Safety and Efficacy of EB-001, a Novel Type E Botulinum Toxin, in Subjects with Glabellar Frown Lines: Results of a Phase 2, Randomized, Placebo-Controlled, Ascending-Dose Study

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Background: Botulinum neurotoxins, which are widely used commercially for therapeutic and cosmetic applications, have historically belonged to serotypes A and B. Serotype E has a distinct profile with a faster onset and shorter duration of effect. EB-001 is a proprietary formulation of serotype E in development for aesthetic (cosmetic) and therapeutic uses.

Methods: This first-in-human, randomized, double-blinded, placebo-controlled, ascending-dose cohort study enrolled 42 subjects who received EB-001 ($n = 35$) or placebo ($n = 7$). The efficacy primary outcome was the proportion of subjects with a two-grade investigator-rated improvement in glabellar frown line severity at maximum frown. Safety evaluations included adverse events, laboratory tests, and physical examinations.

Results: A two-grade investigator-rated response was observed starting in the third cohort (EB-001), with increased rates observed at higher doses. Onset of clinical effect was within 24 hours, with a duration ranging between 14 and 30 days for the highest doses. Adverse event incidence was low, with the most common being mild to moderate headache. There were no serious adverse events or ptosis, and there were no clinically significant changes in other safety assessments.

Conclusions: In this clinical study in glabellar frown lines, EB-001 showed favorable safety, tolerability, and dose-dependent efficacy, with an 80 percent response rate at the highest dose. The maximum clinical effect of EB-001 was seen within 24 hours and lasted between 14 and 30 days. This differentiated EB-001 profile supports its development for aesthetic and therapeutic applications where fast onset and short duration of effect are desirable. (*Plast. Reconstr. Surg.* 142: 847e, 2018.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Botulinum neurotoxins, which inhibit the presynaptic release of acetylcholine, are among the most potent molecules in nature. When injected into muscles, botulinum neurotoxins inhibit neuromuscular transmission and produce dose-dependent local muscle relaxation. Purified botulinum neurotoxins, including serotypes A and B, have been developed as injectable drugs and are widely used to treat a variety of neuromuscular conditions. Botulinum toxin type A products have also been successfully used to relax facial muscles and improve the appearance of wrinkles/facial lines, including glabellar frown lines. The botulinum toxin type A products approved for facial aesthetic use have similar

From Medical Associates; the Center for Dermatology Clinical Research, Inc.; and Bonti, Inc.
Received for publication November 22, 2017; accepted June 6, 2018.
This trial is registered under the name "Evaluate Safety and Efficacy of a Single Treatment Cycle of EB-001 in Subjects With Glabellar Frown Lines," ClinicalTrials.gov identification number NCT02939326 (https://clinicaltrials.gov/ct2/show/NCT02939326).
Presented at the American Society for Dermatologic Surgery Annual Meeting, in Chicago, Illinois, October 5 through 8, 2017.

DOI: 10.1097/PRS.0000000000005029

Disclosure: *D. Vitarella, W. Ahmad, F. Hasan, and S. Abushakra are employees of Bonti. Inc. The other authors have no financial interest to declare in relation to the content of this article.*

clinical profiles, with onset of clinical effect of approximately 7 days and a duration of approximately 3 to 4 months.[1]

Botulinum neurotoxin serotype E is a novel serotype that has not been developed for clinical use to date. Botulinum toxin type E shares the same molecular mechanism of action as type A but has the fastest onset and the shortest duration of action of all the botulinum neurotoxins. Type E has a domain structure similar to type A, consisting of two protein chains, a 100-kDa heavy chain and a 50-kDa light chain linked by a disulfide bond.[2] Type E inhibits neuromuscular transmission by cleaving the same presynaptic vesicular protein (synaptosomal-associated protein 25) as type A, but at a different cleavage site. Two binding sites on motor axons mediate the high-affinity recognition of nerve cells by botulinum neurotoxins. Binding is mediated first by cell surface gangliosides and then by specific protein receptors.[3–6] These receptors are found on motor axon terminals at the neuromuscular junction. Botulinum toxin types A and E have both been shown to bind the specific receptor synaptic vesicle protein 2, and only these two serotypes share this receptor.[3] This was the first clinical study to evaluate the safety and efficacy of ascending doses of botulinum toxin type E in subjects with glabellar frown lines.

PATIENTS AND METHODS

Design

This study was a first-in-human evaluation of the safety and efficacy of EB-001 and focused on the treatment of moderate to severe glabellar frown lines. EB-001 is a proprietary purified form of botulinum toxin type E, formulated as a liquid for injection (Bonti, Inc., Newport Beach, Calif.). This was a randomized, double-blinded, placebo-controlled, ascending-dose cohort study conducted at two expert clinical centers (Steve Yoelin, MD Medical Associates, Newport Beach, Calif.; Center for Dermatology Clinical Research, Fremont, Calif.). This study was approved by the Aspire Institutional Review Board (Santee, Calif.) and was conducted in accordance with the guidelines set forth by the Declaration of Helsinki. Written informed consent was received from all patients before their participation.

