

A Randomized, Comparative Study to Evaluate Efficacy and Safety of Two Injection Volumes of AbobotulinumtoxinA in Treatment of Glabellar Lines

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BACKGROUND Different volumes of 0.9% NaCl may be used to reconstitute abobotulinumtoxinA yielding an injection volume that ranges from 0.05 to 0.1 mL per injection point for treatment of glabellar lines.

OBJECTIVE To evaluate the efficacy, safety, and subject satisfaction of 2 different injection volumes to deliver the same unit dose of abobotulinumtoxinA for treatment of glabellar lines.

MATERIALS AND METHODS This randomized comparative study was conducted using 2 different reconstitution volumes to deliver a fixed unit dose of 10 Speywood units (sU) of abobotulinumtoxinA in either 0.05 mL (labeled volume) or 0.1 mL (twofold volume) per injection point. Evaluations included wrinkle severity, neurophysiological assessment by compound muscle action potential (CMAP), and subject satisfaction.

RESULTS Use of either injection volume of abobotulinumtoxinA resulted in the early onset of effect, high effectiveness, and long duration of effect. The safety profile and injection pain levels were similar in both groups. The twofold injection volume was shown to be noninferior to the labeled injection volume based on CMAP results.

CONCLUSION A twofold increase in injection volume to 0.1 mL per injection point to deliver 10 sU of abobotulinumtoxinA is effective and safe.

The keypoint machine and camera used in this study were loaned by Galderma, who also supplied the abobotulinumtoxinA to the authors. The authors received consulting fees from Galderma. Frida Nyberg and Cindy Wong are employed by Galderma. The remaining authors have indicated no significant interest with commercial supporters.

The reconstitution volume and thereby injection volume of different botulinum neurotoxin type A (BoNT-A) preparations for the same indication are product specific. For treatment of glabellar lines, the recommended labeled injection volume per injection point may range from 0.05 to 0.1 mL for the 3 most widely used BoNT-A preparations.¹⁻³

In Europe, the approved recommendation for abobotulinumtoxinA (Azzalure [Ipsen Biopharm Limited, Slough, UK]) for treatment of glabellar lines is a total dose of 50 Speywood units (sU) reconstituted to give a final injection volume of 0.05 mL (10 sU) per injection point. In the USA, the approved recommendation for abobotulinumtoxinA (Dysport) for treatment of glabellar lines is a total dose of 50 sU reconstituted to

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give a final injection volume of 0.05 mL (10 sU) or 0.08 mL (10 sU) per injection point.

A large postapproval survey recently conducted in 5 European countries, involving 53 practitioners and 718 subjects, showed that the recommended reconstitution volume for abobotulinumtoxinA was only used in 67.5% of the treatment sessions.⁴

The aim of our study was to evaluate the efficacy, safety, and subject satisfaction of 2 different injection volumes of abobotulinumtoxinA to deliver the same unit dose per injection point for treatment of glabellar lines.

Methods

Study Design

This was a randomized comparative study conducted at 2 study sites in Sweden to evaluate the efficacy and safety of 2 different injection volumes of abobotulinumtoxinA using a parallel-group design (Clinicaltrial.gov identifier NCT02108158).⁵ Study subjects were blinded to treatment assignment. A blinded independent evaluator assessment using photographs was also included in addition to live assessment by the treating investigator. The study was conducted in accordance with the recommendations of the International Conference on Harmonization Good Clinical Practice Guideline and was consistent with the principles of the Declaration of Helsinki. Ethics committee approval was obtained (Regional EC in Uppsala Dnr 2013/518. EudraCTnr: 2013-004646-42). All subjects provided signed, informed consent. Women between 18 and 64 years of age were recruited for the study. To be eligible, the subjects had to be treatment naive and seeking treatment for moderate to severe glabellar lines (Grades 2–3 at rest using the 5-grade validated scale for glabellar lines at rest)⁶ assessed to have an important personal psychological impact on the subject by the investigator.

Subjects received a single treatment at the baseline visit (Day 0) and were then followed up for 6 months at Days 1, 3, 7, and 14 and then at Months 1, 3, 4, and 6 (Visits 1–8, respectively).

