PrabotulinumtoxinA for Treatment of Millennials With Moderate to Severe Glabellar Lines: Post Hoc Analyses of the Phase III Clinical Study Data

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BACKGROUND The use of esthetic products by millennials is increasing, yet published clinical trial data in this population are limited.

OBJECTIVE To compare the efficacy and safety of prabotulinumtoxinA for the treatment of moderate to severe glabellar lines in millennial and nonmillennial patients.

METHODS AND MATERIALS: Post hoc analyses were performed on the pooled population of all patients treated with 20U prabotulinumtoxinA in the 3 single-dose Phase III glabellar line clinical studies. Patients were grouped by age: millennials (born 1982–2000) versus nonmillennials (born ≤1981). One key efficacy end point was the proportion of responders with a ≥1-point improvement from baseline at maximum frown on the 4-point Glabellar Line Scale. Adverse events were also summarized.

RESULTS Responder rates among millennials ($n = 65$) were greater than those of nonmillennials ($n = 668$) by 7.7% on average across all visits; differences were statistically significant at Day 90. Responder rates at Day 90 were 90.2% and 76.1%, respectively (absolute difference of 14.0%, $p = .01$). Headache was the most common treatment-related adverse event, occurring in 9.0% and 9.4% of millennials and nonmillennials, respectively.

CONCLUSION A single dose of 20U prabotulinumtoxinA administered for the treatment of glabellar lines was similarly well-tolerated by both millennials and nonmillennials; overall, it was more efficacious in millennials.

Although some regions of the world are dealing with an overaged population, in most developed countries such as the United States, millennials have become the largest generation in the labor force.[1] As defined by the US Census Bureau, millennials were born between 1982 and 2000.[2] Social studies have identified this generation as generally more socially liberal, aware and progressive, more racially diverse, less financially secure, and less religious compared with older demographic groups; they are also marrying later and having fewer children.[3,4] They are the first generation to be raised with access to the internet, social media, mobile devices, and 24/7 connectivity,[3,4] all of which have had a role to play in influencing their attitudes, lifestyle choices, and behaviors.[5] Of key importance to the field of esthetic medicine, millennials not only consider esthetic procedures to be acceptable but also consider them to be a part of normal life.[6] Despite having less disposable income, millennials were planning to outspend boomers 2 to 1 on self-care—an all-encompassing term that includes their mental and physical well-being and health.[5,7] Recent evidence indicates that esthetic treatments, particularly those that are minimally invasive and can be used preventatively, are increasingly popular among this cohort.[8–12] In 2019, the last year for which age-based data were available, 86.7% of all cosmetic procedures performed in the United States patients aged 30 to 39 years were minimally invasive.[9]

Globally, neurotoxin injections are the top minimally invasive esthetic procedure performed.[13] In 2019, 21.7% of worldwide botulinum toxin injection procedures were performed in patients aged 19 to 34 years; 46.1% were performed in patients aged 35 to 50 years.[13] In the same

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year in the United States, 19% of botulinum injection procedures were performed in patients aged 30 to 39 years, representing 56% of all minimally invasive procedures performed in this age group.[9] In summary, millennials are not only key drivers of change but they are also one of the largest patient cohorts for medical esthetics.[14] Although much has been published about this demographic in recent years in the media, clinical trial data for this population are limited.

The 900 kDa botulinum toxin type A, prabotulinumtoxinA (Jeuveau, Evolus, Inc. Newport Beach, CA), is the most recent neuromodulator approved for use in the United States for the treatment of glabellar lines. Three multicenter, 150-day, randomized, double-blind, controlled Phase III clinical studies were undertaken to establish the efficacy and safety of a single dose of 20U prabotulinumtoxinA for this indication.[15,16] Of these, 2 studies (EV-001 and EV-002) were conducted in the United States and a third (EVB-003) was conducted in the United Kingdom, Germany, France, Sweden, and Canada. Given the growing popularity of this type of esthetic treatment among millennials, post hoc analyses of pooled data from these pivotal studies were undertaken to better understand the efficacy and safety of prabotulinumtoxinA for the treatment of glabellar lines in this unique cohort.

