ORIGINAL ARTICLE

Efficacy and Safety of a Novel Botulinum Toxin Type A Product for the Treatment of Moderate to Severe Glabellar Lines: A Randomized, Double-Blind, Active-Controlled Multicenter Study

Chong H. Won, MD,* Hyung M. Lee, MD,* Woo S. Lee, MD,† Hoon Kang, MD,‡ Beom J. Kim, MD,§ Won S. Kim, MD,¶ Ju H. Lee, MD,** Dong H. Lee, MD,†† and Chang H. Huh, MD††

BACKGROUND A new botulinum toxin type A (NBoNT) produced from the same strain of *Clostridium botulinum* as onabotulinumtoxinA (OBoNT) is widely used in Asia.

OBJECTIVES To compare the efficacy and safety of NBoNT and OBoNT for moderate to severe glabellar wrinkles.

METHODS A double-blind, randomized, active-controlled, phase III study was performed. Three hundred fourteen patients were randomized at a 1:1 ratio to receive 20 U of toxin. The primary end point was the responder rate according to investigator live assessment at maximum frown at week 4. Secondary end points were responder rates according to investigator live assessment with frowning and at rest at weeks 8, 12, and 16, with additional photographic assessment by a panel of blinded raters 4 weeks after injection. Subjective satisfaction scores were also evaluated.

RESULTS Four weeks after treatment, responder rates for maximum frown were 93.7% (133/142) in the NBoNT group and 94.5% (138/146) in the OBoNT group. For secondary end points, there was no significant difference between the two groups for any variable at any time point. Noninferiority of NBoNT was confirmed. There were no serious adverse effects with either toxin.

CONCLUSION NBoNT is equally as effective as OBoNT for the treatment of glabellar frown lines. Both toxins were well tolerated.

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The cosmetic use of botulinum toxin type A (BTX-A) for the treatment of dynamic facial wrinkles has increased dramatically over the past 2 decades, particularly in the upper face.[1–3] Five botulinum toxin type A (onabotulinumtoxinA (OBoNT), Botox, Allergan Inc., Irvine, CA; abobotulinumtoxinA (ABoNT), Dysport, Ipsen Inc./Medicis Inc., Basking Ridge, NJ; Xeomin, Merz Pharmaceuticals, Frankfurt am Main, Germany; Neuronox (NBoNT), Medytox Inc., Ochang, Korea; BTXA, Lanzhou Biological Product Institute, Hong Kong, China) and one botulinum toxin type B (Myobloc, Solstice, Louisville, KY) preparation are being marketed worldwide, with several others being developed.[4,5] There has been controversy regarding interchangeability between OBoNT and ABoNT, the prototypical BTX-A products, because they have different characteristics.[6,7]

**Department of Dermatology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea; †The CNP Skin Clinic, Gyeonggi, Korea; ‡Department of Dermatology, College of Medicine, Catholic University of Korea, Seoul, Korea; §Department of Dermatology, College of Medicine, Chung-Ang University, Seoul, Korea; ¶Department of Dermatology, Kangbuk Samsung Hospital, School of Medicine, Sungkyunkwan University, Seoul, Korea; **Department of Dermatology, College of Medicine, Yonsei University, Seoul, Korea; ††Department of Dermatology, Seoul National University Bundang Hospital, Gyeonggi, Korea*

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NBoNT (Neuronox Botulift/Siax/Meditoxin; Medytox Inc.) is a novel product that is produced from the same strain of *Clostridium botulinum* as OBoNT. Both are composed of 100 U of botulinum toxin, 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride, which allows physicians to use both products in a similar manner. NBoNT was first approved in Korea for blepharospasm in 2006 and has since been approved in 22 countries and become popular in Asia. The noninferiority of NBoNT to OBoNT at a 1:1 dose ratio has been proven in phase III clinical studies for essential blepharospasm and focal spasticity in cerebral palsy.[8,9]

We sought to demonstrate the noninferiority of NBoNT to OBoNT at a 1:1 dose ratio for the treatment of moderate to severe glabellar lines.

Methods

This was a prospective, multicenter, randomized, double-blind, parallel, active-controlled, local phase III clinical trial of the efficacy and safety of NBoNT performed in six centers in South Korea. We adhered to the guidelines of 1975 Declaration of Helsinki, and the Institutional Review Board and Ethnics Committee of each center approved the study (http://www.clinicaltrials.gov number NCT01237977). Informed consent was obtained from each patient before all procedures.