Subjects

A total of 42 healthy, toxin-naive male and female subjects, aged 18 to 60 years, were enrolled in the study. Each subject's participation was to last approximately 6 weeks. The main inclusion criteria were as follows: the presence of bilaterally symmetric glabellar frown lines of moderate to severe rating at maximum frown, sufficient visual acuity without the use of eyeglasses (contact lens use acceptable) to accurately assess their facial wrinkles, and the ability to conform with study requirements. The main criteria for exclusion were as follows: any uncontrolled systemic disease or other medical condition, any medical condition that may have put the subject at increased risk with exposure to botulinum neurotoxin (including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that interfered with neuromuscular function), current or prior botulinum neurotoxin treatment, known immunization or hypersensitivity to botulinum neurotoxin, prespecified dermatologic procedures within 3 to 12 months of the study (e.g., nonablative resurfacing, facial cosmetic procedures, topical/oral retinoid therapy), and prior periorbital surgery or treatment. Women were not enrolled if they were pregnant, lactating, or planning to become pregnant. Men with female partner(s) with childbearing potential were enrolled only if they agreed to use dual methods of contraception for 3 months after dosing.

At screening, subject demographics, medical history, and prior and concomitant medications were recorded and an alcohol/drug screen was performed. Standardized facial photography was performed at baseline before treatment, and at every follow-up visit through the end of the study, but the photographs were not used for efficacy evaluations.

Treatments and Procedures

Seven cohorts (six subjects per cohort) were enrolled and received ascending doses of EB-001 or placebo in a 5:1 ratio. The maximum recommended starting dose (with a 10-fold safety factor) in this first-in-human study was developed based on the levels at which no adverse effects were observed from a preclinical safety and toxicity study (unpublished data). From this, a base dose (cohort 1) was calculated and determined to be subefficacious, and cohorts 2 to 7 received 3, 9, 12, 16, 21, and 28 times the base dose, respectively. This represented subefficacious to maximum-efficacious doses of EB-001. The total dose was delivered at five injection sites in equal volumes (0.1 ml per site into the procerus, left and right medial corrugators, and left and right lateral

corrugators) in a standardized fashion. The injection paradigm was similar to that of approved botulinum toxin type A products.[7] The spacing of injections into the lateral corrugators was approximately 1 cm above the supraorbital ridge. EB-001 was supplied in a sterile solution for injection in a 5-ml vial. The placebo was supplied in identical vials without EB-001. Each subject completed visits at screening (days −30 to −1); at baseline/injection (day 0); at days 1, 2, 7, 14, and 30 (end of study); and at day 42 (final safety follow-up).

Safety Measures

Safety was evaluated by adverse events, laboratory testing, electrocardiograms, physical examinations, vital signs (pulse rate, respiratory rate, and blood pressure), urine pregnancy tests (for women with childbearing potential), and focused neurologic examinations to evaluate for the potential spread of botulinum neurotoxin. Treatment-emergent adverse events were defined as any adverse events that started or worsened in severity after exposure to study treatment. Adverse events and treatment-emergent adverse events were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (version 19.0). Serious adverse events (adverse events that fulfilled regulatory criteria for medical seriousness) and discontinuation because of adverse events were also evaluated. Severity of adverse events was recorded as mild, moderate, severe, or life threatening. Before enrollment of each dosing cohort, a safety data review committee met to analyze all safety data from the previous cohort(s).

Efficacy Measures

At screening; baseline; and days 1, 2, 7, 14, and 30, the subject's glabellar frown lines were assessed at maximum frown and at rest using the Facial Wrinkle Scale. Evaluations were completed by the investigator and the subject. The Facial Wrinkle Scale is a widely accepted measure used for the evaluation of facial line severity. In the present study, the four-point scale indicating severity of glabellar frown lines was as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Subjects were considered as treatment responders if they achieved at least a two-grade improvement (reduction) based on the investigator's Facial Wrinkle Scale assessment (two-grade investigator-rated).

The primary efficacy variable was the proportion of two-grade investigator-rated responders at maximum frown at any postbaseline visit through day 30. An additional efficacy endpoint of interest was the proportion of responders achieving an investigator-assessed Facial Wrinkle Scale grade of none or mild at days 1, 2, 7, 14, or 30 (analyzed by visit).

Statistical Analysis

Two analysis populations were prespecified: a safety population and an efficacy population. Subjects receiving placebo were pooled for all analyses.

The safety population included all subjects who received study treatment and had at least one safety assessment thereafter. All treatment-emergent adverse events and serious adverse events were summarized by treatment group. All safety parameters, including laboratory testing, electrocardiograms, physical examinations, vital signs, urine pregnancy tests, and focused neurologic examinations, were reviewed and evaluated for clinical significance by the investigators. The efficacy population was the modified intent-to-treat population, defined as all randomized subjects who received at least one dose of study treatment and had at least one postbaseline efficacy assessment.