Randomization

Randomization was computer generated centrally and stratified by center and wrinkle severity. The treatment assignment to the 2 different reconstitution volumes was based on a 1:1 ratio.

Reconstitution volumes for the 2 study groups are shown in Table 1.

Treatment Procedure

Reconstitution of 125 sU vial of abobotulinumtoxinA was done using the labeled volume of 0.63 mL of 0.9% NaCl or a twofold increase in volume to 1.25 mL of 0.9% NaCl. Thus the 2 different injection volumes administered were 0.05 or 0.1 mL per injection point. AbobotulinumtoxinA was injected at 5 designated injection points in the forehead (one in the procerus muscle and 2 in each corrugator muscle) in accordance with the Summary of Product Characteristics (SmPC).¹ A total dose of 50 sU was administered in 5 equal aliquots of 10 sU per injection point using either of the 2 different injection volumes. A 30-G needle was used. Touch-up treatments were not permitted.

Efficacy Objectives

The objectives of the study were to assess:

- The effect of treatment on the severity of glabellar lines at rest and at maximum frown using a 5-grade, validated wrinkle severity scale, performed both live and by a blinded independent evaluator⁶;
- Compound muscle action potential (CMAP) using electroneurography at one site;
- Subject satisfaction with the treatment using a Subject Satisfaction Questionnaire (SSQ);
- Subject experience of the onset of effect by response to the question “Since being injected, have you noticed any effect on the appearance of your glabellar lines?” until the response is “YES.”

The schedule of assessments is shown in Table 2.

Safety Objectives

Safety was evaluated by recording adverse events (AEs) at each study visit. Injection pain was assessed

TABLE 1. Reconstitution Volumes for Study Groups

<i>Study Groups</i>	<i>Study Product</i>	<i>Reconstitution Volume</i>	<i>No. Injection Sites in Glabella</i>	<i>Injection Volume, mL</i>	<i>Dose/Injection Site, sU</i>
Labeled injection volume	AbobotulinumtoxinA 125 sU/vial	0.63 mL of NaCl (0.9%)	5	0.05	10
Twofold injection volume	AbobotulinumtoxinA 125 sU/vial	1.25 mL of NaCl (0.9%)	5	0.1	10

both immediately and 10 minutes after injection. The pain was assessed by a 100-mm visual analog scale (VAS) where 0 mm was defined as “no pain” and 100 mm as “the worst pain imaginable.”

Compound Muscle Action Potential

The CMAP is an objective and reproducible neurophysiological measurement using electrical stimulation of the motor nerve to evaluate the contraction of innervated muscle. In this study, CMAP of the corrugator muscles was measured by stimulation of the temporal branch of the facial nerve with surface electrodes (4 cm lateral to the outer canthus using the Dantec Keypoint Focus system [Alpine Biomed Aps, Skovlunde, Denmark]). Surface recording over the corrugator supercilii muscle measured the degree of muscle contraction. The assessment was performed bilaterally.

Statistical Methods

Differences between the 2 treatment groups in improvement rate in wrinkle severity were analyzed using Fisher’s exact test. For CMAP, a noninferiority hypothesis was used to test if the twofold injection volume was noninferior to the labeled injection volume, where the noninferiority limit was 10%. In addition, differences between the 2 treatment groups were analyzed with Student’s 2-sample *t*-test. Subject satisfaction was analyzed using descriptive statistics. Differences between the 2 treatment groups in “onset of response” were analyzed using the Wilcoxon rank-sum test.

Results

Baseline Characteristics

A total of 62 treatment-naive subjects were recruited. All were white females, aged 30 to 63 years. Baseline

demographics, medical history, and physical examination were similar between the groups. Baseline characteristics and wrinkle severity (assessed before injection at Day 0) are shown in Table 3.

Wrinkle Severity on Maximum Frown and Improvement Upon Treatment

Live evaluation of wrinkle severity at maximum frown showed early time to onset of effect, with 50% of subjects treated with the labeled injection volume (0.05 mL per injection point), and 53.1% of subjects treated with the twofold injection volume (0.1 mL per injection point) showing at least 1 grade improvement 1 day after treatment; and increasing to 76.7% and 93.8%, respectively, 3 days after treatment.

