

An Analysis of Safety Data from Five Phase III Clinical Trials on the Use of Botulinum Neurotoxin Type A-ABO for the Treatment of Glabellar Lines

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BACKGROUND: A new formulation of a botulinum neurotoxin type A (BoNTA-ABO; *Dysport* [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ) was recently approved by the US Food and Drug Administration for the treatment of moderate to severe glabellar lines.

OBJECTIVE: This article summarizes the safety data from five phase III clinical trials investigating the use of BoNTA-ABO in the treatment of glabellar lines.

METHODS: Of the five phase III studies conducted, three were multicenter, randomized, placebo-controlled, double-blind studies and two were multicenter, open-label, repeat-dose studies (one of which was an extension trial). Two fixed-dose, placebo-controlled studies randomized a total of 416 patients to receive one 50-unit dose of BoNTA-ABO. The single variable-dose study randomized 544 patients to receive 50 to 80 units of BoNTA-ABO, as determined by gender and patient muscle mass. A substudy of this variable-dose study on QT/QTc prolongation included 50 patients randomized to BoNTA-ABO. One open-label repeat-dose study administered 50 units of BoNTA-ABO to 1200 patients. The single extension study (N = 1415) included both fixed (5423 treatments) and variable dosing (1337 treatments) following a protocol amendment. The extension study included patients from the four previously mentioned studies. Safety endpoints were adverse events (AE), laboratory data, and changes in vital signs. Of 2485 healthy adult patients with moderate to severe glabellar lines enrolled in the trials, 2160 received at least one cycle of BoNTA-ABO.

RESULTS: Treatment of glabellar lines with 50 units of BoNTA-ABO was well tolerated, with similar rates of treatment-emergent adverse events (TEAE) observed in the active treatment and placebo groups in terms of type, frequency, severity, and relatedness—with the exception of injection site reactions and ptosis. In the variable-dose, single-treatment study, BoNTA-ABO was well tolerated, with an incidence of active TEAE (31%) only slightly greater than that observed for placebo (28%). In the repeat-dose studies, there was no evidence of cumulative safety issues, the incidence of TEAE decreased over time, and patients did not drop out because of TEAE. The most frequently reported AE were nasopharyngitis, sinusitis, upper respiratory tract infection, headache, and injection site reactions. The majority of TEAE were considered unlikely to be related or were not related to BoNTA-ABO treatment. In all studies, the TEAE that were considered possibly related to treatment were primarily headaches (with rates comparable to those observed for placebo), injection site reactions, and eye disorders (such as blepharospasm and eyelid ptosis). There were no clinically significant changes in hematologic or biochemical parameters or in vital signs. The cardiovascular substudy revealed that BoNTA-ABO had no effect on QT/QTc prolongation.

CONCLUSIONS: Treatment of glabellar lines with BoNTA-ABO is well tolerated. Overall, the safety profile of BoNTA-ABO is comparable to that of placebo in terms of type, frequency, severity, and relatedness of AE. (*Aesthet Surg J*; 29:S50–S56.)

In the past decade, the number of aesthetic procedures performed in the United States has increased by more than 162% and nonsurgical procedures account for more than 80% of the total. Since 1997, such nonsurgical procedures have increased by more than 233%.¹ Statistics from the American Society for Aesthetic Plastic Surgery show that there were nearly 2.5

million *Clostridium botulinum* toxin injections performed in 2008, making it the top nonsurgical aesthetic procedure performed in the United States.¹

C botulinum toxin type A (BoNT-A) has a high potency at the neuromuscular junction, inhibiting acetylcholine release. When it is injected into a specific target muscle, it can produce a reduction in muscle

tone. Onset of action occurs within a few days of treatment and the maximum effect is achieved after two to four weeks.^{2,3} Targeted muscle weakening can have a therapeutic advantage for patients who have disorders that result from inappropriate or excessive muscle tone. To provide the maximum clinical effect with minimum spread to adjacent muscles, the dose of botulinum toxin needs to be tailored to each target muscle group. Low doses of the toxin have been shown to suppress the muscular activity of the glabellar area by temporary paralysis of the procerus and corrugator muscle complex.^{3,4}