Methods

Conduct of the Original Studies

All patients in the EV-001, EV-002, and EVB-003 studies were adults, at least 18 years, who had moderate to severe glabellar lines at maximum frown; patients in the EVB-003 study also had to have believed that their glabellar lines had an important psychological impact.[15,16] Those enrolled in the EV-001 and EV-002 studies had not received a botulinum toxin in any area of the body within the previous 6 months; those in the EVB-003 study had not received a botulinum toxin in the forehead within the previous 6 months. In total, 737 patients were treated with 20U prabotulinumtoxinA in these studies: 246 in each of EV-001 and EV-002 and 245 in EVB-003; patients in these studies were broadly similar in their baseline characteristics. At the time that participants were enrolled in these studies (between January and November 2015), millennial patients were between the ages of 21 and 33 years and nonmillennial patients were between the ages of 33 and 81 years (Table 1). Patients were followed for 150 days at each of Days 2, 7 (EV-001 and EV-002 only), 14, 30, 90, 120, and study end. Efficacy measures included glabellar lines at maximum frown on the 4-point Glabellar Line Scale (GLS, 0 = no lines, 1 = mild, 2 = moderate, and 3 = severe), esthetics on the 5-point Global Esthetic Improvement Scale (GAIS, 2 = much improved, 1 = improved, 0 = no change, −1 = worse, and −2 = much worse), and satisfaction on the 5-point Subject Satisfaction Scale (SSS, 2 = very satisfied, 1 = satisfied, 0 = indifferent, −1 = unsatisfied, and −2 = very unsatisfied). Key safety measures included investigator assessment of adverse events.

Statistical Methods of the Post hoc Analyses

Pooled data extracted from these single-dose glabellar line studies were summarized for millennials (born 1982–2000) and nonmillennials (born ≤1981) by numbers and percentages of prabotulinumtoxinA-treated patients. Safety data are reported for all 737 participants who were randomized and received treatment with prabotulinumtoxinA; efficacy data are presented for the subset of 733 participants for whom any postbaseline efficacy data were available. For efficacy end points, the Fisher exact test was used to compare the proportion of responders between groups. Two-sided exact 95% confidence intervals and associated p values were calculated for the absolute differences in the proportions of responders at each visit, based on inversion of 2 1-sided tests (in some instances, percent differences between groups may seem inconsistent at the first decimal place because of rounding). Key efficacy end points, based on the GLS at maximum frown by investigator assessment, included the percentage of responders with a ≥1-point improvement from baseline and those with a postbaseline score of 0 or 1 (none or mild). Other efficacy end points included the percentage of responders with a postbaseline score of improved or much improved on the GAIS and those with a postbaseline score of satisfied or very satisfied on the SSS. All treatment-related adverse events (all events assessed by the investigator as possibly, probably, or definitely treatment related) were summarized, including those of particular interest for this type of treatment and indication, that is, headache and ptosis.

Results

Patient Disposition and Demographics

Of the 737 prabotulinumtoxinA-treated patients who participated in the single-dose Phase III studies, 67 (9.1%) were born between the years of 1982 and 2000 and, accordingly, were identified as millennials and 670 (90.9%) were born before or during 1981 and, as such, were identified as nonmillennials (Table 1). The mean ages of the 2 groups were 28.2 and 52.4 years, respectively. Most patients were females who self-identified as White and had severe glabellar lines at maximum frown. Slightly fewer millennials (by an absolute difference of 4.1%) had severe glabellar lines at maximum frown (71.6% and 75.7% by investigator assessment, respectively). As might be expected of a millennial population, only 3.0% of the prabotulinumtoxinA-treated millennials who participated in these studies had severe glabellar lines at rest (i.e., 20.4% fewer than nonmillennials) and only 14.9% had moderate glabellar lines at rest (i.e., 25.7% fewer than nonmillennials). Of the 67 millennials who participated in these studies, 41 (61.2%) were from the Unites States, 16 (23.9%) were from Germany, 8 (11.9%) were from Canada, and 1 (1.5%) each were from France and Sweden.

