelated to study drug. In total, the 9 patients who did not complete were followed-up for between 1 and 126 days (mean follow-up, 40.2 days). No patient was withdrawn specifically due to an AE. Most randomized patients (527/540, 97.6%) qualified for inclusion in the PP population; 13 patients (10 prabotulinumtoxinA, 2 onabotulinumtoxinA, 1 placebo) were excluded. Most commonly (12/13), these patients either missed the day 30 GLS measure because they missed the visit or had already been withdrawn, or they attended the day 30 visit outside the ±7-day window, which was defined as a major protocol deviation. In addition, one prabotulinumtoxinA patient was excluded because they had been enrolled despite having had botulinum toxin treatment in the forehead within the past 4 months (an exclusion criterion).

PrabotulinumtoxinA, onabotulinumtoxinA, and placebo groups were mostly similar in their demographic and other baseline characteristics (Table 1). The 540 patients who formed the ITT/Safety population were aged a mean of approximately 49 years (range, 22-79 years); most (92.6%) were younger than 65 years of age. Most patients (88.1%) were female (476 vs 64 males) and most (384 of the 414 patients for whom race data were allowed to be collected, 92.8%) were racially identified as white. Note that France does not permit listing the race of clinical trial patients. More patients had severe, rather than moderate, glabellar lines at maximum frown on the GLS at baseline: 73.1% had a GLS score of severe by investigator assessment and 81.7% by patient assessment. Mean baseline HADS-A scores (maximum possible of 21) were 5.3, 5.6, and 5.2 for prabotulinumtoxinA, onabotulinumtoxinA, and placebo patients, respectively; 25.4% (137/540) had a score outside the normal range (ie, a score >7). Mean baseline HADS-D scores (maximum possible of 21) were 2.4, 3.1, and 2.7 for prabotulinumtoxinA, onabotulinumtoxinA, and placebo patients, respectively; 6.7% (36/540) had a score greater than 7.

Efficacy

Representative photographs of patients' glabellar lines taken at baseline and at 30 days following treatment with each of 20 U prabotulinumtoxinA, 20 U onabotulinumtoxinA, and placebo are presented in Figures 3-8. At baseline, all 3 representative patients had a GLS score of 3 (severe) at maximum frown; at day 30, the prabotulinumtoxinA, onabotulinumtoxinA, and placebo patients had GLS scores at maximum frown of 0, 0, and 3, respectively.

Primary Efficacy Endpoint

The percentages of responders for the primary efficacy endpoint in the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups of the PP population were 87.2%, 82.8%, and 4.2%, respectively (Table 2). Both tests of superiority vs placebo were highly statistically significant: the absolute differences between prabotulinumtoxinA and placebo groups and between onabotulinumtoxinA and placebo groups were 83.1% and 78.6%, respectively (both $P < 0.001$). The absolute difference between prabotulinumtoxinA and onabotulinumtoxinA groups in the percentages of responders was 4.4% and the associated 95% CI was −1.9, 10.8. Given that the lower bound of the 95% CI interval was greater than −10.0%, noninferiority of prabotulinumtoxinA vs onabotulinumtoxinA was concluded for the primary efficacy endpoint. Similar results were achieved when the sensitivity analysis of the primary efficacy endpoint was performed utilizing the ITT population (Table 2).

Secondary Efficacy Endpoints

As presented in the subsections that follow, the *P* value for each sequential test of the secondary efficacy endpoints was observed to be <0.05. Because differences proved to be statistically significant for all secondary endpoints, the order was not a critical feature for the presentation of these results. For clarity of presentation, secondary efficacy endpoints are grouped according to each of the scales employed rather than the order they were tested (ie, by GLS, SSS, and HADS, respectively).