BoNT-A formulations currently available for clinical use in the United States include Botox and Botox Cosmetic (BoNTA-ONA [onabotulinumtoxinA]; Allergan, Irvine, CA) and *Dysport* (BoNTA-ABO [abobotulinumtoxinA]; Medicis Aesthetics, Scottsdale, AZ). Botox is approved for various therapeutic indications,⁵ while Botox Cosmetic is approved for the treatment of moderate to severe glabellar lines.⁶ BoNTA-ABO has been recently approved by the US Food and Drug Administration (FDA) for the treatment of cervical dystonia and moderate to severe glabellar lines.⁷ It has been in clinical use outside of the United States for more than 15 years for therapeutic indications such as dystonia and spasticity in both adult and pediatric patients. It is currently approved in more than 70 countries for therapeutic indications and in at least 20 countries for the treatment of hyperkinetic facial lines. In addition, a botulinum toxin type B formulation, Myobloc (Solstice Neurosciences, San Francisco, CA), is approved for therapeutic use (cervical dystonia).⁸

Several studies have demonstrated the efficacy and safety of BoNTA-ABO in the treatment of glabellar lines.^{3,4,9-11} The data validating the efficacy of BoNTA-ABO in treating glabellar lines are presented elsewhere in this supplement. This article reviews the data supporting the safety of BoNTA-ABO from five phase III clinical trials investigating its use in the treatment of glabellar lines. Three early studies are not covered in this paper. Rather, this paper covers safety data from the following studies: Rubin et al¹² (fixed-dose after open-label treatment cycles), Brandt et al¹³ (single, fixed-dose treatment), Kane et al¹⁴ (single, variable-dose treatment), Moy et al¹⁵ (multiple treatment cycles), and Cohen et al¹⁶ (long-term fixed unit and variable-dose treatment).

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METHODS

Of these clinical trials, three were multicenter, randomized, placebo-controlled, double-blind studies, including two fixed-dose studies^{12,13} and one variable-dose study.¹⁴ The other trials were open-label; one was a fixed-dose study¹⁵ and one was an extension trial involving both fixed and variable doses.¹⁶ The study designs are summarized in [Table 1](#).

The two fixed-dose studies randomized a total of 416 patients to receive a single 50-unit dose of BoNTA-ABO.^{12,13} The variable-dose study randomized 544 patients to receive 50 to 80 units of BoNTA-ABO, as determined by gender and patient muscle mass.¹⁴ The open-label repeat-dose study administered a fixed dose (50 units) of BoNTA-ABO to 1200 patients.¹⁵ Safety endpoints were adverse events (AE), laboratory data, and changes in vital signs. Of 2485 healthy adult patients with moderate to severe glabellar lines enrolled in the phase III trials, 2160 received at least one treatment cycle of BoNTA-ABO.

RESULTS

In these clinical trials, a large number of patients received as many as seven cycles of treatment and there were no serious treatment-emergent adverse events (TEAE) deemed possibly or probably related to treatment. The TEAE reported in the safety population (in which there was an incidence of more than 1%, regardless of causality) are listed in [Table 2](#). The reported TEAE were generally mild to moderate and the majority of them were considered unrelated or unlikely to be related to treatment.

Rubin et al: Fixed-Dose After Open-Label Treatment Cycles

Rubin et al¹² published a multicenter, phase III, randomized, placebo-controlled, double-blind study comparing the efficacy of BoNTA-ABO 50 units with placebo for retreatment of glabellar lines following two to three cycles of open-label BoNTA-ABO treatment in 311 patients. The disposition of patients in the various cycles is summarized in [Table 1](#).