Efficacy

Of the 737 prabotulinumtoxinA-treated patients, efficacy data were available for 733 (99.5%) including 65

TABLE 1. Baseline Demographic and Glabellar Line Characteristics		
Characteristic	**Millennials (*N* = 67)**	**Nonmillennials (*N* = 670)**
Age in yr, mean (range)	28.2 (21–33)	52.4 (33–81)
Female, *n* (%)	61 (91.0)	606 (90.5)
Male, *n* (%)	6 (9.0)	64 (9.6)
White, *n* (%)	57 (85.1)	528 (78.8)
Black/African American, *n* (%)	2 (3.0)	38 (5.7)
Asian, multiple or other, *n* (%)	8 (11.9)	104 (15.5)
Fitzpatrick skin types I + II + III, *n* (%)	50 (74.6)	511 (76.3)
Fitzpatrick skin types IV + V + VI, *n* (%)	17 (25.4)	159 (23.7)
GLS score at maximum frown, *n* (%) Moderate by investigator assessment Severe by investigator assessment	 19 (28.4) 48 (71.6)	 163 (24.3) 507 (75.7)
GLS score at rest, *n* (%) Moderate by investigator assessment Severe by investigator assessment	 10 (14.9) 2 (3.0)	 272 (40.6) 157 (23.4)

GLS, Glabellar line scale.

millennials and 668 nonmillennials. Representative photographs of a millennial patient's glabellar lines at maximum frown taken at baseline and at 2 days, 7 days, 30 days, 90 days, 120 days, and 150 days after treatment with 20U prabotulinumtoxinA are presented as supplemental digital content (see **Supplemental Digital Content 1**, Figures S1a-g, http://links.lww.com/DSS/B54).

Responders on the GLS

The percentages of responders who had a ≥1-point improvement on the GLS at maximum frown by investigator assessment were higher at all time points (by an absolute mean difference of 7.7% across all visits) for millennials compared with nonmillennials (see **Supplemental Digital Content 2**, Table S1, http://links.lww.com/DSS/B58; see **Supplemental Digital Content 3**, Figure S2, http://links.lww.com/DSS/B55). Differences, which were apparent from the first post-treatment evaluation day on Day 2 (absolute difference of 8.6%, $p = .226$), reached statistical significance at Day 90 (absolute difference of 14.0%, $p = .01$). At each of Days 7, 14, and 30, 100% of millennials achieved a ≥1-point improvement on the GLS at maximum frown by investigator assessment. By Day 90, 90.2% of millennials continued to experience this degree of improvement. Millennial response rates remained numerically greater through to the end of study on Day 150, with 41.0% of millennials and 37.4% of nonmillennials continuing to show a ≥1-point improvement on the GLS at maximum frown.

With the caveat noted above that 4.1% fewer millennials had severe glabellar lines at maximum frown at baseline, differences between millennials and nonmillennials were also pronounced for the percentages of responders who achieved a postbaseline score of 0 or 1 (none or mild) on the GLS at maximum frown by investigator assessment (Figure 1). Again, the percentages of responders were higher at all time points (by an absolute mean difference of 11.7% across all visits) for millennials compared with nonmillennials. In this case, differences, which were again apparent from the first post-treatment evaluation day on Day 2 (difference of 7.9%, $p = .250$), reached statistical significance at each of Day 7 (difference of 17.2%, $p = .011$), Day 14 (difference of 14.1%, $p < .001$), and Day 30 (difference of 14.6%, $p < .001$) (Figure 1).

Responders on the GAIS

Data for the percentages of responders based on the GAIS (those assessed as either improved or much improved) tended to parallel that of responders based on the GLS. That is, the percentages of responders on the GAIS by investigator assessment were higher at all time points (by an absolute mean difference of 6.5% across all visits) for millennials compared with nonmillennials (see **Supplemental Digital Content 4**, Figure S3, http://links.lww.com/DSS/B56). Between Days 7 and 120, 75.0% or more of millennials and 70.4% or more of nonmillennials were assessed by the investigator as responders on the GAIS. Similar trends were observed when esthetic improvement was assessed by the patients themselves (see **Supplemental Digital Content 5**, Figure S4, http://links.lww.com/DSS/B57).