Maximum effect was attained 1 month after treatment when nearly all subjects experienced an improvement in wrinkle severity of at least 1 grade, 96.7% and 100% in the labeled and the twofold volume groups, respectively (Figures 1 and 2).

Four months after treatment, 58.6% of subjects in the labeled volume group and 67.7% of the subjects in the twofold volume group still experienced an improvement in wrinkle severity of at least 1 grade (Figure 2).

Duration of effect was seen in both treatment groups beyond 4 months. At 6 months after treatment, an improvement of 1 grade was observed in 17.2% of subjects in the labeled volume group and in 28.1% of the twofold volume group.

There were no statistically significant differences between the 2 treatment groups in any of the aforementioned comparisons.

TABLE 2. Schedule of Efficacy Assessments

Efficacy Assessment	Visit Number								
	0	1	2	3	4	5	6	7	8
	Baseline	Day 1	Day 3	Day 7	Day 14	Month 1	Month 3	Month 4	Month 6
Wrinkle severity (live)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Wrinkle severity (independent assessment)	✓*	✓	✓	✓	✓	✓	✓	✓	✓
Subject satisfaction questionnaire	✓					✓	✓		✓
Subject evaluation of onset of effect†		✓	✓	✓	✓	✓			
CMAP‡	✓*	✓	✓	✓		✓	✓		✓

*Pretreatment.

†Question asked: "Since being injected, have you noticed any effect on the appearance of your glabellar lines?" until response is "Yes."

‡CMAP performed at one study site.

CMAP, compound muscle action potential.

TABLE 3. Baseline Characteristics and Wrinkle Severity (Pretreatment)

Treatment Group	n	Age, yr				
		Mean	SD	Minimum	Median	Maximum
Labeled injection volume	30	50.2	8.0	30	50.5	63
Twofold injection volume	32	48.3	6.1	38	49.0	58
Total	62	49.2	7.1	30	49.5	63

Treatment Group	Wrinkle Severity Rating Scale		
	Grade II, n (%)	Grade III, n (%)	Grade IV, n (%)
At rest			
Labeled injection volume	26 (86.7)	4 (13.3)	0 (0)
Twofold injection volume	26 (81.3)	6 (18.8)	0 (0)
At maximum frown			
Labeled injection volume	4 (13.3)	20 (66.7)	6 (20.0)
Twofold injection volume	2 (6.3)	18 (56.3)	12 (37.5)

In a post-hoc analysis carried out by applying the criteria in the draft FDA guidance document for development of botulinum toxin drug products,⁷ 80% of subjects in both treatment groups attained a wrinkle severity score of none to mild and an improvement of ≥ 2 grades from baseline at 1 month after treatment. In addition, there was a higher proportion of subjects with an improvement ≥ 2 grades in the twofold injection volume group at subsequent visits (Figure 3).

Blinded independent evaluation of wrinkle severity confirmed comparable reduction in wrinkle severity at maximum frown.

Wrinkle Severity at Rest and Improvement Upon Treatment

Response in wrinkle severity at rest (as determined by live evaluation) was equally high in both treatment groups. At 6 months after treatment, an improvement of 1 grade in wrinkle severity at rest was still present in 55.2% of the labeled injection volume group and 59.4% of the twofold injection volume group. There was no statistically significant difference shown between the 2 groups.

Compound Muscle Action Potential Amplitude Was Reduced as a Measure of Muscle Paralysis

CMAP was performed in 31 subjects at 1 study site, and results are presented as a percentage of baseline