Overall, 207 (67%) patients experienced TEAE. The incidence of TEAE was highest in cycle A1 (41%). For cycles B and C, which employed a control group, a slightly higher percentage of patients experienced TEAE in the BoNTA-ABO groups versus the placebo groups (37% versus 26% respectively in cycle B; 38% versus 30% respectively in cycle C). For all treatment cycles (A, B, and C), the majority of TEAE were mild or moderate in severity. The total number of severe TEAE (25 of 599 TEAE; 4%) was low overall. More severe TEAE occurred in the BoNTA-ABO group in cycle B (10 events) than in any other cycle or treatment group. Most severe TEAE occurred once; however, severe headache was reported twice in cycle A1. In addition, 15 serious TEAE were reported in 12 (<4%) patients, but all were considered unlikely to be related or unrelated to treatment.

Table 1. Designs of phase III studies of botulinum toxin type A for the treatment of glabellar lines

Study description	No. of patients			Dosages
	BoNTA-ABO	Placebo	Total	
Rubin et al ¹² : multicenter, randomized, placebo-controlled, double-blind study of retreatment following open-label treatment	A1: 311* A2: 190 B: 171 C: 71	84 71	N = 311* n = 190 n = 255 n = 142	Up to four treatments [†] : fixed dose of 50 U
Kane et al ¹⁴ : multicenter, randomized, placebo-controlled, double-blind study	544	272	816	Single treatment: males, 60–80 U; females, 50–70 U Dose determined by patient's muscle mass
EKG study (Kane et al ¹⁴ substudy): multicenter, randomized, placebo-controlled, double-blind study	50	29	79	Single treatment: males, 60–80U; females, 50–70 U Dose determined by patient's muscle mass
Brandt et al ¹³ : multicenter, phase III, randomized, placebo-controlled, double-blind study	105	53	158	Single treatment: fixed dose of 50 U
Moy et al ¹⁵ : multicenter, phase III, open-label, repeat-dose study of treatment	1200		1200	Up to five repeat treatments [†] : fixed dose of 50 U
Cohen et al ¹⁶ : multicenter, phase III/IV, open-label, extension, repeat-dose study	1415		1415	Up to eight repeat treatments, [†] fixed dose of 50 U or variable dose (60–80 U for males, 50–70 U for females [†]). Variable dose determined by patient's muscle mass [‡]

BoNTA-ABO, abobotulinumtoxinA; EKG, electrocardiogram.

*Total for the study: N = 311. All other figures are subsets of this total and all 311 received BoNTA-ABO in the initial open-label treatment cycle.

[†]All repeat treatments were ≥ 85 days apart.^{12,15,16}

[‡]Patients received variable dosing if they entered this extension study from Kane et al¹⁴ and received treatment following a protocol amendment–permitted variable dosing.¹⁶

The most frequently reported instances of AE considered to be probably or possibly related to study treatment were nervous system disorders (predominantly headaches or migraines), general disorders and administrative site conditions, and eye disorders. The frequency of these events was comparable in the BoNTA-ABO groups and the placebo groups in cycles B and C for all TEAE except ptosis, which had a low incidence but occurred in a greater percentage of patients treated with BoNTA-ABO than placebo (3.2% versus 0%, respectively). There were no clinically significant changes from baseline over time in any of the mean measured laboratory values, nor were there any clinically significant abnormalities or mean changes in vital signs. Multiple treatment cycles of BoNTA-ABO were well tolerated. Most AE occurred at a comparable rate in the placebo and BoNTA-ABO groups; the only exception was ptosis, which occurred rarely (3.2%).

Kane et al: Single, Variable-Dose Treatment

Kane et al's study¹⁴ was a phase III, randomized, placebo-controlled, double-blind study of the safety and duration of efficacy of BoNTA-ABO for the correction of moderate to severe glabellar lines. Of the 816 subjects enrolled, 272 received placebo and 544 received a single treatment of BoNTA-ABO with variable dosing dependent on gender and muscle mass (50 to 70 units in female patients; 60 to 80 units in male patients).