Responders on the SSS

Patient satisfaction remained high throughout this study (Figure 2). At each of Day 7 through to end of study at Day 150, the percentage of responders based on the SSS (those

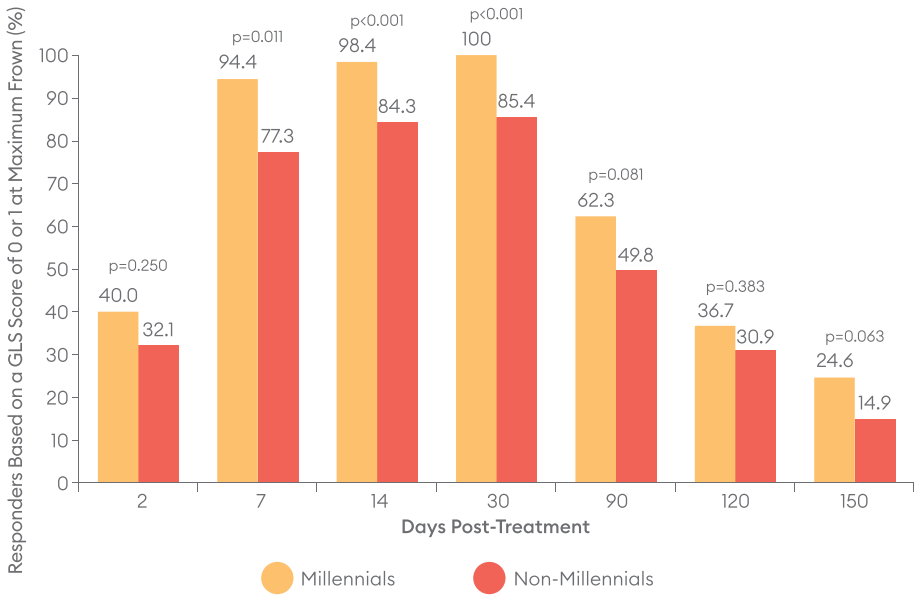

Figure 1. Percentage of responders based on achieving a score of 0 or 1 on the GLS at maximum frown by investigator assessment (N = 733). GLS = Glabellar line scale (0 = no lines, 1 = mild, 2 = moderate, and 3 = severe).

who rated their level of satisfaction as satisfied or very satisfied) was 78.7% or greater for millennials and 68.7% or greater for nonmillennials. In parallel with findings based on the GLS and GAIS, the percentages of responders based on the SSS were higher at all time points (by an absolute mean of 10.2%) for millennials compared with nonmillennials; in this case, differences were statistically significant at each of Days 7, 14, 30, and 120.

Safety

Safety data are reported for all 737 prabotulinumtoxinA-treated patients. The overall incidence of adverse events assessed by the investigator as treatment related was higher among millennials: 16.4% versus 13.3% in nonmillennials (see **Supplemental Digital Content 6**, Table S2, http://links.lww.com/DSS/B59). The most common treatment-related event was headache, which was reported in 9.0% and 9.4% of millennials and nonmillennials, respectively. Other treatment-related adverse events of particular interest were uncommon. Among millennials, 1 patient experienced treatment-related eyelid ptosis (1.5%). Among nonmillennials, 8 patients experienced eyelid ptosis (1.2%) and 2 experienced brow ptosis (0.3%).

