An Analysis of Efficacy Data from Four Phase III Studies of Botulinum Neurotoxin Type A-ABO for the Treatment of Glabellar Lines

Leslie Baumann, MD; Fredric S. Brandt, MD; Michael A. C. Kane, MD; and Lisa M. Donofrio, MD

Background: A new formulation of a botulinum neurotoxin type A (BoNTA-ABO; *Dysport* [abobotulinumtoxinA], Medicis Aesthetics, Scottsdale, AZ) has recently been approved in the United States for the treatment of moderate to severe glabellar lines.

Objective: We describe the results of four phase III studies of BoNTA-ABO for the treatment of glabellar lines.

Methods: Of the four studies reported here, three were double-blind, multicenter, randomized, placebo-controlled studies and one was an open-label extension study. A second phase III, open-label extension study is ongoing. Studies enrolled ethnically diverse, healthy adults with glabellar lines of at least moderate severity at maximum frown. Patients were followed for up to 180 days after treatment. The fixed-dose, single treatment study randomized 158 patients to receive placebo or a single 50-unit BoNTA-ABO dose. The fixed-dose, repeat treatment study enrolled 311 patients to assess treatment following repeat BoNTA-ABO treatment of 50 units. A variable-dose study randomized 816 patients to receive placebo or a single variable dose (50 to 80 units, based on gender and muscle mass assessment). The fourth phase III study was open-label to evaluate repeat dosing (50 units). Clinical evaluations were performed on days 14 and 30, and monthly thereafter. Primary efficacy endpoints were based on the investigators' and patients' assessment of glabellar line severity at day 30 using wrinkle severity rating scales. Responders were defined as patients who had a composite 2+ grade improvement in wrinkle severity, meaning that a patient had a baseline Glabellar Line Severity Scale (GLSS) score of 2 (moderate glabellar lines) and a day 30 GLSS score of 0 (no glabellar lines/none), or a baseline GLSS score of 3 (severe glabellar lines) and a day 30 GLSS score of 0 (no glabellar lines/none) or 1 (mild glabellar lines), for both the blinded investigator's and patient's assessments.

Results: Patients (1116 total; 720 BoNTA-ABO, 396 placebo) treated with BoNTA-ABO received 50 to 80 units. The median duration of response was 85 days for fixed dosing and 109 days for variable dosing. Similar efficacy occurred at doses adjusted for gender and muscle mass, although male patients required higher doses than female patients in the variable-dose study. Responses appeared as early as 24 hours, with a median time to onset of three days. The open-label extension study evaluated 1200 patients for 13 months. Maintenance of efficacy was seen after multiple treatment cycles, indicating that patients did not develop a tolerance. A second open-label study is ongoing and is not included in this report.

Conclusions: BoNTA-ABO significantly improved moderate to severe glabellar lines compared with placebo, with onset of effect seen as soon as 24 hours after treatment and a median duration of effect of 85 and 109 days for fixed and variable dosing, respectively. *(Aesthet Surg J;29:S57–S65.)*

Dr. Baumann is Chief of the Division of Cosmetic Dermatology and a Professor of Dermatology, University of Miami School of Medicine, and the Director of the University of Miami Cosmetic Dermatology Center, Miami, FL. Dr. Brandt is from the Dermatology Research Institute, LLC, Coral Gables, FL. Dr. Kane is from The Manhattan Eye, Ear and Throat Hospital, New York, NY. Dr. Donofrio is an Associate Clinical Professor of Dermatology at the Yale University School of Medicine, New Haven, CT.

The use of *Clostridium botulinum* toxin type A for the treatment of moderate to severe glabellar lines is widely accepted. Many studies have been published on the use of this biologic agent.[1-13] A new formulation of a botulinum neurotoxin type A (BoNTA-ABO; *Dysport* [abobotulinumtoxinA], Medicis Aesthetics, Scottsdale, AZ) has recently been approved in the United States for the treatment of moderate to severe glabellar lines.[14]

Treatment with botulinum neurotoxin type A (BoNT-A) suppresses muscular activity in the glabellar area and leads to inhibition of the formation of glabellar lines caused by muscle activity during facial expression.[15] Expression-related generation of glabellar lines is apparent at maximum frown and BoNT-A may not be expected to completely relieve glabellar lines noted at rest. Therefore, clinical studies focus on the correction of glabellar lines appearing at maximum frown. Nevertheless, lines appearing when the patient's face is at rest are also evaluated because some glabellar lines caused by increased resting tone in glabellar muscles may be relieved with BoNT-A treatment.