Subjects

Eligible subjects were men and women aged 20 to 65 with moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the Facial Wrinkle Scale (FWS), Table 1). Exclusion criteria included any medical condition (e.g.,

TABLE 1. Clinical Outcome Measures: Rating Scales and Definitions

Measure	*Scale*	*Definition*
Facial Wrinkle Scale, maximal frown	3	Severe; lines appear clearly formed. The bottoms of the deepest lines are not visible from the surface
	2	Moderate; lines appear clearly formed. The bottoms of the deepest lines are visible from the surface
	1	Mild; lines noted
	0	None; lines not noted
Facial Wrinkle Scale, rest	3	Severe; lines readily apparent
	2	Moderate; lines noticeable
	1	Mild; lines somewhat noticeable
	0	None; lines not noticeable
Subject improvement assessment	+4	Complete improvement (~100% improvement)
	+3	Marked improvement (~ 75% improvement)
	+2	Moderate improvement (~50% improvement)
	+1	Slight improvement (some improvement, 25% improvement)
	0	Unchanged
	−1	Slight worsening (~25% worse)
	−2	Moderate worsening (~50% worse)
	−3	Marked worsening (~75% worse)
	−4	Very marked worsening (~100% worse)
Subject satisfaction	7	Very satisfied
	6	Satisfied
	5	Somewhat satisfied
	4	Indifferent
	3	Somewhat dissatisfied
	2	Dissatisfied
	1	Very dissatisfied

myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis) that might have put the patient at risk with botulinum toxin, prior use of medications that might affect the neuromuscular junction (e.g., muscle relaxants, spectinomycin hydrochloric acid, aminoglycosides, polypeptide antibiotics, anticholinergics, benzodiazepines), any allergies or hypersensitivity to the investigational drugs or their components, previous treatment with botulinum toxin within 3 months, other procedures that might affect glabellar and forehead lines within 6 months, or any history of glabellar treatment (including forehead) such as a face lift and/or permanent implants or scars that might affect the treatment results. Patients whose glabellar lines could not be satisfactorily improved with manual pressure were also excluded. Patients were not eligible if they had dermatologic disorders or infection at potential injection sites or a history of facial nerve paralysis or ptosis. Pregnant or lactating women were excluded

Study Procedures and Treatment

After confirmation of eligibility, patients were randomized into two groups at a 1:1 ratio and treated at visit 1 (week 0, baseline). Each patient received a total dose of 20 U (4 U/0.1 mL) of NBoNT or OBoNT in a double-blind manner. The 0.5-mL total injection volume was divided into five injections: 0.1 mL (4 U) in the procerus, 0.1 mL (4 U) in each medial corrugator, and 0.1 mL (4 U) in the middle of each corrugator (Figure 1).

During the 16-week observation period, patients were assessed every 4 weeks. At each visit, the investigator and the patient assessed efficacy and safety, and standardized digital photographs of the treated facial area were taken using the same setting and equipment (EOS-350D; Canon Inc., Tokyo, Japan) to ensure reproducibility. Three blinded raters assessed the photographs according to the FWS.

Efficacy Measures

Physicians assessed the glabellar line severity using the FWS. Subjects assessed the change in line severity on a 9-point scale and rated their degree of satisfaction with the treatment on a 7-point scale (Table 1). The primary end point was the responder rate at maximum frown at week 4 based on investigator live assessment (face-to-face observation). Secondary end points were responder rate at maximum frown at weeks 8, 12, and 16; responder rate of glabellar lines at rest based on investigator live assessment at weeks 4, 8, 12, and 16; and responder rate at maximum frown and at rest based on photographic assessment at week 4. In accordance with previous studies of OBoNT, responders were defined as having a post-treatment score of 0 or 1 and a pretreatment score of 2 or 3.[10,13–15] This means an improvement of at least 1 point in patients with moderate wrinkles and at least 2 points in those with severe wrinkles. In addition, we included the glabellar line improvement rates determined according to subjects' own