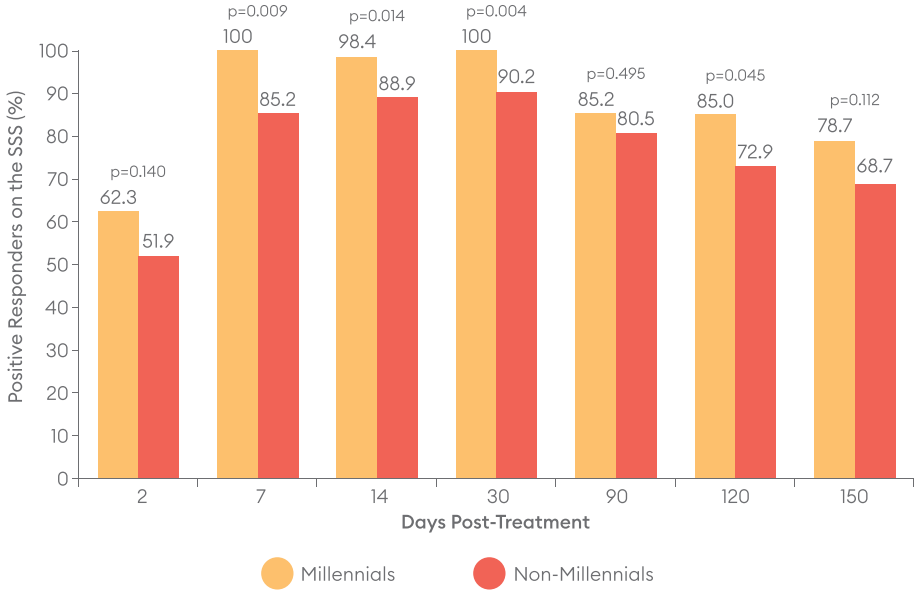

Figure 2. Percentage of positive responders (Satisfied + Very satisfied) on the SSS (N = 733). SSS = subject satisfaction scale (2 = very satisfied, 1 = satisfied, 0 = indifferent, −1 = unsatisfied, and −2 = very unsatisfied).

Discussion

Annual survey data collected from facial esthetic plastic surgeons and other specialists in this field indicate that, year over year, more and more millennials are investing in minimally invasive cosmetic treatments, most notably botulinum toxin injections.[8–10,13] Given the proliferation of new technologies, including the sharing of selfies on social media, the need for "head shots" on professional networking platforms, and the increased use of video conferencing, it is hardly surprising that millennials have become increasingly aware of their physical appearance, particularly that of the face. Not only have cosmetic procedures become normalized in this population, preventative strategies are becoming increasingly popular even among patients still in their teens and early 20s. New with this generation, when deciding on an esthetic treatment or product or even physician, millennials may choose to crowd source their research online rather than rely on a celebrity endorsement or trust in a brand's reputation.[5,12]

As evident from the results of our post hoc analyses, 20U prabotulinumtoxinA was a highly effective treatment for moderate to severe glabellar lines in the millennial population. With the obvious exceptions of age and the age-related factor of severity of glabellar lines at rest, millennials and older patients who participated in the single-dose Phase III studies were otherwise fairly similar in their baseline characteristics. Of particular interest, with incidence rates of 71.6% of millennials and 75.7% of nonmillennials, most participants had severe glabellar lines at maximum frown at baseline. Yet, despite these and other similarities at baseline, a greater percentage of millennials experienced a 1-point or greater improvement on the GLS at maximum frown at every postbaseline visit from the first post-treatment assessment day on Day 2 through to the end of study visit at Day 150 (by an overall mean of 7.7%), and a greater percentage achieved a postbaseline GLS score of none or mild (by an overall mean of 11.7%). At some visits, differences were not only substantive but also statistically significant. Similar outcomes were observed for all other efficacy outcomes assessed including those evaluated by the patients themselves. Importantly, satisfaction among millennials remained very high throughout this study, with 100% feeling satisfied with their treatment by Day 7 and 78.7% or more feeling satisfied throughout the remainder of this study.

Given the consistency observed across all efficacy measures assessed, it is probable that 20U prabotulinumtoxinA is not only more efficacious in a millennial population but it may also have a faster onset and longer duration of effect than it does in nonmillennial patients. It may be that, with fewer and less advanced age-related physiological changes, younger skin and the underlying musculature is more responsive to botulinum toxin treatments and that response is more easily maintained. Of interest, 2 recent prabotulinumtoxinA publications noted that, after 1 year of continuous use, there was an improvement in glabellar line severity at rest, implying that there may be a soft tissue remodeling benefit with prolonged use.[17,18] Further studies will be needed to see if, as they age, early millennial adopters such as those who participated in the prabotulinumtoxinA Phase III studies ultimately experience better long-term outcomes than their age-matched toxin-naive peers who delayed seeking treatment for their facial wrinkles.