BoNTA-ABO was well tolerated and the incidence of TEAE was only slightly higher for patients treated with BoNTA-ABO than for those receiving placebo (31% versus 28%, respectively). The majority of TEAE ($\geq 93\%$) in both the placebo and BoNTA-ABO groups were mild or moderate in severity. Only 12 patients (7%) treated with BoNTA-ABO experienced severe TEAE and, of these, only one patient had an event that was considered probably related to treatment (ptosis). In the BoNTA-ABO group, more patients had TEAE that were considered unrelated to study treatment (22%) than related events (9%). This ratio was similar to that observed in the placebo group (20% versus 7%, respectively). The majority of eyelid ptosis events (14/17) were mild in severity. There were 19 serious AE (SAE) in 11 patients ($\sim 1\%$; three for patients receiving placebo and eight for patients receiving BoNTA-ABO); all were considered unrelated to study treatment. There were no deaths and no patient discontinuations related to TEAE.

A secondary objective of this study was to compare the safety of BoNTA-ABO treatment in treatment-naïve versus non-naïve patients. In this study population, 158 patients (19.3%) had received BoNTA-ABO treatment within the preceding 12 months; 51 of these non-naïve patients were randomized to receive placebo and the remainder (107) were randomized to treatment with BoNTA-ABO. In general, patients previously treated with BoNTA-ABO had a slightly lower incidence of ocular and injection site TEAE

Table 2. Number of patients with treatment-emergent adverse events with >1% incidence (%)

Adverse event	Rubin et al ¹²		Kane et al ¹⁴		Brandt et al ¹³		Moy et al ¹⁵	Cohen et al ¹⁶
	BoNTA-ABO N = 311	BoNTA-ABO N = 544	Placebo N = 272	BoNTA-ABO N = 105	Placebo N = 53	BoNTA-ABO N = 1200	BoNTA-ABO 1415	
No. of patients with any TEAE (%)	207 (67)	168 (31)	75 (28)	49 (47)	21 (40)	880 (73)	Fixed-dose group, 818/1390 (59%); variable-dose group 260/715 (36%)*	
Nasopharyngitis (%)	38 (12)	15 (3)	6 (2)	12 (11)	6 (11)	153 (13)	Fixed-dose group, 168 (12); variable-dose group, 22 (3)	
Headache (%)	42 (14)	19 (3)	8 (3)	10 (10)	4 (8)	178 (15)	Fixed-dose group, 81 (6); variable-dose group, 30 (4)	
Eyelid ptosis (%)	6 (2)	13 (2)	1 (<1)	3 (3)	0 (0)	45 (4)	Fixed-dose group 30 (2); variable-dose group, 10 (<1)	
Blepharospasm (eyelid twitching) (%)	3 (<1)	1 (<1)	0 (0)	1 (1)	2 (4)	15 (1)	Fixed-dose group, 12 (<1); variable-dose group, 1 (<1)	
Injection site pain (%)	12 (4)	2 (1)	4 (1)	4 (4)	2 (4)	83 (7)	Fixed-dose group, 50 (4); variable-dose, 10 (1)	
Injection site bruising (%)	16 (5)	4 (1)	0 (0)	0 (0)	1 (2)	72 (6) (coded as injection site hemorrhage)	Fixed-dose group, 30 (2); variable-dose group, 7 (1)	
Upper respiratory tract infection (%)	6 (2)	10 (2)	4 (1)	1 (1)	0 (0)	82 (7)	Fixed-dose group, 67 (5) (6); variable-dose group, 15 (2)	
Sinusitis (%)	14 (5)	6 (1)	3 (1)	2 (2)	0 (0)	92 (8)	Fixed-dose group, 84 (6); variable-dose group, 9 (1)	
Influenza (%)	10 (3)	5 (<1)	0 (0)	2 (2)	2 (4)	44 (4)	Fixed-dose group, 32 (2); variable-dose group, 5 (1)	

BoNTA-ABO, abobotulinumtoxinA; TEAE, treatment-emergent adverse event.