Analyses of demographics and baseline characteristics were performed on the modified intent-to-treat population. Medical history was based on the safety population and coded using Medical Dictionary for Regulatory Activities and summarized by system organ class and preferred term. Prior and concomitant medications were based on the safety population and coded using the World Health Organization Anatomical Therapeutic Chemical classification index and summarized by drug class and treatment group.

Efficacy analyses were performed using the modified intent-to-treat population. Facial Wrinkle Scale grades were summarized by treatment and study day using frequency counts and rates of response (percent). An analysis comparing the proportion of two-grade investigator-rated responders in each EB-001 cohort versus placebo (pooled) was performed using Fisher's exact test with a 0.05 level of significance.

RESULTS

Demographic

Of the 59 subjects who were screened for the study, 43 were enrolled into one of seven cohorts. One subject did not receive treatment; consequently, 42 subjects were included in the modified intent-to-treat and safety populations (35 treated with EB-001 and seven treated with placebo). Forty-one subjects completed the study, with one subject lost to follow-up. The demographic and

baseline characteristics of the modified intent-to-treat population are displayed in Table 1. The mean (range) ages of subjects for the EB-001 (pooled) versus placebo (pooled) groups were 47.9 years (range, 22 to 60 years) and 50.4 years (range, 32 to 57 years), respectively. The majority of subjects were female (EB-001, 91.4 percent; placebo, 85.7 percent) and white (71.4 percent for both groups). The baseline mean ± SD investigator-assessed glabellar frown lines at maximum frown were 2.6 ± 0.50 and 2.9 ± 0.38 for the EB-001 and placebo groups, respectively. The EB-001 and placebo groups were well balanced, with no substantial between-group differences.

Efficacy

The proportions of subjects in the modified intent-to-treat population achieving a two-grade investigator-rated response for glabellar frown line severity at maximum frown at any postbaseline visit through day 30 are presented by dose cohort in Figure 1. In cohort 3, 40 percent of subjects were two-grade investigator-rated responders. This responder rate was the same or greater in all higher dose cohorts, with cohorts 6 and 7 having 80 percent two-grade investigator-rated responders. Cohorts 6 and 7 demonstrated significantly greater percentages of two-grade investigator-rated responders versus placebo ($p = 0.046$). Figure 2 summarizes the proportions of subjects in each cohort with investigator-assessed Facial Wrinkle Scale grades of none or mild glabellar frown lines at maximum frown, at any postbaseline visit through day 30. Cohorts 2 to 7 (inclusive) had greater percentages of responders versus placebo, with rates of 60 to 100 percent achieved for cohorts 3 and higher. The proportions of subjects achieving investigator-assessed Facial Wrinkle Scale grades of none or mild glabellar frown lines at maximum frown are further detailed by visit in Figure 3. In cohorts 3 to 7, most none or mild responses were observed at days 1, 2, and/or 7. One responder (20 percent) was observed at day 14 in cohorts 3, 5, 6, and 7 and at day 30 in cohorts 3 and 5. Figure 4 shows an example of a patient observed at rest at baseline and at days 1 (24 hours), 2, and 7 after injection. Figures 5 and 6 show an example of patients at maximum frown at baseline and at days 1 (24 hours), 2, and 7 after injection. Each of these patients showed an effect of EB-001 within 24 hours of dosing.

Safety

The safety results support the safety of all evaluated doses of EB-001, administered as intramuscular injections, in this population. No clinically significant changes from baseline in neurologic examinations, electrocardiograms, physical examinations, or laboratory tests were observed for any subject. A summary of treatment-emergent adverse events is presented in Table 2. Five subjects treated with EB-001 reported treatment-emergent adverse events, and none were reported in the placebo group. No serious adverse events were reported and no treatment-emergent adverse event led to discontinuation of the study. All treatment-emergent adverse events were mild or moderate in severity. The events of sore throat and flu-like symptoms were considered unrelated to treatment. Three subjects reported

Table 1. Demographic and Baseline Characteristics in the Modified Intent-to-Treat Population

Parameter	Placebo (Pooled) (%)	Cohort							EB-001* (Pooled) (%)
		1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	
No.	7	5	5	5	5	5	5	5	35
Age, yr									
Mean	50.4	52.0	39.4	52.2	50.8	45.4	53.2	42.6	47.9
Range	32–57	45–68	22–58	37–60	42–59	30–59	45–56	25–49	22–60
Sex									
Male	1 (14.3)	1 (20.0)	1 (20.0)	0	1 (20.0)	0	0	0	3 (8.6)
Female	6 (85.7)	4 (80.0)	4 (80.0)	5 (100.0)	4 (80.0)	5 (100.0)	5 (100.0)	5 (100.0)	32 (91.4)
Race									
Asian	2 (28.6)	2 (40.0)	0	1 (20.0)	0	2 (40.0)	0	0	5 (14.3)
Black	0	0	0	2 (40.0)	0	1 (20.0)	0	0	3 (8.6)
Native Hawaiian	0	0	0	0	0	0	1 (20.0)	0	1 (2.9)
White	5 (71.4)	3 (60.0)	4 (80.0)	2 (40.0)	5 (100.0)	2 (40.0)	4 (80.0)	5 (100.0)	25 (71.4)
Multiple	0	0	1 (20.0)	0	0	0	0	0	1 (2.9)
Mean baseline IR GL at maximum frown ± SD	2.9 ± 0.38	2.6 ± 0.55	2.6 ± 0.55	2.4 ± 0.55	2.6 ± 0.55	2.6 ± 0.55	2.4 ± 0.55	2.8 ± 0.45	2.6 ± 0.50