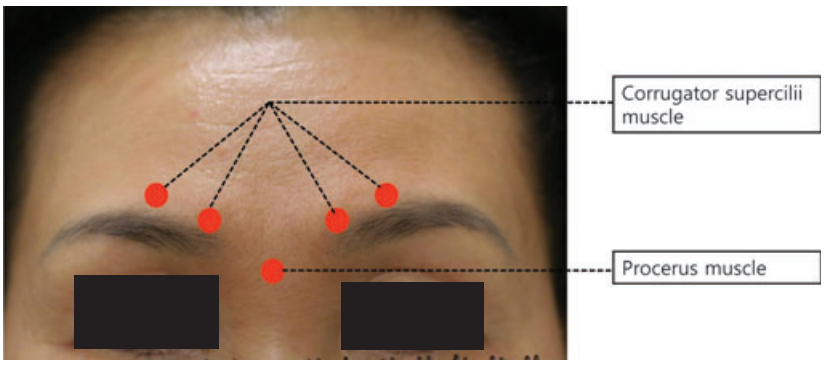

Figure 1. Treatment injection sites.

assessment and satisfaction rates as secondary end points. Scores more than 2 points higher (moderately improved) were considered to be improvement, and scores more than 6 points higher (satisfied) were considered to be satisfaction.

Safety Measures

Adverse events (AEs) were documented based on investigator- and subject-reported signs and symptoms, physical examination, and laboratory tests. BTX-A antibody testing was performed in 100 subjects in two of six study centers (Asan Medical Center and Seoul National University Bundang Hospital) at weeks 0 (visit 1) and 16 (visit 5) using a mouse bioassay.

Statistical Methods

All randomized and treated subjects with data for primary end points were included in the full analysis set (FAS). The per protocol (PP) set was the subset of patients of the FAS that did not commit any major protocol violations.

For the primary end-point parameter, we calculated the lower limit of the 97.5% one-sided confidential interval (CI) for the difference in responder rates between two groups. The interpretation of the CI was based on the null hypothesis that the expected difference in responder rates between the treatment groups was lower than the noninferiority margin of −15%. If the lower bound of the estimated CI exceeded the limit of −15%, one could conclude that the NBoNT was not inferior to OBoNT. This confirmatory analysis was based on the PP analysis. For secondary end points, paired *t*-tests, Pearson chi-square tests, or Fisher exact tests were performed. Safety analysis was based on a safety evaluation set that included all patients who received a study drug.

Results

Two hundred ninety-one of 314 patients enrolled completed the study without major deviation and therefore constituted the PP set: 142 in the NBoNT group and 146 in the OBoNT group (Figure 2). Demographic characteristics of the two

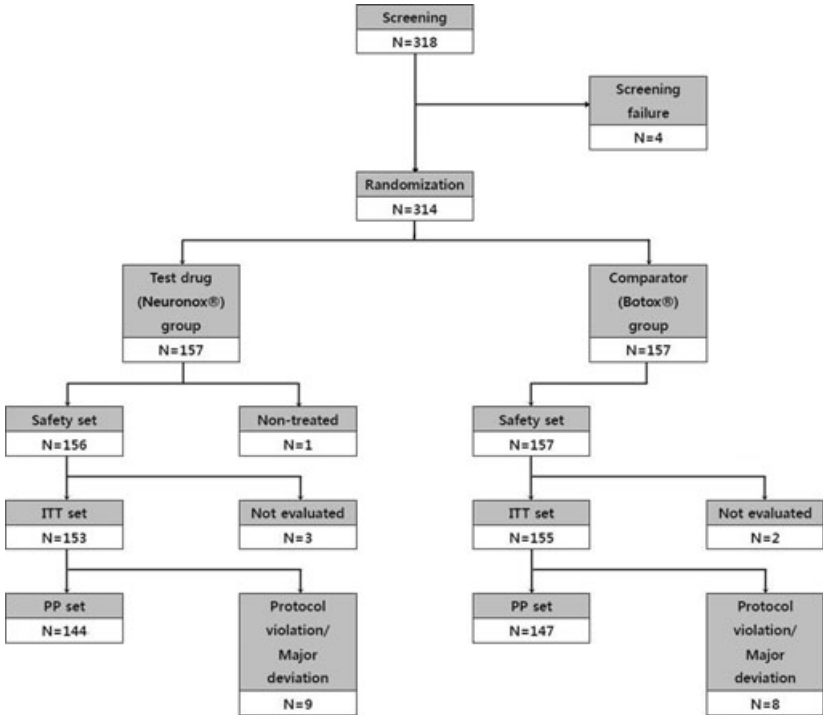

Figure 2. Disposition of patients.

groups were comparable, and the groups did not differ in their pretreatment line severity at rest or maximum frown. The majority of patients had moderate to severe glabellar frown lines at rest (54.9% NBoNT group, 56.1% OBoNT group) and severe glabellar frown lines at maximum frown (53.5% NBoNT group; 54.8% OBoNT group) (Table 2).