*Patients who received both fixed- and variable-dose treatments were counted in both groups; therefore, the sum total number of patients in the fixed- and variable-dose groups is greater than the total number in the study.

than BoNTA-ABO-naïve patients. The difference was neither clinically nor statistically significant.

Single, variable-dosing treatment was well tolerated in this study. The majority of TEAE were mild or moderate in severity and were unrelated to study treatment or to dose.

Cardiovascular Safety Substudy

Within this study—and at the request of the FDA—a subset of 79 patients (50 of whom received BoNTA-ABO and 29 of whom received placebo) was assessed for any treatment-emergent QT/QTc interval change. These data are often requested for biologic agents. Electrocardiogram (EKG) results for each patient were screened before study treatment to ensure that their values were within normal limits for inclusion, to permit assessment of QTc interval changes.

Specifically, patients were evaluated for QT/QTc prolongation using a 12-lead EKG with 10-second rhythm strip tracings at three time points specified within the protocol. Cardiovascular safety was assessed by analysis of the mean change from time-matched baseline in QT/QTc interval by QTcF (QT interval corrected by the Fridericia formula) or QTcB (QT interval corrected by the Bazett formula) to each posttreatment measurement for both BoNTA-ABO and placebo. Abnormal prolongation in the QTc interval

was evaluated by comparison of the mean time-averaged change from baseline between treatment groups to assess whether the postexposure EKG results indicated an increase from baseline in the active treatment group of 10 or more milliseconds longer than in the placebo group.

Neither the differences nor the changes in mean intervals from screening in the BoNTA-ABO group to the two posttreatment times increased by 10 or more milliseconds. The majority of patients in the BoNTA-ABO treatment group had QT, QTcB, and QTcF intervals of less than 450 msec at all times specified in the protocol. One patient had a QT interval of 481 msec. Also, in the BoNTA-ABO treatment group, the majority of patients had changes in QT, QTcB, and QTcF intervals from -30 to less than +30 milliseconds. In addition, abnormal waveform morphologies were found in one patient who received placebo. Mean changes in QT, QTcB, and QTcF intervals from baseline in all treatment groups at all scheduled times were similar. In summary, the EKG results showed that BoNTA-ABO has no effect on QT/QTc prolongation.

Brandt et al: Single, Fixed-Dose Treatment

The analysis by Brandt et al¹³ was a phase III, multicenter, randomized, placebo-controlled, double-blind study

involving 158 patients. Of this number, 105 received a single dose (50 units) of BoNTA-ABO and 53 received placebo. The proportion of patients with TEAE was similar in the BoNTA-ABO and placebo groups (47% versus 40%, respectively). The majority of TEAE were considered unlikely to be or not related to treatment.

The most frequently reported TEAE, experienced by more than 3% of patients, were blepharospasm, eyelid ptosis, vomiting, injection site reactions, injection site pain, nasopharyngitis, influenza, and headache (Table 2). There were six SAE in two patients (~1%), both of whom were in the BoNTA-ABO group. None of these SAE (vomiting, malignant melanoma, squamous cell carcinoma of the skin, parotidectomy, and skin neoplasm excision) was considered related to study therapy. No significant changes in hematologic or biochemical parameters were observed, nor were there any clinically significant abnormalities or changes in vital signs. Investigators concluded that a single, fixed-dose (50-unit) treatment of BoNTA-ABO was well tolerated.

Moy et al: Multiple Treatment Cycles

This study was a phase III, multicenter, open-label, repeat-dose study of 1200 patients who received a single 50-unit dose of BoNTA-ABO (divided equally among five injection points in the glabellar area) with up to five repeat treatments over 13 months.