IR, investigator-rated; GL, glabellar frown lines.
*Proprietary (Bonti, Inc.) purified liquid formulation of botulinum neurotoxin serotype E.

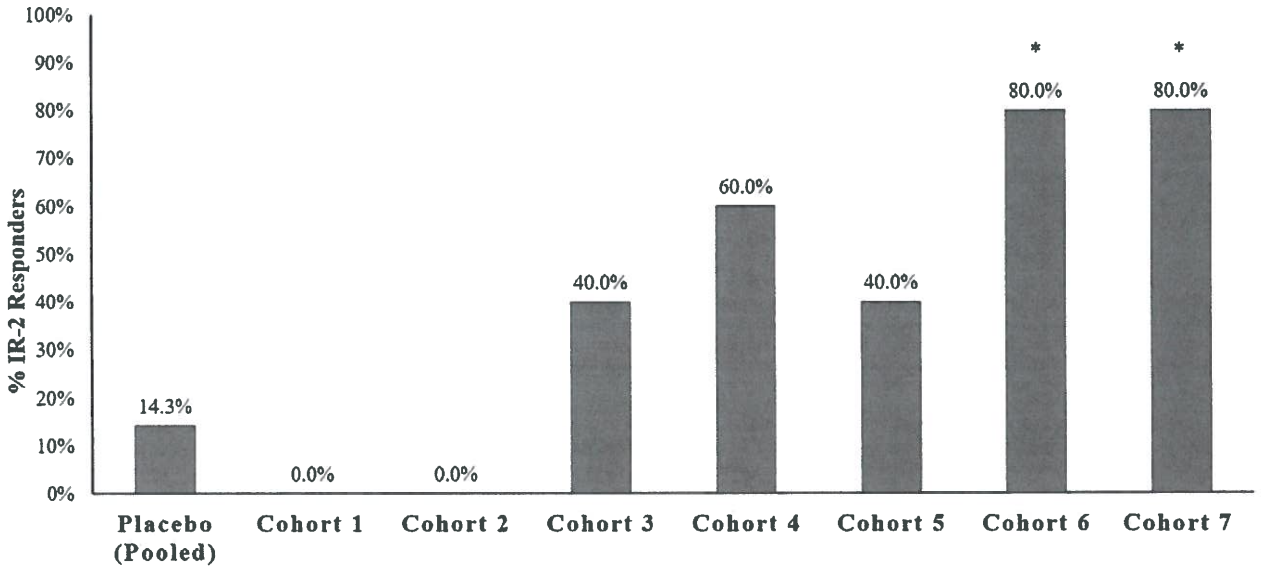

Fig. 1. Achievement of a two-grade investigator-rated response (improvement) using the Facial Wrinkle Scale at maximum frown for subjects receiving placebo or EB-001 (proprietary [Bonti, Inc.] purified liquid formulation of botulinum toxin type E) any time between days 0 and 30 in the modified intent-to-treat population. Note: $n = 5$ for each of the EB-001 cohorts and $n = 7$ for the pooled placebo cohort. *Statistical significance versus placebo ($p < 0.05$).