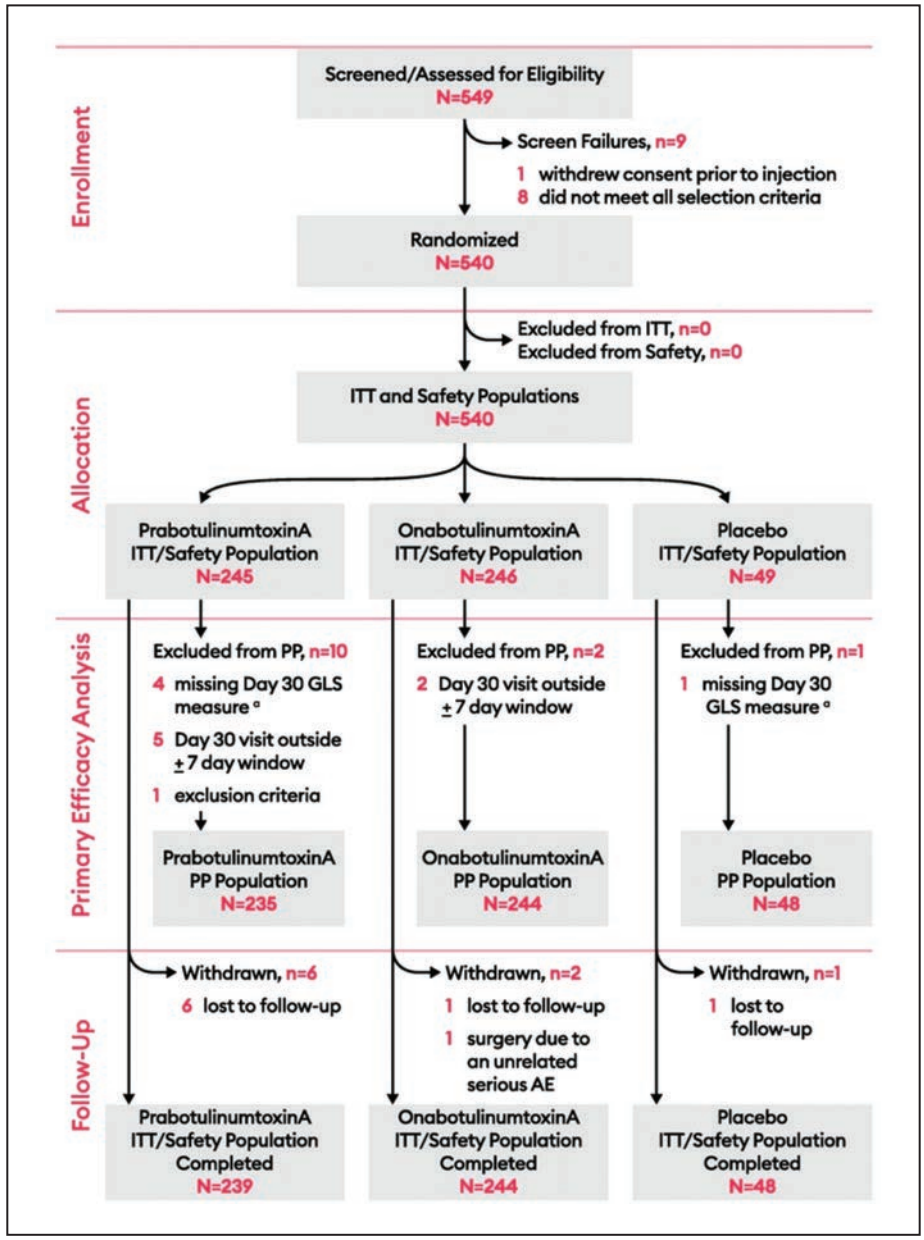

Figure 2. CONSORT flow diagram. Intention-to-treat (ITT) population: all patients who were randomly assigned to treatment; safety population: all patients who were randomized and received treatment; PP population: all patients who were randomized, received the protocol-required treatment, and had the primary outcome measure assessed on day 30, without a major protocol deviation. For the purposes of inclusion in the PP population, a day 30 visit outside the ±7-day window was considered a major protocol deviation. GLS, Glabellar Line Scale. [a]One placebo and 3 prabotulinumtoxinA patients did not have any Glabellar Line Scale assessments after day 14 and were lost to follow-up; 1 prabotulinumtoxinA patient did not attend the day 30 visit but otherwise completed the study.

Secondary Endpoints Based on the Glabellar Line Scale

The first of the secondary endpoints confirmed results observed for the primary efficacy endpoint based on investigator assessment. When the definition of a responder was based on patients with a GLS score of 0 or 1 at maximum frown on day 30 by patient rather than investigator assessment (Table 3), the percentages of responders in each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups of the ITT population were 78.8%, 76.0%, and 6.3%, respectively. The test of superiority of prabotulinumtoxinA vs placebo was highly statistically significant: the absolute difference in the percentages of responders was 72.6% ($P < 0.001$).

Table 1. Demographic and Glabellar Line Characteristics, and HADS Scores at Baseline (ITT/Safety Population)

Characteristic	PRA (N = 245)		ONA (N = 246)		Placebo (N = 49)	
Age, years						
Mean ± SD	48.8 ± 10.73		49.7 ± 10.41		48.4 ± 10.84	
[min, max]	[22, 79]		[24, 75]		[26, 71]	
<65, n (%)	228	(93.1)	227	(92.3)	45	(91.8)
≥65, n (%)	17	(6.9)	19	(7.7)	4	(8.2)
Sex, n (%)						
Male	25	(10.2)	31	(12.6)	8	(16.3)
Female	220	(89.8)	215	(87.4)	41	(83.7)
Race, n (%)						
White	165	(67.3)	183	(74.4)	36	(73.5)
Black or African American	3	(1.2)	1	(0.4)	1	(2.0)
Asian	6	(2.4)	5	(2.0)	1	(2.0)
Multiple	1	(0.4)	1	(0.4)	0	(0.0)
Other	8	(3.3)	2	(0.8)	1	(2.0)
Missing[a]	62	(25.3)	54	(22.0)	10	(20.4)
Investigator assessment of glabellar lines						
GLS score at maximum frown, n (%)[b]						
Moderate	62	(25.3)	70	(28.5)	13	(26.5)
Severe	183	(74.7)	176	(71.5)	36	(73.5)
GLS score at rest, n (%)						
None	10	(4.1)	15	(6.1)	4	(8.2)
Mild	94	(38.4)	80	(32.5)	17	(34.7)
Moderate	97	(39.6)	105	(42.7)	15	(30.6)
Severe	44	(18.0)	46	(18.7)	13	(26.5)
Patient assessment of glabellar lines						
GLS score at maximum frown, n (%)						
None	0	(0.0)	0	(0.0)	0	(0.0)
Mild	0	(0.0)	2	(0.8)	0	(0.0)
Moderate	44	(18.0)	44	(17.9)	9	(18.4)
Severe	201	(82.0)	200	(81.3)	40	(81.6)
GLS score at rest, n (%)						
None	9	(3.7)	13	(5.3)	3	(6.1)
Mild	56	(22.9)	50	(20.3)	8	(16.3)
Moderate	114	(46.5)	105	(42.7)	26	(53.1)
Severe	66	(26.9)	78	(31.7)	12	(24.5)

Table 1. Continued

Characteristic	PRA (N = 245)		ONA (N = 246)		Placebo (N = 49)	
HADS-Anxiety						
Score, mean ± SD	5.3 ± 3.20		5.6 ± 3.53		5.2 ± 2.74	
Score, [min, max]	[0, 15]		[0, 17]		[0, 10]	
Outside normal range (score > 7), n (%)	59	(24.1)	64	(26.0)	14	(28.6)
HADS-Depression						
Score, mean ± SD	2.4 ± 2.45		3.1 ± 2.93		2.7 ± 2.43	
Score, [min, max]	[0, 15]		[0, 14]		[0, 10]	
Outside normal range (score > 7), n (%)	12	(4.9)	21	(8.5)	3	(6.1)

GLS, Glabellar Line Scale (0 = no lines, 1 = mild, 2 = moderate, 3 = severe); HADS, Hospital Anxiety and Depression Scale; ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA; SD, standard deviation. [a]All 126 patients for whom race was "missing" were from sites located in France; per national laws, France does not permit listing the race of patients participating in clinical trials. [b]To be eligible for enrollment, all patients had a baseline GLS score of moderate or severe by investigator assessment.

When the definition of a responder was based on the percentage of patients with a ≥1-point improvement on the GLS at maximum frown from day 0 by investigator assessment (Table 3):

- At day 2, the percentages of responders in each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups were 54.2%, 57.0%, and 12.2%, respectively. The test of superiority of prabotulinumtoxinA vs placebo was highly statistically significant: the absolute difference in the percentages of responders was 41.9% ($P < 0.001$).
- At the day 150 or early termination visit, the percentages of responders in each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups were 37.7%, 34.4%, and 8.3%, respectively. Again, the test of superiority of prabotulinumtoxinA vs placebo was highly statistically significant: the absolute difference in the percentages of responders was 29.3% ($P < 0.001$).

Secondary Endpoints Based on the Subject Satisfaction Scale

When the definition of a responder was based on the percentage of patients with a ≥1-point improvement in SSS score from day 0 to day 30 (Table 4), the percentages of responders in each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups were 91.3%, 86.6%, and 6.3%, respectively. The test of superiority of prabotulinumtoxinA vs placebo was highly statistically significant: the absolute difference in the percentages of responders was 85.0% ($P < 0.001$).