In this study, 73% of patients experienced TEAE, most of which were considered mild or moderate in severity: 482 patients (40%) experienced mild AE, 324 (27%) experienced moderate AE, and 74 (6%) patients experienced SAE. The majority of TEAE were considered unlikely to be or not related to therapy. TEAE that were considered possibly or probably related to therapy were reported in 36% of patients and included eye disorders (eg, ptosis or blepharospasm), administration site conditions (eg, injection site pain or bruising), and nervous system disorders (eg, headache). In most patients reporting injection site pain (79/83, ~95%), the AE were considered possibly or probably related to treatment. Possibly or probably related injection site bruising occurred in 5% of patients. Headache was often attributed to treatment; 178 patients (15%) reported headaches and 138 of those patient reports (11%) were considered to be related to treatment. The incidence of ptosis generally decreased with repeat cycles of therapy, from 2.4% in cycle 1 to 1.1% in cycle 2, 0.6% in cycle 3, 0.4% in cycle 4, and 0.6% in cycle 5. Cumulatively, across all cycles, ptosis was reported by a total of 4% of patients (45/1200) in the study; all episodes of ptosis were considered possibly or probably related to treatment.¹⁵

During all treatment cycles, eight patients (<1%) experienced severe events that were possibly or probably related to treatment: four patients in cycle 1, three in cycle 2, and one in cycle 3. These included eyelid ptosis (one event), streptococcal pharyngitis (one event), headache (three events), sinus headache (one event), dizziness (one event), and injection site irritation (one event). Over time, the researchers reported a decrease in the severity of

events, meaning that events were fewer and milder. No related event scored as severe met the criteria for an SAE (ie, results in death or significant or persistent disability, results in or prolongs hospitalization, threatens life, or is a congenital malformation). There were 72 SAE reported in 43 (<4%) patients; all were considered unrelated to study treatment. Eight patients discontinued the study because of AE, but only one case was determined to be treatment-related (injection site reaction and moderate cutis laxa, which resolved in 55 days).¹⁵

No clinically significant mean changes from baseline in vital signs were observed. Most reported cases of hypertension occurred in patients who had pretreatment hypertensive systolic or diastolic readings.

Investigators concluded that there was no decrease in efficacy and no evidence of cumulative safety issues in this study. In fact, the incidence of TEAE decreased over time.

Cohen et al: Long-Term Fixed Unit and Variable Dosing

The Cohen et al¹⁶ study involved an interim analysis of a phase III/IV, open-label, extension, repeat-dose study of BoNTA-ABO treatment. Subjects (n = 1415) could enter from any of four phase III studies. Three of these studies (Rubin et al,¹² Brandt et al,¹³ and Moy et al¹⁵) used a fixed dose (50 units of BoNTA-ABO) and one (Kane et al¹⁴) used variable dosing (50 to 80 units depending on gender and muscle mass).¹⁶ Patients who entered from a fixed-dose study received the same fixed dose (50 units) in this study. Patients entering from the variable-dose study received a fixed dose until a protocol amendment permitted those subjects to receive a variable dose according to gender and muscle mass assessment, as in Kane et al.¹⁴

The most frequently reported TEAE were nasopharyngitis, sinusitis, upper respiratory tract infection, and headache. The majority of these were considered mild or moderate in severity. The incidence of TEAE around the eyes was low and tended to decrease with each subsequent cycle of treatment. The most commonly reported TEAE around the eyes were eyelid ptosis (3%), eyelid edema (1%), and dry eye (1%).

Of the 3861 reported TEAE, 2707 (70%) were mild, 758 (20%) were moderate, and 200 (5%) were severe. The remaining 5% of TEAE were medical or cosmetic procedures recorded as AE in accord with the study design; therefore, no severity rating is associated with these events. Most TEAE were considered unlikely to be related or not related to study treatment; 500 (13%) were considered possibly or probably related to study treatment. There were 95 patients (7%) who experienced 145 SAE. Only one SAE in one patient (mild eyelid ptosis) was considered probably related to study treatment. This was coded as serious because the patient was hospitalized to rule out stroke.¹⁶

As of the data cutoff, 176 patients had discontinued from the study before completion. The majority of the discontinuations were related to patient decision (109 patients;

8%) or because patients were lost to follow-up (48 patients; 3%). Ten patients (<1%) were removed from the study for noncompliance to study requirements, eight patients (<1%) discontinued because of an AE, and one patient was discontinued from the study by the investigator's decision (the patient suffered from chronic lymphocytic leukemia, which was unrelated to study treatment).