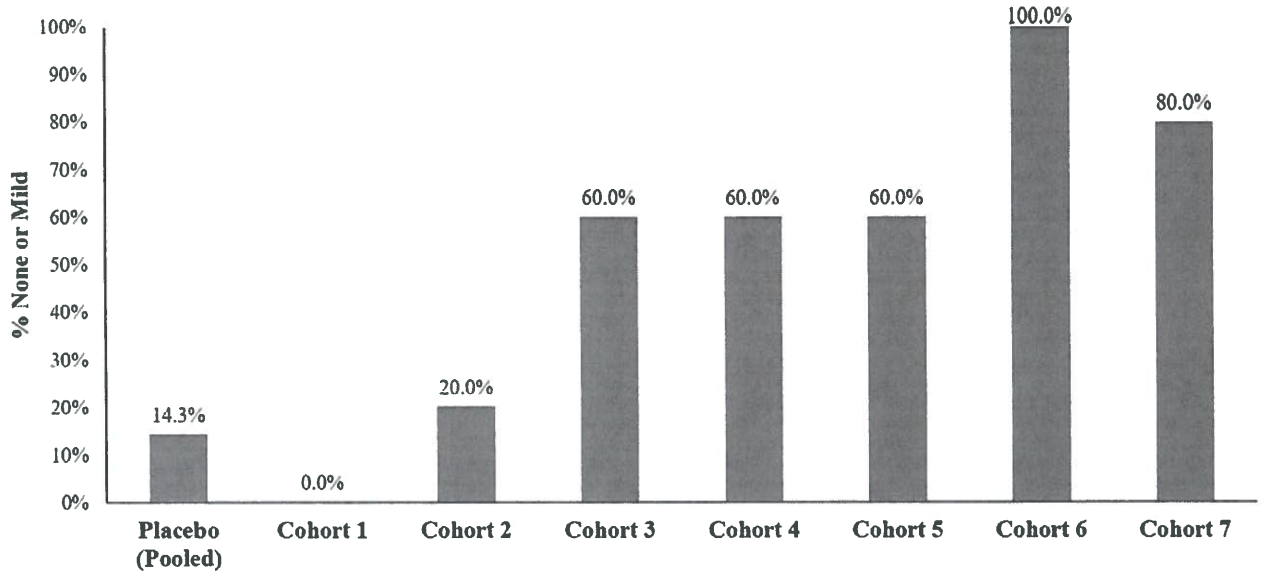

Fig. 2. Proportion of subjects achieving an investigator-rated none or mild grade using the Facial Wrinkle Scale at maximum frown for subjects receiving placebo or EB-001 (proprietary [Bonti, Inc.] purified liquid formulation of botulinum toxin type E) any time between days 0 and 30 in the modified intent-to-treat population. Note: $n = 5$ for each of the EB-001 cohorts and $n = 7$ for the pooled placebo cohort.

treatment-emergent adverse events of headache, one of which was considered related to treatment. There was no dose-related increase in the incidence of headaches. There were no events of ptosis or other treatment-emergent adverse event possibly related to spread of toxin.

DISCUSSION

To our knowledge, this is the first controlled clinical trial of a botulinum toxin type E product in any aesthetic or therapeutic use. This first-in-human study of EB-001, a novel purified form of botulinum toxin type E administered

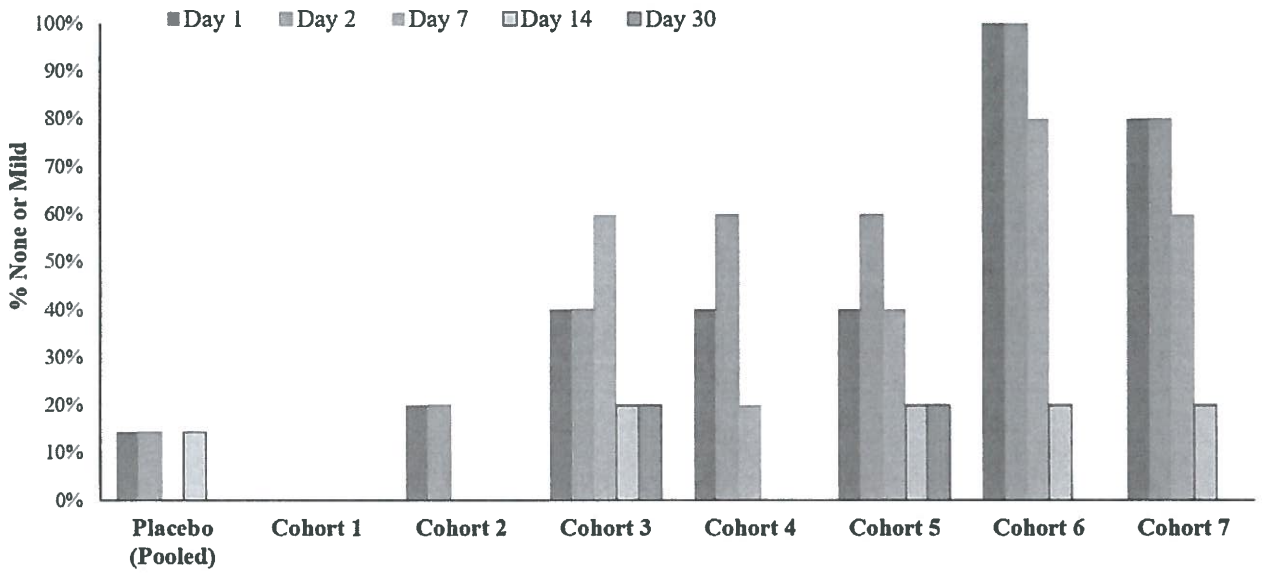

Fig. 3. Proportion of subjects achieving an investigator-rated none or mild grade using the Facial Wrinkle Scale at maximum frown by visit after treatment with placebo or EB-001 (proprietary [Bonti, Inc.] purified liquid formulation of botulinum toxin type E) in the modified intent-to-treat population. Note: $n = 5$ for each of the EB-001 cohorts and $n = 7$ for the pooled placebo cohort.