Secondary Endpoints Based on the Hospital Anxiety and Depression Scale

Of note, sequential testing of secondary efficacy endpoints for HADS scores was based on the mean changes in HADS-A and HADS-D scores from baseline to day 90 for all prabotulinumtoxinA patients, not on comparisons with placebo. Based on the HADS-A subscale (Table 5), statistically significant mean changes from baseline to day 90 were evident within each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups: −1.1, −0.9, and −0.9, respectively ($P < 0.001$, $P < 0.001$, and $P = 0.013$, respectively). Based on the HADS-D subscale, mean changes from baseline to day 90 within each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups were only statistically significant for the prabotulinumtoxinA and onabotulinumtoxinA groups: −0.6, −0.6, and −0.5, respectively ($P < 0.001$, $P < 0.001$, and $P = 0.071$, respectively).

Exploratory Efficacy Endpoints Based on the Glabellar Line, Global Aesthetic Improvement, and Subject Satisfaction Scales

Positive outcomes were also clearly evident when patients in the PP population were evaluated at each posttreatment visit for the exploratory efficacy endpoints of the percentage of patients with a ≥1-point improvement on the GLS at maximum frown from day 0 and for overall aesthetic improvement and level of satisfaction (Figures 9-13). When the definition of a responder was based on the percentage of patients with a ≥1-point improvement on the

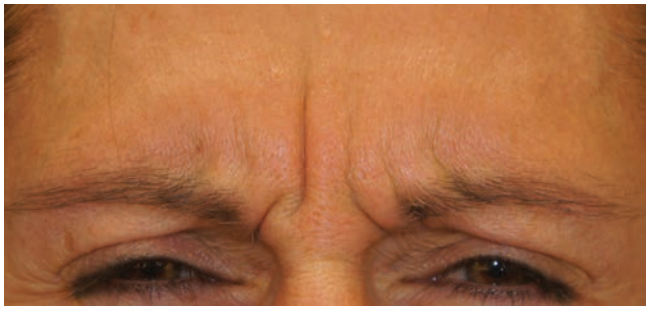

Figure 3. Glabellar lines at maximum frown at baseline prior to treatment with 20 U prabotulinumtoxinA. This representative 52-year-old female prabotulinumtoxinA patient had a Glabellar Line Scale score at maximum frown assessed as severe (score of 3) by both investigator and patient at baseline (day 0).

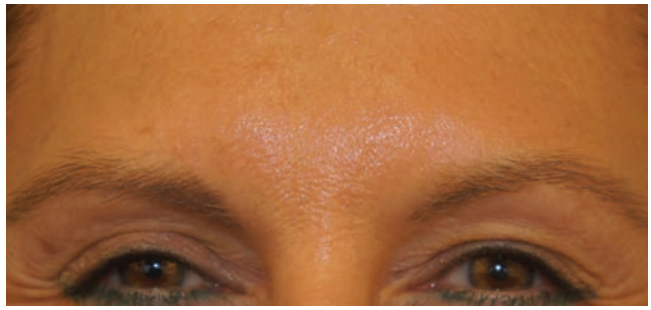

Figure 4. Glabellar lines at maximum frown at day 30 following treatment with 20 U prabotulinumtoxinA. The same 52-year-old female prabotulinumtoxinA patient from Figure 3 had a Glabellar Line Scale score at maximum frown assessed as none (score of 0) by both investigator and patient at day 30.

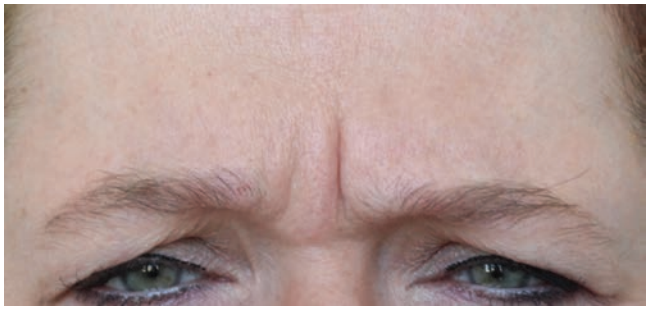

Figure 5. Glabellar lines at maximum frown at baseline prior to treatment with 20 U onabotulinumtoxinA. This representative 47-year-old female onabotulinumtoxinA patient had a Glabellar Line Scale score at maximum frown assessed as severe (score of 3) by both investigator and patient at baseline (day 0).

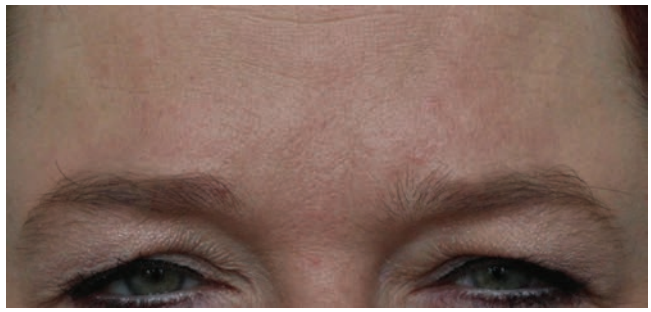

Figure 6. Glabellar lines at maximum frown at day 30 following treatment with 20 U onabotulinumtoxinA. The same 47-year-old female onabotulinumtoxinA patient from Figure 5 had a Glabellar Line Scale score at maximum frown assessed as none (score of 0) by both investigator and patient at day 30.

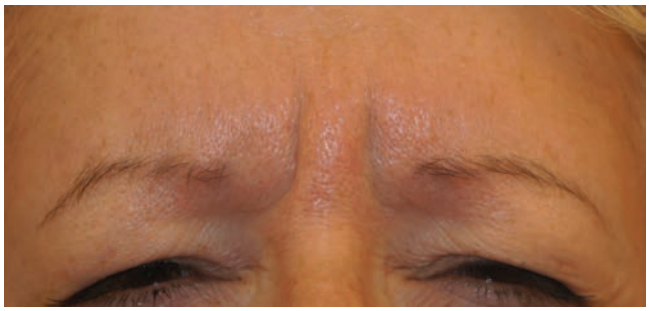

Figure 7. Glabellar lines at maximum frown at baseline prior to treatment with placebo. This representative 49-year-old female placebo patient had a Glabellar Line Scale score at maximum frown assessed as severe (score of 3) by both investigator and patient at baseline (day 0).