Investigator Assessment

Both groups had significant improvement of glabellar lines (Figure 3). Four weeks after injection, the responder rate at maximum frown for the PP set was 93.7% (133/142) in the NBoNT group and 94.5% (138/146) in the OBoNT group. In addition, the responder rate of the FAS (94.1%) was similar to that of the PP set (94.8%). The 95% CIs for the difference in responder rates between the two treatment groups (−6.3 to 4.6% for PP; −5.8 to 4.4% for FAS) clearly supported the hypothesis that NBoNT was not inferior to OBoNT, because the lower limit of the 97.5% one-sided CI (−6.3 for PP; −5.8 for FAS) exceeded the predefined noninferiority margin of −15%. There was no statistically significant difference between responder rates of the two groups at week 4 in the PP set or the FAS (p = .77). Responder rates remained high in both groups at weeks 8 and 12 (85.1% and 75.0% NBoNT group, 86.9% and 70.8% OBoNT group) and decreased to 46.0% for the NBoNT group and 48.3% for the OBoNT group at week 16. There was no statistically significant difference in the responder rate between the groups at any time point (p = .42) (Figure 4A).

TABLE 2. Patient Demographic and Baseline Characteristics (Per Protocol Set)

Characteristic	*New Botulinum Toxin Type A*	*Onabotuli-numtoxinA*
Demographic	n = 157	n = 157
Age		
Mean ± standard deviation, median (range)	48 ± 8.8, 49 (25–64)	47 ± 8.8, 48 (27–64)
<50, n (%)	79 (50.3)	85 (54.1)
≥50, n (%)	78 (49.7)	72 (45.9)
Sex, n (%)		
Male	22 (14.0)	33 (21.0)
Female	135 (86.0)	124 (79.0)
Previous botulinum toxin exposure, n (%)		
Naïve	146 (93.0)	142 (90.4)
Not naïve	11 (7.0)	15 (9.6)
Baseline	n = 142	n = 146
Facial Wrinkle Scale score, n (%)*		
At rest		
None	8 (5.5)	16 (10.9)
Mild	58 (40.3)	48 (32.6)
Moderate	38 (26.4)	46 (31.3)
Severe	40 (27.8)	37 (25.2)
At maximum frown		
None	0 (0.0)	0 (0.0)
Mild	0 (0.0)	0 (0.0)
Moderate	66 (47.5)	66 (45.2)
Severe	76 (53.5)	80 (54.8)

*Glabellar frown lines according to investigator live assessment (per protocol set).

The responder rates at rest based on investigator live assessment were lower than those at maximum frown at all time points, with no intergroup differences (41.6%, 44.0%, 42.9%, and 40.3% for the NBoNT group; 45.2%, 45.5%, 43.8%, and 38.6% for the OBoNT group at weeks 4, 8, 12, and 16, respectively, p = .53). Because of the larger proportion of subjects with baseline resting scores of 0 or 1, a subgroup analysis of subjects with baseline scores of 2 or 3 was performed. This comprised 78 subjects in the NBoNT group and 82 in the OBoNT group. In this analysis, responder rates were lower than those at maximum frown at weeks 4 and 8 but higher at weeks 12 and 16 (Figure 4B).

In the blinded rater photographic assessment, similar results were observed for both groups (Table 3). Responder rates at maximum frown were higher than in a resting state, and there was no significant difference between two groups (p = .39). The investigators observed higher responder rates during direct encounters than during indirect photographic assessment for both treatment groups at rest and at maximum frown (Figure 4, Table 3).

Figure 3. Representative clinical photographs showing patients at maximum frown: (A) patient treated with new botulinum toxin type A, (B) patient treated with onabotulinumtoxinA. Standardized photographs of two patients at maximal frown, at baseline (left) and 4 (center) and 16 (right) weeks after treatment. The dramatic lessening of glabellar lines for all patients at week 4 should be noted. By week 16, the glabellar lines have begun to reappear but are still less severe than at baseline.