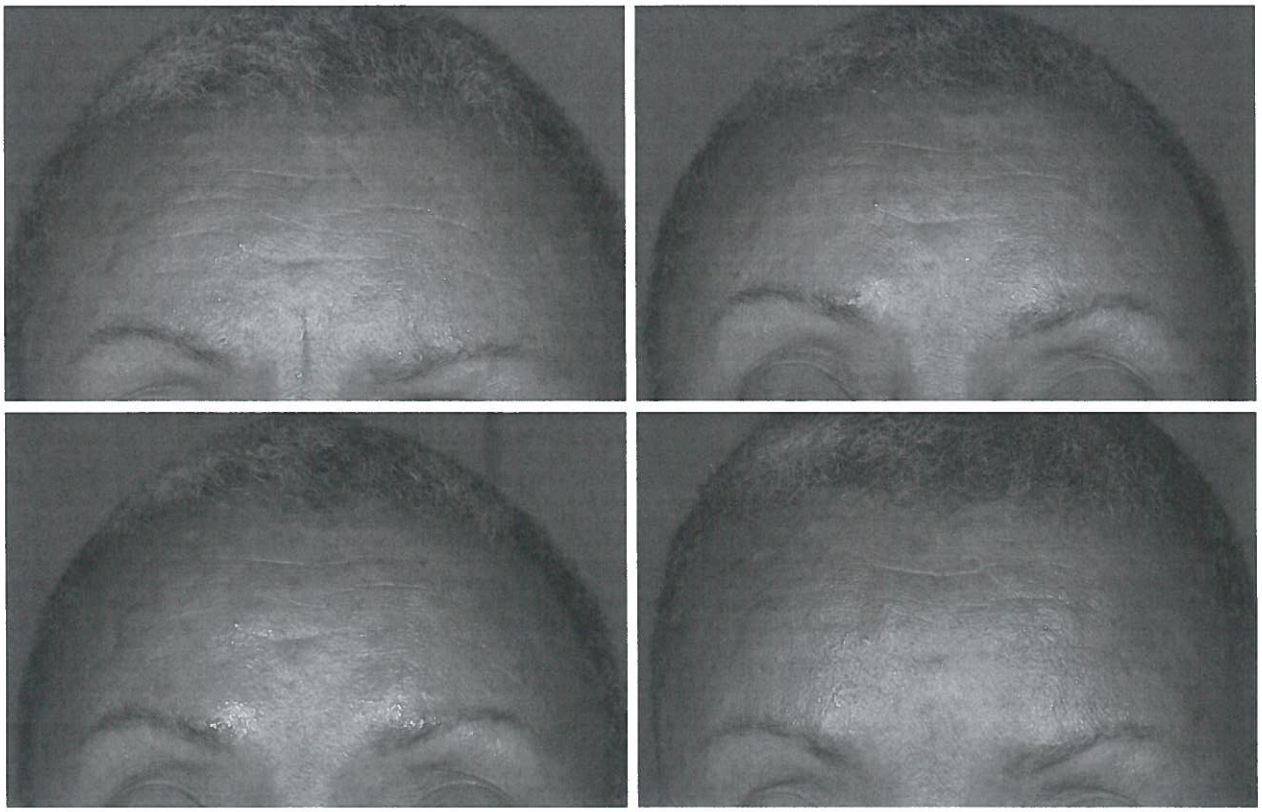

Fig. 4. Patient observed at rest. An effect was seen within 24 hours of injection (day 1). (*Above*, *left*) Baseline, (*above*, *right*) day 1, (*below*, *left*) day 2, and (*below*, *right*) day 7.