Notably, in the current analyses, prabotulinumtoxinA was well tolerated by both millennials and nonmillennials and no new safety issues were detected. Over the 150 days of double-blind observation, the only treatment-related adverse event of particular interest that was reported in a millennial patient was eyelid ptosis; 1 millennial (1.5%) experienced this type of event. In comparison, the rate of eyelid ptosis among older patients was 1.2% (n = 8). Although older patients also experienced brow ptosis (n = 2, 0.3%), it may be that any differences between the 2 populations in the incidence of these rare events are more reflective of differences in the size of the 2 populations studied (67 millennials and 670 nonmillennials) than a true difference in incidence. By way of comparison, the overall incidence rates of eyelid and eyebrow ptosis associated with the treatment of glabellar lines across all botulinum toxin Type A formulations were summarized in a recent review of published clinical trial data as 0.14% and 2.32%, respectively.[19] An important caveat is that in general, nonregistration studies, such as Phase IV and Investigator Initiated Trials, under report adverse events compared with Phase II and Phase III registration studies. The incidence rates reported in this post hoc analysis were derived solely from Phase III glabellar line studies, which of necessity use the highest degree of rigor, including proactively soliciting patients for adverse events such as those involving the eye—an added level of vigilance that is generally not performed in nonregistration studies.

Limited data comparing outcomes in millennial patients have been published with other botulinum toxins. Of note, our findings are consistent with those from an earlier report of a post hoc analysis of pooled data from 2 placebo-controlled Phase III studies investigating the effectiveness of onabotulinumtoxinA (Botox Cosmetic; Allergan plc, Dublin, Ireland) in patients with moderate to severe forehead lines.[20] In those studies, patients in the active treatment arm received 20U for their forehead lines and 20U for their glabellar lines and, in 1 of the studies, patients also received 24U for their crow's feet lines. For the analysis of responders achieving a ≥1-point improvement on the 4-point Facial Wrinkle Scale at maximum eyebrow elevation, millennials had numerically higher responder rates than older patients at each visit from Day 30 through Day 180. Outcomes specific to glabellar lines were not reported in this publication nor did a PubMed literature search generate any other clinical trial data with botulinum toxins in the millennial population.

Given the limited number of millennial patients in any one of the prabotulinumtoxinA Phase III studies, it was necessary to pool prabotulinumtoxinA-treated patients across all 3 similar studies to obtain a millennial population of sufficient size to support these post hoc analyses. It would have been preferable if each study had been intentionally designed to enroll more patients in this demographic and

that this type of analysis had been planned a priori. Finally, it should be noted that while all patients in these studies were administered a single dose of 20U prabotulinumtoxinA to treat their glabellar lines and that this dose is in keeping with the approved dosing recommendations, it is not necessarily in keeping with current clinical practice. Based on a single-center retrospective analysis, it may be that millennial patients are more typically administered lower doses of toxin than older patients.[14] This observation is in keeping with recent consensus panel recommendations which indicate that, because the treatment of facial lines for millennials is often preventative in nature, younger patients tend to need lower doses and those doses can be administered less frequently.[21]

Conclusion

Millennials are becoming increasingly important consumers of esthetic services, yet limited data are available on clinical outcomes in this population. Based on post hoc analyses of pooled data from the 737 prabotulinumtoxinA-treated patients who participated in the 3 multicenter, randomized, double-blind, controlled, Phase III clinical studies, a single dose of 20U prabotulinumtoxinA was well-tolerated by millennials (21–33 years at the time of enrollment). Compared with nonmillennials (33–81 years), prabotulinumtoxinA was more efficacious by all measures assessed and at all time points assessed. With 80% or more rating themselves as satisfied or very satisfied, satisfaction of millennials with their treatment remained high throughout the 150 days of follow-up.

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