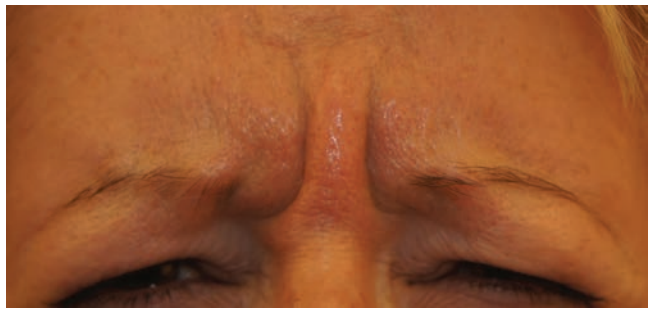

Figure 8. Glabellar lines at maximum frown at day 30 following treatment with placebo. The same 49-year-old female placebo patient from Figure 7 had a Glabellar Line Scale score at maximum frown assessed as severe (score of 3) by both investigator and patient at day 30.

GLS at maximum frown from day 0, investigator and patient assessments were similar to each other (within 10%) at all postbaseline visits (Figures 9 and 10). For example, at peak effect on day 30, the percentages of responders based on this definition in each of the prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups of the PP

Table 2. Number and Percentage of Responders for the Primary Efficacy Endpoint

Responders for primary efficacy endpoint[a]	PRA	ONA	Placebo	Absolute difference		
				PRA vs placebo	ONA vs placebo	PRA vs ONA
PP population (primary)						
Number[b]	205/235	202/244	2/48			
Percentage, %	87.2	82.8	4.2	83.1	78.6	4.4
(% CI)[c,d]	(83.0, 91.5)[c]	(78.1, 87.5)[c]	(0.0, 9.8)[c]	(70.3, 89.4)[d]	(66.5, 85.5)[d]	(−1.9, 10.8)[c]
P value				<0.001	<0.001	
ITT population (sensitivity)						
Number[b]	209/241	204/246	2/48			
Percentage, %	86.7	82.9	4.2	82.6	78.8	3.8
(% CI)[c,d]	(82.4, 91.0)[c]	(78.2, 87.6)[c]	(0.0, 9.8)[c]	(70.2, 89.1)[d]	(66.5, 85.7)[d]	(−2.6, 10.2)[c]
P value				<0.001	<0.001	

The PP population included all patients who were randomized, received the protocol-required treatment, and had the primary outcome assessed on day 30 without any major protocol deviations. The ITT population included all patients who were randomized. CI, confidence interval; GLS, Glabellar Line Scale ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA. [a]*A patient was considered a responder for the primary efficacy endpoint only if the patient had a GLS score of 0 or 1 at maximum frown on day 30 by investigator assessment.* [b]The denominator included all patients in the PP Population. [c]Within each of the placebo, onabotulinumtoxinA, and prabotulinumtoxinA treatment groups, and for the comparison of prabotulinumtoxinA vs onabotulinumtoxinA, the CI was a two-sided 95% asymptotic CI. To conclude noninferiority of prabotulinumtoxinA vs onabotulinumtoxinA, the lower bound of the 95% CI for the difference between groups in the proportion of primary efficacy endpoint responders was required to be greater than –0.10 (ie, greater than –10.0%). [d]For the comparisons of onabotulinumtoxinA vs placebo and prabotulinumtoxinA vs placebo, the CI was a 97.5% Exact CI, for which the exact CI and the associated unconditional exact test were based on the inversion of 2 one-sided tests. To conclude superiority of onabotulinumtoxinA to placebo, and of prabotulinumtoxinA to placebo, a *P* value < 0.025 was required for each test.

population were 95.3% 93.9%, and 6.3%, respectively, by investigator assessment, and 91.5% 91.8%, and 14.6%, respectively, by patient assessment.

When GAIS scores of either "improved" or "much improved" (ie, positive responders on the GAIS) were pooled, investigator and patient assessments were also similar to each other (±5%) at most postbaseline visits (Figures 11 and 12). At day 2, compared with 8.3% and 10.4% of placebo patients by each of investigator and patient assessment, respectively, 60.1% and 55.6% of prabotulinumtoxinA patients and 58.7% and 55.8% of onabotulinumtoxinA patients had a positive response on the GAIS, respectively. Among placebo patients, no more than 10.6% of patients at any visit by either investigator or patient assessment had a positive response on the GAIS. In contrast, at each of days 14 and 30, no fewer than 93% of prabotulinumtoxinA and onabotulinumtoxinA patients had a positive response on the GAIS. By the day 150 or early termination visit, compared with 2.1% and 4.2% of placebo patients (ie, 1 or 2 patients) by each of investigator and patient assessment, respectively, 49.6% and 55.2% of prabotulinumtoxinA patients and 41.3% and 48.3% of onabotulinumtoxinA patients continued to report a positive response on the GAIS, respectively.

When SSS scores of "satisfied" or "very satisfied" were pooled (ie, positive responders on the SSS), 10.4% of placebo patients had a positive response on day 2; by day 14, only 2.1% of placebo patients had a positive response (Figure 13). After day 2, less than 10% of placebo patients had a positive response on the SSS at any visit. In contrast, at day 2, 58.5% of prabotulinumtoxinA patients and 56.6% of onabotulinumtoxinA patients had a positive response on the SSS. By day 150 or the early termination visit, compared with 8.3% of placebo patients, 67.7% of prabotulinumtoxinA patients and 63.2% of onabotulinumtoxinA patients continued to have a positive response to their treatment as scored on the SSS.

Safety

A total of 211 patients (211/540, 39.1%) experienced a total of 344 AEs over the course of this 150-day study (Table 6). PrabotulinumtoxinA and onabotulinumtoxinA groups were similar in the percentages of patients who experienced one or more AEs (37.6% prabotulinumtoxinA, 41.9% onabotulinumtoxin A; incidence difference of −4.3%) and in the percentages who experienced the most common AEs (incidence differences of 3.7% for headache and −2.8% for nasopharyngitis); none of these differences were statistically significant (ie, in all cases, the 95% CI for that difference contained zero). PrabotulinumtoxinA and onabotulinumtoxinA groups were also similar in the

Table 3. Secondary Efficacy Endpoints: Number and Percentage of Responders Based on the Glabellar Line Scale at Maximum Frown (Intention-to-Treat Population)