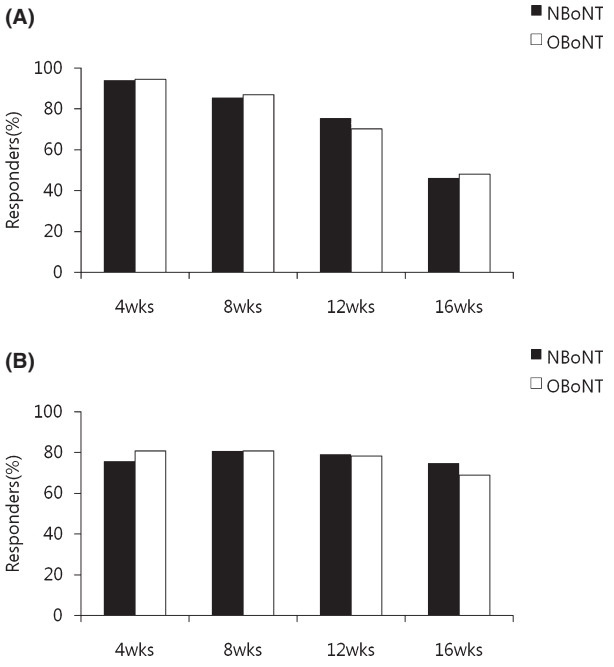

Figure 4. Percentage of responder based on physician's live assessment for the per protocol set. (A) At maximum frown, responders were 93.7%, 85.1%, 75.0%, and 46% for the new botulinum toxin type A (NBoNT) group and 94.5%, 86.9%, 70.8%, and 48.3% for the onabotulinumtoxinA (OBoNT) group, at weeks 4, 8, 12, and 16, respectively; (B) At rest, responders were 75.6%, 80.5%, 79.0%, and 74.7% for the NBoNT group and 80.5%, 80.5%, 77.8%, and 68.3% for OBoNT group at weeks 4, 8, 12, and 16, respectively.

TABLE 3. Investigator Photograph Assessment at Week 4 for Per Protocol Set

	NBoNT n = 142	*OBoNT* n = 146	p-*Value**
Rest			
Responder	42 (29.2)	36 (24.7)	.56
Nonresponder	102 (70.8)	110 (75.3)	
Maximum frown			
Responder	103 (73.6)	113 (77.9)	.39
Nonresponder	37 (26.4)	32 (22.1)	

Number of missing values: 1 in onabotulinumtoxinA (OBoNT) group at rest, 2 in new botulinum toxin type A (NBoNT) group, and 1 in OBoNT group at maximum frown.
*Pearson chi-square test.

Subject Assessment

Subject assessment of improvement of glabellar lines and satisfaction (Table 1) yielded comparable results for both groups. Peak improvement rate, defined as the proportion of patients who scored more than 2 points more (moderately improved) were 86.5% (122/142 patients) for the NBoNT group and 90.3% (131/146) for the OBoNT group at week 8 (Figure 5A) and afterward gradually decreased to 71.2% and 66.9% by week 16. Subjective satisfaction reached its peak at week 4

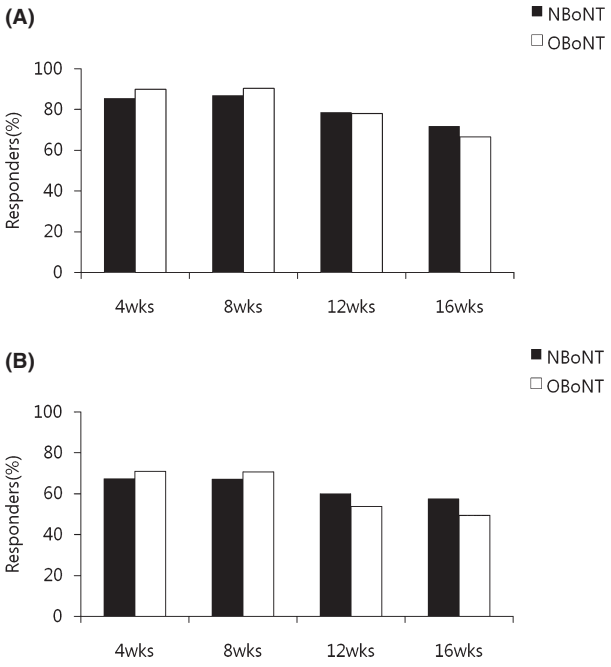

Figure 5. Subject improvement assessment and satisfaction for per protocol set. (A) According to subject assessment, improvement rates were 85.2%, 86.5%, 79.3%, and 71.2% for the new botulinum toxin type A (NBoNT) group and 90.4%, 90.3%, 77.8%, and 66.9% for the onabotulinumtoxinA (OBoNT) group at weeks 4, 8, 12, and 16, respectively. (B) Subject satisfaction rates were 67.6%, 67.4%, 60.0%, and 56.8% for the NBoNT group and 70.6%, 70.3%, 53.5%, and 49.7% for the OBoNT group at weeks 4, 8, 12, and 16, respectively.