No clinically significant mean changes from baseline in vital signs (systolic and diastolic blood pressures and heart and respiratory rates) were observed during the interim analysis period.

Repeat administration of the variable dosing was well tolerated. The incidence of all TEAE remained relatively constant or decreased over repeat cycles of BoNTA-ABO treatment, indicating no evidence of cumulative safety issues. Overall, the incidence of TEAE was comparable in the variable-dose groups and the 50 unit fixed-dose group.

DISCUSSION

Each of these phase III studies represents a different aspect of the safety profile of BoNTA-ABO. Rubin et al¹² compared subjects who received different cycles of open-label treatments before entering the double-blinded, randomized treatment phase. In this study involving multiple open-label treatments, the incidence of TEAE did not increase over the various treatment cycles. Similarly, the efficacy of BoNTA-ABO did not decrease after multiple treatments.¹²

A study designed to ascertain the safety of variable dosing reported only slightly more TEAE with BoNTA-ABO than placebo (31% and 28%, respectively).¹⁴ In the cardiovascular substudy, there was no QT/QTc prolongation despite the fact that the majority of the subjects received more than 50 units of BoNTA-ABO.

The safety of a single treatment with BoNTA-ABO was shown by Brandt et al.¹³ in which similar proportions of patients with TEAE were found in both the BoNTA-ABO treatment and placebo groups. Further, the majority of TEAE were considered unlikely to be or not related to treatment.¹³

Moy et al¹⁵ found that multiple cycles of treatment with 50 units of BoNTA-ABO were well tolerated. The results revealed no evidence of cumulative safety issues and no decrease in efficacy over the course of 13 months.¹⁵

The long-term cumulative safety of BoNTA-ABO in both fixed-unit and variable-dosing settings was shown by Cohen et al,¹⁶ in which the incidence of all TEAE and related TEAE remained relatively constant or decreased over repeat cycles of BoNTA-ABO treatment.

BoNTA-ABO was readministered with a minimum of 85 days between treatments, and then only if glabellar lines returned to a moderate or severe level. The repeat-dose studies summarized in this article showed no evidence of cumulative safety issues.

Ptosis events in these trials were recorded based on either the patient's report or the physician's observation. Independent reviews of baseline photos of patients who developed ptosis in these trials showed that many of them had preexisting eyelid ptosis or brow ptosis with frontalis compensation that was unmasked by the injection of

BoNTA-ABO. The variable incidence of ptosis in clinical studies may be caused by the percentage of patients with this condition on entry. The risk of ptosis can be identified before injection by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lid ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess frontalis compensation. Evaluation of patients before application of BoNTA-ABO should mitigate the risk of new ptosis events. Even so, the incidence of ptosis was low. An interim analysis of data from the study with the largest cohort (N = 1415) indicated that the incidence of eyelid ptosis events per patient ranged from 0.01 to 0.03 events, depending on dosing group and gender.¹⁶

The excellent safety profile demonstrated by BoNTA-ABO in these trials is likely attributable to the fact that the effect of BoNTA-ABO is local with limited diffusion beyond the injection site.¹⁷

CONCLUSIONS

The treatment of glabellar lines with BoNTA-ABO is well tolerated. The safety profile of BoNTA-ABO is comparable to that of placebo in terms of type, frequency, severity, and relatedness of TEAE for fixed-dose and variable-dose treatment regimens, as well as for single- and repeat-dose treatment. ▀

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