Responders based on GLS at maximum frown	PRA (N = 245)	ONA (N = 246)	Placebo (N = 49)	Absolute difference	
				PRA vs placebo	PRA vs ONA
Score of 0 or 1 on day 30 by PA					
Number[a]	190/241	187/246	3/48		
Percentage, %	78.8	76.0	6.3	72.6	2.8
(95% CI)[c,d]	(73.7, 84.0)[c]	(70.7, 81.4)[c]	(0, 13.1)[c]	(60.8, 79.9)[d]	(−4.6, 10.2)[c]
P value				<0.001	
≥1-point improvement from day 0 to day 2 by IA					
Number[b]	130/240	139/244	6/49		
Percentage, %	54.2	57.0	12.2	41.9	−2.8
(95% CI)[c,d]	(47.9, 60.5)[c]	(50.8, 63.2)[c]	(3.1, 21.4)[c]	(28.7, 51.8)[d]	(−11.7, 6.1)[c]
P value				<0.001	
≥1-point improvement from day 0 to day 150/ET by IA					
Number[b]	90/239	84/244	4/48		
Percentage, %	37.7	34.4	8.3	29.3	3.2
(95% CI)[c,d]	(31.5, 43.8)[c]	(28.5, 40.4)[c]	(0.5, 16.2)[c]	(17.0, 38.2)[d]	(−5.3, 11.8)[c]
P value				<0.001	

The ITT population included all patients who were randomly assigned to treatment. CI, confidence interval; ET, early termination; GLS, Glabellar Line Scale; IA, investigator assessment; ITT, intention to treat; ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA; PA, patient assessment. [a]The denominator included all patients in the ITT population in each group who had data for this endpoint. [b]The denominator included all patients in the ITT population in each group who had data for this endpoint on both day 0 (baseline) and the specified postbaseline day, with baseline defined as the last nonmissing value collected at the time closest to, but prior to, randomization. [c]Within each of the placebo, onabotulinumtoxinA, and prabotulinumtoxinA treatment groups and for the comparison of prabotulinumtoxinA vs onabotulinumtoxinA, the CI was a two-sided 95% asymptotic CI. [d]For the comparison of prabotulinumtoxinA vs placebo, the CI was a 95% Exact CI for which the CI and the associated test were based on the inversion of 2 one-sided tests.

Table 4. Secondary Efficacy Endpoints: Number and Percentage of Responders Based on the SSS (ITT Population)

Responders based on SSS	PRA (N = 245)	ONA (N = 246)	Placebo (N = 49)	Absolute difference	
				PRA vs placebo	PRA vs ONA
≥1 point improvement from day 0 to day 30[a]					
Number[b]	219/240	213/246	3/48		
Percentage, %	91.3	86.6	6.3	85.0	4.7
(95% CI)[c,d]	(87.7, 94.8)[c]	(82.3, 90.8)[c]	(0, 13.1)[c]	(74.2, 91.1)[d]	(−0.9, 10.2)[c]
P value				<0.001	

The ITT population included all patients who were randomly assigned to treatment. CI, confidence interval; ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA; SSS, Subject Satisfaction Scale. [a]A SSS score of 1 (satisfied) or 2 (very satisfied) was considered a ≥1-point improvement in patient satisfaction. [b]The denominator included all patients in the ITT population in each group who had both day 0 (baseline) and day 30 data for this endpoint, with baseline defined as the last nonmissing value collected at the time closest to, but prior to, randomization. [c]Within each of the placebo, onabotulinumtoxinA, and prabotulinumtoxinA treatment groups and for the comparison of prabotulinumtoxinA vs onabotulinumtoxinA, the CI was a two-sided 95% asymptotic CI. [d]For the comparison of prabotulinumtoxinA vs placebo, the Exact CI and the associated test were based on the inversion of 2 one-sided tests.

Table 5. Secondary Efficacy Endpoints: Change from Baseline to Day 90 in Mean HADS-Anxiety and HADS-Depression Scores (ITT Population)

Change from baseline to day 90 in HADS scores	PRA (N = 245)	ONA (N = 246)	Placebo (N = 49)	Absolute difference	
				PRA vs placebo	PRA vs ONA
HADS-Anxiety					
N[a]	231	239	47		
Mean change ± SD	−1.1 ± 2.40	−0.9 ± 2.72	−0.9 ± 2.50	−0.2	−0.2
95% CI[b]	(−1.4, −0.8)	(−1.3, −0.6)	(−1.7, −0.2)	(−0.9, 0.6)	(−0.6, 0.3)
P value[c]	<0.001	<0.001	0.013		
HADS-Depression					
N[a]	231	239	47		
Mean change ± SD	−0.6 ± 2.19	−0.6 ± 2.15	−0.5 ± 1.98	−0.1	0.0
95% CI[b]	(−0.9, −0.3)	(−0.9, −0.3)	(−1.1, 0.0)	(−0.7, 0.6)	(−0.4, 0.4)
P value[c]	<0.001	<0.001	0.071		

The ITT population included all patients who were randomly assigned to treatment. HADS-Anxiety and HADS-Depression were scored by patient assessment only. CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ITT, intention to treat; ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA; SD, standard deviation. [a]Number of patients in each group in the ITT population who had a day 0 and day 90 assessment. [b]For prabotulinumtoxinA vs placebo and prabotulinumtoxinA vs onabotulinumtoxinA, the 95% CI for the mean was calculated based on two independent samples *t* test. [c]*P* value was based on paired *t* test.

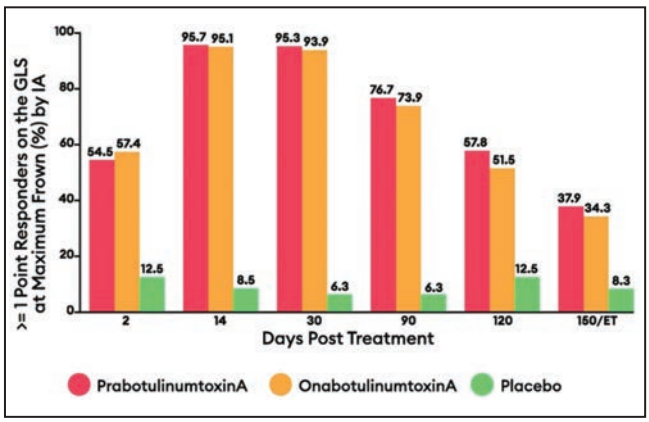

Figure 9. Percentage of responders based on a ≥1-point improvement on the Glabellar Line Scale (GLS) at maximum frown by investigator assessment (IA) by visit (Per Protocol population). ET, early termination.

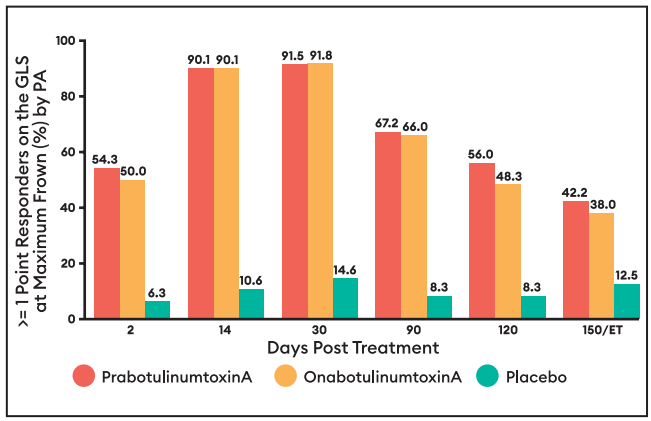

Figure 10. Percentage of responders based on a ≥1-point improvement on the Glabellar Line Scale (GLS) at maximum frown by patient assessment (PA) by visit (Per Protocol population). ET, early termination.

percentages of patients who experienced AEs assessed as possibly, probably, or definitely study drug related: 15.5% and 14.6%, respectively.