and gradually decreased over weeks 8, 12, and 16 (Figure 5B). There was no statistically significant difference between the two groups for any secondary end point at any point in time.

Safety

Three hundred thirteen subjects were evaluated: 156 for the NBoNT group and 157 for the OBoNT group. Overall incidence of AEs was 26.9% in the NBoNT group and 22.3% in the OBoNT group. There were two cases of serious AEs (1.3%) in the NBoNT group; one was a case of gastroenteritis, and the other was of acute pyelonephritis. Both cases were considered not to be related to the treatment. The incidence of AEs from which the causal relationship with treatment could not be excluded was 10.9% (17/156) in the NBoNT group and 7.6% (12/157) in the OBoNT group. All cases were mild. The common (>1%) treatment-related AEs were eyelid ptosis (5/156, 3.2% NBoNT group; 3/157, 1.9% OBoNT group) and extraocular muscle disorder (1/156, 0.6% NBoNT group; 4/157, 2.6% OBoNT group). All other related AEs had a total incidence of <1%. There were no treatment-related AEs resulting in discontinuation of the study in either group and no statistically significant difference in the incidence and severity of AEs between the two groups. No patient from two selected centers developed neutralizing BTX-A antibodies during the course of study.

Discussion

This study was designed to compare the efficacy and safety of NBoNT with that of OBoNT, which has the largest world market share. Both agents led to clinical improvement, and there was no significant difference between the two groups in any variable at any point. The noninferiority of NBoNT to OBoNT was confirmed in the responder rate at 4 weeks at maximum frown. These results suggest that NBoNT and OBoNT are equally efficacious, as shown in previous clinical trials using a 1:1 dose ratio.[8,9]

OBoNT has been studied in large worldwide clinical trials since the Food and Drug Administration approved it for glabellar lines in 2002. Previous studies using 20 U of OBoNT have suggested the possibility of differences in response between ethnic groups. The responder rates for maximum frown at week 4 were 76.7% and 83.7% in pivotal studies for OBoNT conducted in the United States, whereas responder rates were 88.6%, 95.1%, and 94.1% in similar studies in China and Japan.[2,10–15] Our results of 93.8% and 94.6% are comparable with those of studies conducted in Asia, which may reflect the difference in muscle mass or frowning habits between Asian and Western individuals. The mean age of our cohort was comparable with those of studies done in the United States (48.2 and 47.5 in our study vs 44.7 and 47.7 in the United States), with more severe baseline wrinkles (53.5% and 55.8% vs 33.5% and 46.0%).

The primary end point was responder rate at week 4 based on face-to-face direct assessment for maxi-

mum frown, and we added photograph-based evaluations to provide additional objectivity. The investigators observed higher responder rates during direct encounters than indirect photographic assessment, which has been demonstrated in other studies.[2,12–14] Direct face-to-face assessment has advantages over photographic assessment in that the assessor is able to evaluate how much effort the participant makes in attempting to frown; at times, photographs failed to capture maximum frown.

Limitations of our study include that the majority of the patients were female and that all subjects were Korean, which may not represent a broader patient population. The total duration of the study was 16 weeks, without any long-term data.

In terms of safety, ptosis was the most common treatment-related AE. In recent large-scale clinical studies, the incidence of ptosis with BTX-A was reported to range from 0.7% to 3%.[16] According to the recent meta-analysis of the safety of OBoNT, eyelid ptosis was reported in 3.6% of OBoNT-treated patients.[17] Our study result is in accordance with previous literature.

In conclusion, NBoNT is as effective and safe as OBoNT in the treatment of moderate to severe glabellar lines over a period of at least 16 weeks.

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Address correspondence and reprint requests to: Chang Hun Huh, MD, PhD, Department of Dermatology, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam, Gyeonggi, 463-707, Korea, or e-mail: chhuh@snu.ac.kr