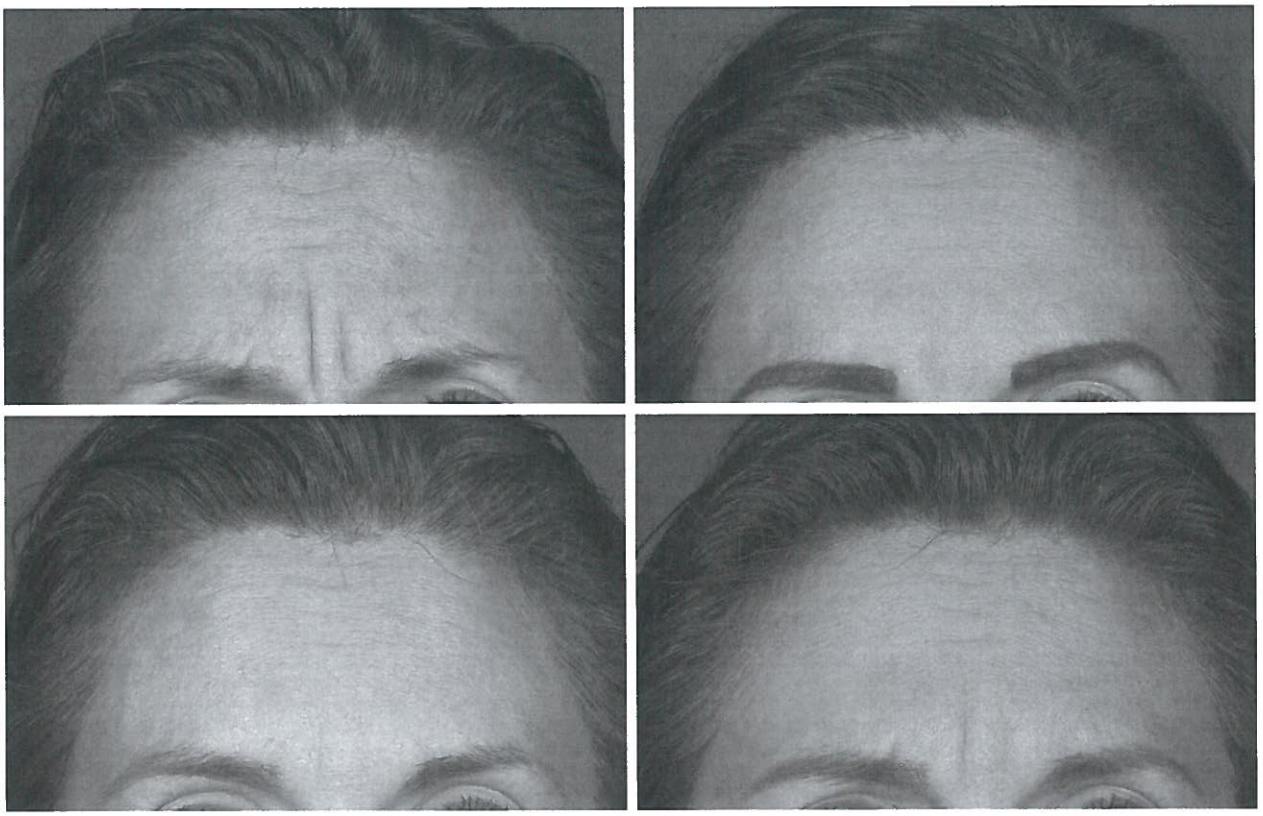

Fig. 5. Patient observed at maximum frown. A maximum effect was seen within 24 hours (day 1). (*Above, left*) Baseline, (*above, right*) day 1, (*below, left*) day 2, and (*below, right*) day 7.

Table 2. Summary of Treatment-Emergent Adverse Events in the Safety Population*

Adverse Event	Cohort							Placebo (%)
	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	
No.	5	5	5	5	5	5	5	7
Sore throat	1 (20.0)	0	0	0	0	0	0	0
Headache†	0	1 (20.0)	0	0	0	1 (20.0)	1 (20.0)	0
Flu-like symptoms	0	0	0	1 (20.0)	0	0	0	0
Eyelid ptosis	0	0	0	0	0	0	0	0
Abnormal ECG	0	0	0	0	0	0	0	0
Shortness of breath	0	0	0	0	0	0	0	0
Corneal ulceration, ectropion, and dry eye	0	0	0	0	0	0	0	0

ECG, electrocardiogram.
*Subjects are counted only once regardless of the number of adverse events they experienced during the study.
†Only one event of headache was assessed as treatment-related by the investigator.

intramuscularly, fulfilled its objectives of evaluating the safety, tolerability, and efficacious dose range of EB-001. A dose response was observed, with greater proportions of treatment responders in the higher dosing cohorts of EB-001. A two-grade investigator-rated response was observed starting with cohort 3 and increased in higher dose cohorts, suggesting that the efficacious dose range of EB-001 may be at doses used in cohorts 4 to 7. Cohorts 6 and 7 had 80 percent two-grade investigator-rated responders, a response rate similar to approved botulinum toxin type A products.[8–10] Subjects achieving none or mild Facial Wrinkle Scale grades were observed starting at cohort 2. In terms of onset of effect, treatment response was observed as early as 24 hours after dosing, which supports prior reports suggesting that botulinum toxin type E has a faster onset than type A.[11] Regarding the duration of effect (defined as the proportion of responders with a none or