One onabotulinumtoxinA patient was withdrawn after 118 days due to surgery and hospitalization following a serious AE (cardiac valve fibroelastoma) assessed as unrelated to study drug. No other patient experienced an AE that led to study discontinuation. No deaths were reported. Three prabotulinumtoxinA patients (3/245, 1.2%), 1 onabotulinumtoxinA patient (1/246, 0.4%), and 1 placebo patient (1/49, 2.0%) experienced serious AEs. No serious event was assessed as study drug related. Among the 3 prabotulinumtoxinA patients with serious AEs, 1 experienced worsening of a conjunctival cyst, 1 experienced spasms and severe pain of the facial muscles, with onsets 151 days and 164 days after treatment, and 1 had a spontaneous abortion 114 days after treatment. Only one other pregnancy (in a prabotulinumtoxinA-treated patient) was reported during the course of this study; it ended with the delivery of a healthy baby approximately 6 months after

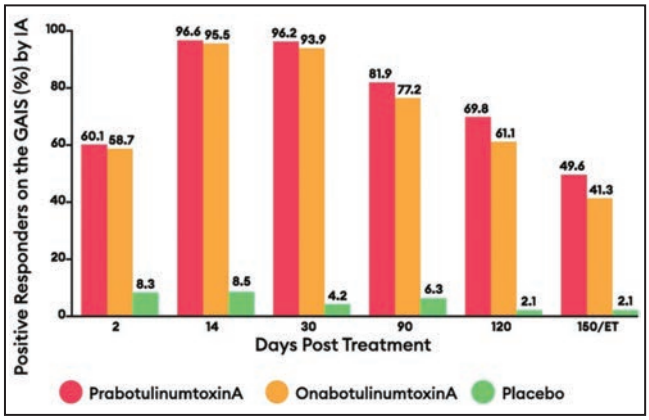

Figure 11. Percentage of patients with a positive response (improved/much improved) on the Global Aesthetic Improvement Scale (GAIS) by investigator assessment (IA) by visit (Per Protocol population). ET, early termination.

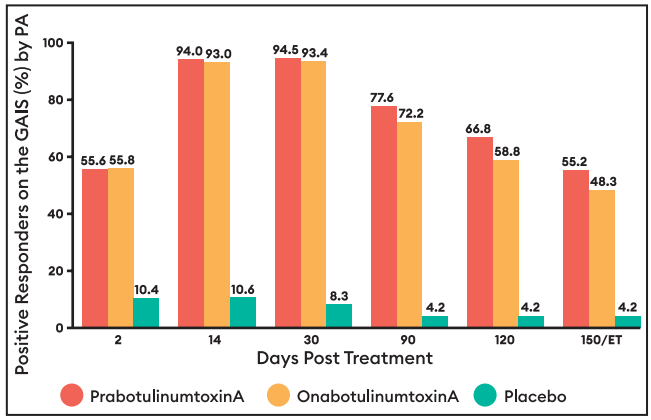

Figure 12. Percentage of patients with a positive response (improved/much improved) on the Global Aesthetic Improvement Scale (GAIS) by patient assessment (PA) by visit (Per Protocol population). ET, early termination.

study completion. The onabotulinumtoxinA patient experienced the cardiac valve fibroelastoma mentioned above and reported twice. The placebo patient experienced the serious AEs of breast cancer, a mastectomy, and breast reconstruction.

Few AEs were assessed as both of special interest and as study drug related; none were assessed as serious and all resolved. None were reported for placebo patients and the incidence among prabotulinumtoxinA and onabotulinumtoxinA patients was low. Five prabotulinumtoxinA patients (2.0%) experienced 5 study drug-related AESIs: 4 mild eyelid ptosis (1.6%; onsets at 10, 10, 10, and 18 days posttreatment with durations of 33, 33, 58, and 3 days, respectively), and 1 mild muscle twitching (0.4%; onset 4 days posttreatment with a duration of 4 days). In addition, 3 onabotulinumtoxinA patients (1.2%) experienced 3 study drug-related AESIs: 2 mild blepharospasm (0.8%; 1 with an onset the day of treatment and 1 with an onset 1 day posttreatment; both resolved on the days of onset) and 1 mild eyebrow ptosis (0.4%; onset at 2 days posttreatment with a duration of 27 days).

By preferred term, 9 types of AEs occurred in 1% or more prabotulinumtoxinA patients and 11 types of AEs occurred in 1% or more onabotulinumtoxinA patients (ie, in 3 or more patients in either group [Table 7]). Five types of events occurred in 1% or more of patients in both groups; these included headache, influenza, nasopharyngitis, oral herpes, and oropharyngeal pain. In addition, muscle tone disorder, sinusitis, eyelid ptosis, and procedural headache occurred at a frequency of ≥1% in the prabotulinumtoxinA group, and bronchitis, eyelid sensory disorder, pyrexia, cough, contusion, and hypertension occurred at a frequency of ≥1% in the onabotulinumtoxinA group. Only headache and nasopharyngitis (previously discussed) occurred at a frequency of greater than 2% in either group.

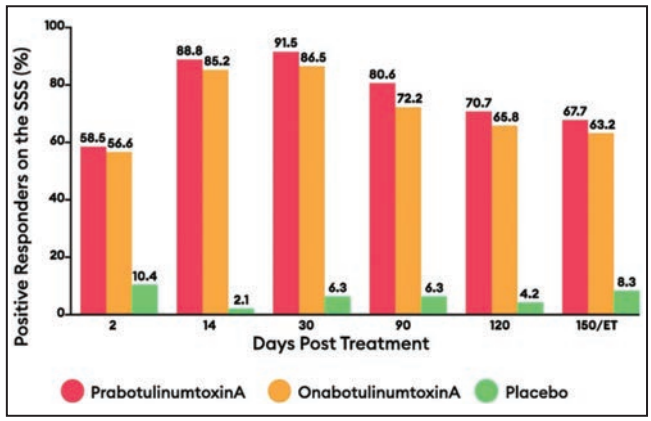

Figure 13. Percentage of patients with a positive response (satisfied/very satisfied) on the Subject Satisfaction Scale (SSS) by visit (Per Protocol population). ET, early termination.