We report the combined efficacy results of four phase III studies conducted to evaluate BoNTA-ABO for the treatment of glabellar lines.[16-19] A fifth phase III study is being conducted[20] and the results of this ongoing safety study are not included in this report. The individual study designs are summarized here and individual study results have been previously reported.[16-20] The combined efficacy was analyzed across studies for specific doses. These results are presented for the BoNTA-ABO 50-unit fixed dose, the variable dose (50 to 80 units), and repeat administrations of BoNTA-ABO 50 units. Subset populations were also analyzed and are reported across studies.

METHODS

Three of the four phase III trials[16-18] were designed as multicenter, double-blind, placebo-controlled, randomized trials. The fourth phase III study[19] was open-label. All studies enrolled ethnically diverse healthy adults (18 years of age or older) with glabellar lines of at least moderate severity at maximum frown. Patients were excluded if they had eyelid or brow ptosis, deep dermal scarring, or a substantial inability to lessen glabellar lines by physically spreading them apart. The majority of participants were never exposed to botulinum toxin before the time of study recruitment.

All clinical investigations were conducted according to the principles of the Declaration of Helsinki and approval was obtained from the appropriate institutional review board before initiation of the study. A signed informed consent form was provided by each patient.

Patients received either placebo or a total dose of 50 to 80 units of BoNTA-ABO administered in five injection sites in a V-shaped pattern in the glabellar region (Figure 1). A single-use sterile 300-unit vial of BoNTA-ABO was reconstituted with 2.5 mL or 1.5 mL of 0.9% sodium chloride injection USP without preservative. The total dose was delivered in equally divided aliquots to five specified injection sites in the glabellar region (0.04 to 0.07 mL per injection point) on day zero. Follow-up visits occurred on days 14, 30, and monthly thereafter up to 180 days. Patients completed a diary card on days one through seven to record the onset of treatment effect.

The Brandt et al study, the first of three double-blind studies, was a fixed-dose single treatment study of 158 botulinum toxin–naïve patients randomized to receive

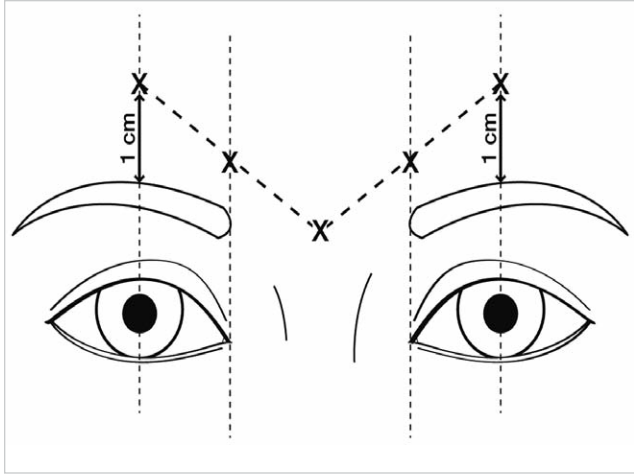

Figure 1. Schematic of glabellar region injection sites.

either placebo or 50 units of BoNTA-ABO.[16] The Rubin et al study was a fixed-dose retreatment study of BoNTA-ABO administered to 311 botulinum toxin–naïve patients. Patients initially received either one or two open-label treatments (cycles A1 and A2) with 50 units of BoNTA-ABO for up to 270 days.[17] Patients who had returned to a glabellar line severity score (GLSS) of moderate or severe were then randomized 2:1, BoNTA-ABO (50 units) to placebo, for retreatment (cycle B). Upon return to a GLSS of moderate or severe, BoNTA-ABO treated patients from cycle B were rerandomized to either placebo or BoNTA-ABO 50 units (cycle C). Cycle C was used to evaluate efficacy in order to assess response after multiple cycles of BoNTA-ABO treatment. Study participation lasted for a maximum of 23 months and patients received up to four treatments. The third double-blind, randomized study, by Kane et al,[18] was a variable-dose study that randomized 816 patients to receive a single BoNTA-ABO treatment or placebo, with dose based on gender and muscle mass (50, 60, or 70 units in women and 60, 70, or 80 units in men).[18] This study also included patients of African ethnicity and Fitzpatrick skin types IV, V, or VI.[21]

The fourth phase III study, by Moy et al,[19] was an open-label extension study to evaluate the long-term use of BoNTA-ABO (50 units) after repeat treatments. Another open-label, phase III extension study[20] is ongoing and interim safety results have been reported. Data from the Monheit et al study[20] are not included in this report. The four phase III studies discussed in this report are listed in Table 1.

The severity of glabellar lines was assessed based on an investigator's or blinded evaluator's live assessments using a validated four-point photographic scale (0 = no glabellar lines, 1 = mild, 2 = moderate, and 3 = severe; Table 2). Patients evaluated the appearance of their glabellar lines using a static four-point categorical scale (Table 3). For Brandt et al,[16] as a secondary global assessment, patients also evaluated the appearance of their glabellar lines using a nine-point scale (Table 4).