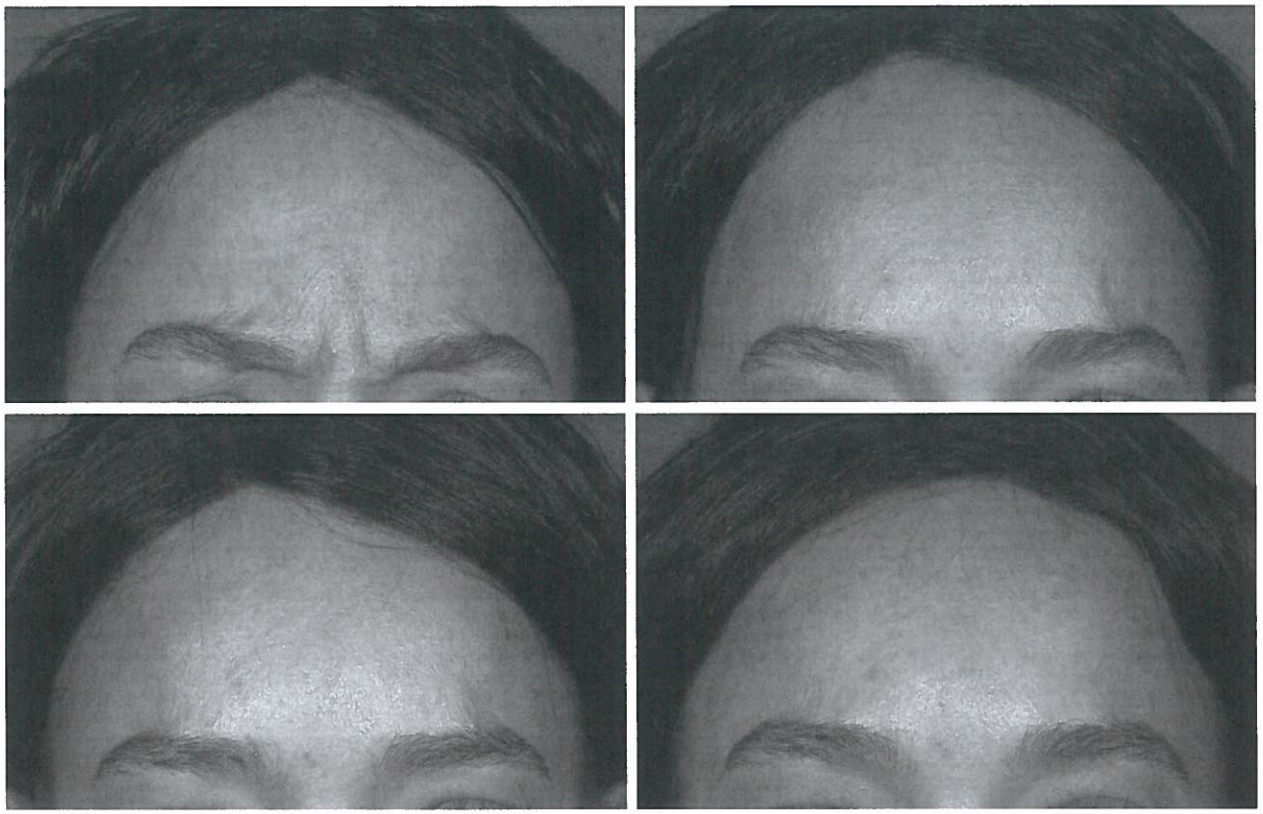

Fig. 6. Patient observed at maximum frown. A maximum effect seen within 24 hours (day 1). (*Above, left*) Baseline, (*above, right*) day 1, (*below, left*) day 2, and (*below, right*) day 7.

mild rating), an effect was observed through day 14 in one subject in most of the five higher dose cohorts, and through day 30 in one subject in two of the five higher dose cohorts.

All doses of EB-001 showed good tolerability, with no local injection-site reactions. There were no serious adverse events or severe treatment-emergent adverse events reported, and there were no discontinuations because of a treatment-emergent adverse event. The most common treatment-emergent adverse event of headache was mild or moderate in severity, and there were no other treatment-related adverse events. There were no events of ptosis at any dose levels, and there were no events potentially related to spread of toxin. Therefore, the clinical safety and tolerability profile seems favorable in this study.

A limitation of this study is the small number of subjects evaluated in each cohort. The small sample and ascending-cohort design was appropriate for a first-in-human study. Statistical testing demonstrated significantly greater two-grade investigator-rated responders for EB-001 in cohorts 6 and 7 versus placebo (pooled). These results provide valuable insight that informs dose selection and adequate powering of future larger parallel arm studies.

The efficacy and safety profiles of EB-001 are promising and support the potential of EB-001 as a unique treatment option in the treatment of glabellar frown lines and other facial aesthetic uses. The fast onset can fulfill an unmet need for individuals seeking a rapid treatment for facial wrinkles before unexpected social or professional events. The limited duration of effect can be beneficial for individuals who may be considering first-time use of a botulinum neurotoxin treatment and are unwilling to make a longer term commitment. An EB-001 treatment would allow them to assess the aesthetic effect over a shorter duration of effect compared with the 12-week duration of effect of botulinum toxin type A products.

CONCLUSIONS

In this first clinical study in subjects with glabellar frown lines, EB-001 showed favorable safety and tolerability in all cohorts. Five of the seven cohorts showed numerically higher response rates compared with placebo, supporting the efficacy of EB-001 in the reduction of glabellar frown line

severity. The two highest doses provided an 80 percent response rate, similar to approved botulinum toxin type A products. In contrast to the known time course of type A products, the clinical effect of EB-001 was seen within 24 hours (onset) and lasted between 14 and 30 days (duration). This differentiated clinical profile supports the future development of EB-001 for facial aesthetic and key therapeutic uses, where fast onset and short duration of effect are desirable.

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ACKNOWLEDGMENTS

The authors would like to acknowledge the advice and contributions of Alan Matarasso, M.D., Jean Carruthers, M.D., Lynn Chiu-Collins, M.D., and Cory Maas, M.D.

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