Other than a higher percentage of patients in the placebo group with abnormal diastolic blood pressure measures, prabotulinumtoxinA, onabotulinumtoxinA, and placebo groups did not differ markedly from each other in the changes or shifts from baseline for any of the vital signs assessed at any of days 2, 14, 30, or at the day 150 or early termination visit. The 3 groups were also similar in their use of concomitant medications. None of the differences between groups in the utilization of concomitant medications or in the utilization of concomitant therapies were particularly noteworthy.

DISCUSSION

The primary analysis of the primary efficacy endpoint in this European and Canadian study population establishes the effectiveness of prabotulinumtoxinA, its superiority over placebo, and its noninferiority to onabotulinumtoxinA

Table 6. Summary of Adverse Events (Safety Population)

AE parameter	PRA (N = 245)			ONA (N = 246)			Placebo (N = 49)		
	n	(%)	Events	n	(%)	Events	n	(%)	Events
Any AEs	92	(37.6)	152	103	(41.9)	165	16	(32.7)	27
Incidence difference, % (95% CI)[a]	−4.3 (−13.3, 4.4)								
Any serious AE	3	(1.2)	6	1	(0.4)	2	1	(2.0)	3
Any study drug-related AE[b]	38	(15.5)	46	36	(14.6)	45	2	(4.1)	2
Any study drug-related AE of special interest[c]	5	(2.0)	5	3	(1.2)	3	0	(0.0)	0
Any AE leading to study discontinuation	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0
Any AE leading to death	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Any AE with frequency ≥5%	52	(21.2)	59	48	(19.5)	54	9	(18.4)	12
Nervous system disorder, headache[d]	34	(13.9)	38	25	(10.2)	26	7	(14.3)	10
Incidence difference, % (95% CI)[a]	3.7 (−5.2, 12.5)								
Infections and infestations, nasopharyngitis[d]	21	(8.6)	21	28	(11.4)	28	2	(4.1)	2
Incidence difference, % (95% CI)[a]	−2.8 (−11.7, 6.0)								

AEs regardless of relationship or seriousness were collected at all study visits from the time of study enrollment until the follow-up or early termination visit period, and could be reported in response to a query, observed by the investigator or site personnel, or reported spontaneously by the patient. AE, adverse effect; CI, confidence interval;; ONA, onabotulinumtoxinA; PRA, prabotulinumtoxinA. [a]Incidence difference between prabotulinumtoxinA and onabotulinumtoxinA groups with exact two-sided 95% CI. [b]Study drug-related AEs include all AEs assessed by the investigator as possibly, probably, or definitely study drug-related. [c]AEs of special interest were those 50 events potentially suggestive of distant spread of botulinum toxin effects, identified in the FDA's "Guidance for Industry. Upper Facial Lines: Developing Botulinum Toxin Drug Products." [d]System organ class and preferred term.

at day 30 for the PP population. For this endpoint, a patient was considered a responder only if they had a GLS assessment of 0 or 1 (ie, none or mild) at maximum frown on day 30 by investigator assessment. The absolute difference between prabotulinumtoxinA and placebo groups in the percentages of responders was 83.1% ($P < 0.001$). The absolute difference between prabotulinumtoxinA and onabotulinumtoxinA groups was 4.4% and the associated 95% CI was −1.9, 10.8. In this study, the conclusion of noninferiority was based on the fact that the lower bound of the 95% CI for the absolute difference between groups exceeded −10.0%. Given that the CI for the difference crosses zero, this suggests that there is no statistically significant difference between prabotulinumtoxinA and onabotulinumtoxinA. However, an absolute difference of 4.4% shows a numeric trend in favor of prabotulinumtoxinA. A similar difference in responder rates was evident when the GLS was scored by patient assessment (a secondary efficacy endpoint). Parallel observations were evident when patients scored their level of satisfaction on the SSS at day 30 (also a secondary efficacy endpoint).

These data collected for the primary efficacy endpoint in this study population were similar in magnitude and confirm preliminary results obtained in the earlier Korean study conducted with the original formulation of prabotulinumtoxinA.[1] In that study, employing a 4-point facial wrinkle severity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), the absolute difference between prabotulinumtoxinA and onabotulinumtoxinA in the percentages of patients with an assessment of 0 or 1 at maximum frown on day 30 by investigator assessment was 5.26 (93.89% vs 88.64%). The lower limit of the one-sided 97.5% CI was −1.53, which did not cross the lower limit of the noninferiority margin for that study (−15.0%). Importantly, this type of outcome of a GLS score of 0 or 1 at maximum frown on day 30 by investigator assessment is clinically meaningful.

Evidence of the early onset and effectiveness of prabotulinumtoxinA beyond day 30 was observed for secondary efficacy endpoints based on a ≥1-point improvement on the GLS at maximum frown by investigator assessment. Compared with 12.2% of placebo patients, 54.2% of prabotulinumtoxinA patients exhibited a ≥1-point improvement at day 2; compared with 8.3% of placebo patients, 37.7% of prabotulinumtoxinA patients exhibited a ≥1-point improvement at day 150 or the early termination visit. In both cases, the tests of superiority of prabotulinumtoxinA vs placebo were highly statistically significant ($P < 0.001$). Differences between prabotulinumtoxinA and placebo treatments at each of the day 2 and the end-of-study visits

Table 7. Summary of Adverse Events Occurring with a Frequency of ≥1% in Either the PrabotulinumtoxinA or OnabotulinumtoxinA Groups (Safety Population)

System organ class and preferred term	PRA (N = 245)		ONA (N = 246)		Placebo (N = 49)	
	n	(%)	n	(%)	n	(%)
Nervous system disorders						
Headache	34	(13.9)	25	(10.2)	7	(14.3)
Muscle tone disorder	3	(1.2)	1	(0.4)	0	(0.0)
Infections and infestations						
Bronchitis	1	(0.4)	3	(1.2)	0	(0.0)
Influenza	3	(1.2)	5	(2.0)	0	(0.0)
Nasopharyngitis	21	(8.6)	28	(11.4)	2	(4.1)
Oral herpes	3	(1.2)	4	(1.6)	0	(0.0)
Sinusitis	3	(1.2)	1	(0.4)	1	(2.0)
Eye disorders						
Eyelid ptosis	4	(1.6)	0	(0.0)	0	(0.0)
Eyelid sensory disorder[a]	0	(0.0)	4	(1.6)	0	(0.0)
General disorders and administration site conditions						
Pyrexia	1	(0.4)	3	(1.2)	0	(0.0)
Respiratory, thoracic, and mediastinal disorders						
Cough	1	(0.4)	3	(1.2)	0	(0.0)
Oropharyngeal pain	3	(1.2)	4	(1.6)	1	(2.0)
Injury, poisoning, and procedural complications						
Contusion	0	(0.0)	3	(1.2)	0	(0.0)
Procedural headache	3	(1.2)	2	(0.8)	0	(0.0)
Vascular disorders						
Hypertension	1	(0.4)	4	(1.6)	1	(2.0)

At each level of summarization, a patient was counted once if the patient reported one or more events. AEs were coded using MedDRA Version 17.0. AE, adverse event; ONA = onabotulinumtoxinA; PRA, prabotulinumtoxinA. [a]Sensation of heaviness; eyes feel more open.

were also seen for the exploratory endpoints based on the GAIS and SSS.

For those secondary endpoints intended to evaluate changes in psychological well-being, patients randomized to prabotulinumtoxinA experienced statistically significant mean changes from baseline to day 90: −1.1 on HADS-A and −0.6 on HADS-D. HADS is a validated scale that utilizes a self-administered questionnaire; it detects and distinguishes between anxiety and depression and measures the severity of the emotional disorder.[3,6] As part of the inclusion criteria for this study, patients needed to find that their glabellar lines had an important psychological impact. However, they did not need to have a clinical state of anxiety or depressive disorder to be enrolled. In fact, most baseline scores fell within the normal ranges of the HADS subscales: 74.6% for HADS-A and 93.3% for HADS-D. As such, it was expected that mean changes would be small. Importantly, the directional change in score indicated that patient ratings of their overall anxiety and depression had improved following treatment. The small number of placebo participants (n = 49, few of whom had scores outside the normal range at baseline) precludes meaningful comparisons between active and placebo groups for this secondary endpoint. At the same time, the authors acknowledge that there are also inherent limitations with analyses such as this one based

on a patient's change from baseline score (eg, potential regression to the mean).

The safety of a single treatment of 20 U of prabotulinumtoxinA, administered as 5 injections of 0.1 mL each, for the treatment of moderate to severe glabellar lines was established in comparison with placebo treatment and with a single treatment of 20 U of onabotulinumtoxinA, based on a broad range of safety outcomes. The overall incidences of AEs, and of the most common events (headache and nasopharyngitis), were not statistically significantly different between prabotulinumtoxinA and onabotulinumtoxinA groups. The incidence of AEs assessed as study drug related were also similar between active treatment groups. Both the overall incidence of AEs and of study drug-related AEs were somewhat more common among active treatment groups than among placebo patients. However, it may be that this observation was also in part a function of the 5:5:1 randomization scheme in which only 49 patients received treatment with placebo compared with 245 patients who received treatment with prabotulinumtoxinA and 246 who received treatment with onabotulinumtoxinA. No deaths were reported. No serious AEs were assessed as study drug related. Only 1 patient was withdrawn after 118 days as a result of a cardiac valve fibroelastoma assessed as unrelated to study drug. No other patient experienced an event that led to study discontinuation. Few AEs, 8 in total, were assessed as both of special interest and as study drug related. All were mild in severity; none were serious. The incidences of these events were 2.0% and 1.2% in the prabotulinumtoxinA and onabotulinumtoxinA groups, respectively; none were reported for placebo patients.

AEs, both related and unrelated to study drug, occurring in 1% or more patients were not dissimilar from those reported for other botulinum toxin products utilized for the same indication.[7-9] Mild eyelid ptosis, which was observed to occur at an incidence of 1.6% in prabotulinumtoxinA patients, was not dissimilar from the incidence rate of between 0.2% and 3% reported for placebo-controlled trials with other toxin products.[7-9]

One limitation of this study is that the relatively small number of patients in the placebo group may have impacted the ability to make meaningful comparisons between active and placebo groups for safety outcomes of less frequently reported AEs. Another limitation is the underrepresentation of males and of patients 65 years of age and older. Although most patients in the study were female (88.1%) and younger than 65 years (92.6%), this is reflective of the profile seen clinically. Finally, given the significant treatment effect of the botulinumtoxinA products tested, patients may have become unblinded as to whether they had been randomized to active or placebo treatment. This limitation, however, was not expected to compromise the study because those patients randomized to a toxin would have remained blinded to which active treatment they had received.

CONCLUSIONS

In this Phase III multicenter, randomized, double-blind, placebo- and active-controlled study, a single treatment of 20 U of prabotulinumtoxinA, administered as 5 injections of 4U/0.1 mL each, was safe and effective in adult patients for the treatment of moderate to severe glabellar lines. Furthermore, it was noninferior to 20 U of onabotulinumtoxinA.

Disclosures

Dr Avelar is a current employee of Evolus, Inc. and receives compensation in salary, stock, and stock options. Prior to and during the time of this study and manuscript preparation, Dr Gross was the Chief Scientific Officer at Evolus, Inc.; he will receive royalty and milestone payments should the product be approved. The remaining authors served as clinical trial investigators for this study. Of these, Drs Bodokh, Cartier, Delmar, Hilton, Inglefield, Sattler, Solish, Swift, and Trévidic have indicated no other conflicts of interest that have supported their work within the past 36 months. The remaining 10 investigators have disclosed potential conflicts as follows. Dr Rzany serves as an advisor and/or speaker for Almirall, Evolus, and Merz. Dr Ascher serves as an investigator for Symatese. Drs Bergdahl and Hedén hold stock in Strathspey Crown Holdings LLC (which has an indirect interest in Evolus, Inc.). Dr Bertucci has served as an investigator for Allergan, Galderma, Evolus, Merz, and Revance, as a speaker for Allergan, Galderma, Merz, and Revance, and as a consultant for Allergan, Croma, Galderma, Prollenium, Revance, and Teoxane. Dr Carruthers has received support from Alpheon, Allergan, Merz, Bonti, and Revance. Dr Denfeld has served as an investigator and speaker for Novartis Pharma GmbH, an investigator for Infecto Pharm Arzneimittel und Consilium GmbH, and as a consultant to AbbVie Deutschland GmbH and Stallergenes Greer GmbH. Dr Heckmann has received honoraria for scientific presentations on the use of botulinum toxin A, and has participated as an investigator in other clinical trials using botulinum toxin A. Dr Ogilvie has received honoraria from Evolus for advisory services. Dr Sebastien has received grants or support from Abbvie Novartis, Jannsen-Cilag, Elli Lilly, Leo Pharma, Galderma, UCB, Pfizer, Dermira, Dr. August Wolf Pharma, Merck Pharma, Almirall, Affibody, Menlo, Genentech, Regeneron, Sanofi-Synthelabo, Boehringer-Ingelheim, Dr. Reddys, and Accovion.

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