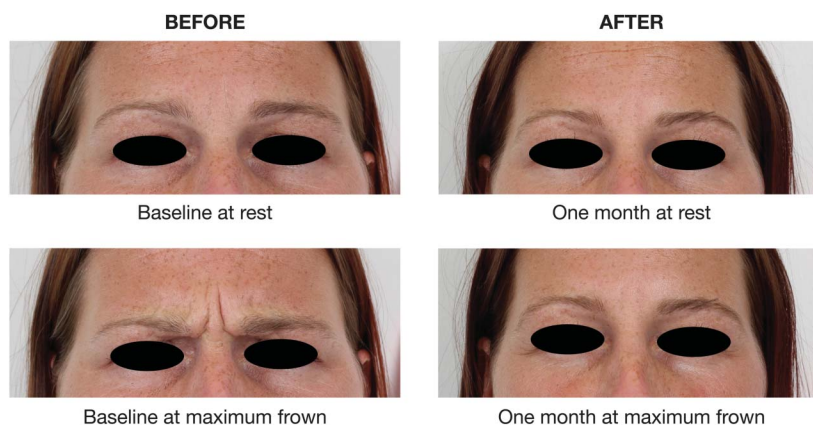


Figure 1. Before and after photographs at baseline and at 1 month showing wrinkle severity at rest and at maximum frown in one subject treated with the twofold injection volume.

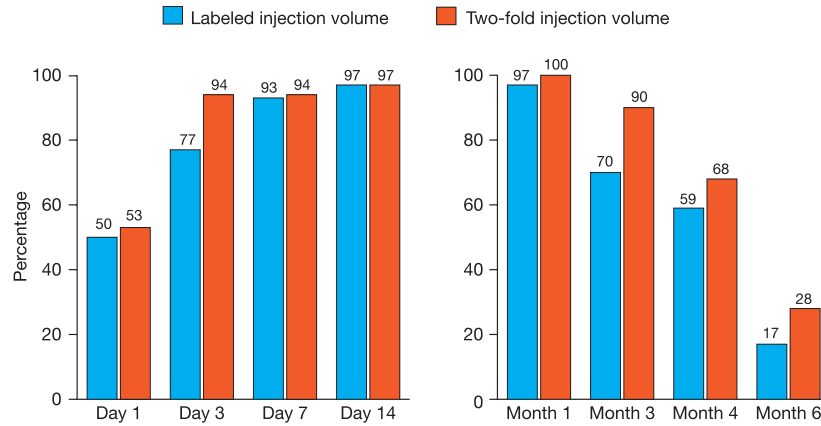


Figure 2. Percentage of subjects with at least 1-grade improvement in wrinkle severity at maximum frown (by live assessment).

value. The results showed that 1 day after treatment, the CMAP amplitude was reduced to 79.5% of the baseline value for the group that received the labeled injection volume, to 69.5% for the group that received the twofold volume, and to 54.8% and 44.1% by Day 3, respectively (Figure 4). Maximum effect was demonstrated at 1 month with CMAP values of 34.5% and 24.9% of the baseline value for the labeled and twofold injection volume groups, respectively.

Interestingly, a substantial reduction was still seen in CMAP 6 months after treatment, with values being reduced to 59.7% of the baseline amplitude in the labeled volume and to a numerically greater reduction of 51.6% in the twofold volume group (Figure 5). The reduction in CMAP was greater in the group who received the twofold injection volume at every time point, including time to the onset of effect and dura-

tion. However, the difference between groups was statistically significant only at Month 1. In conclusion, noninferiority of the larger injection volume of 0.1 mL per injection point compared with the labeled injection volume of 0.05 mL was demonstrated.

Subject Satisfaction and Experience of Onset of Response

Subjects were questioned about aesthetic outcome, feelings of attractiveness, and feelings about themselves. The results of the SSQ were similar between the 2 treatments. The majority of subjects responded positively at every scheduled time point throughout the study period (Figure 6).

Approximately 90% of subjects were satisfied with the aesthetic outcome of treatment at 1 and 3 months. Nearly all subjects (93%–100%, between 1 and 6 months) found the results natural looking and more than half of the subjects felt more attractive after the treatment.

At study end (6 months), 63.9% of all subjects said they looked more rested, “as if they had just returned from vacation.” The vast majority said that they would have the treatment again (98.3% of all subjects) and they would also recommend it to someone else (96.8% of all subjects).

The onset of response was experienced within 3 days in 93.7% of subjects who received the twofold injection volume and in 76.7% of subjects who received the labeled injection volume. All the subjects had

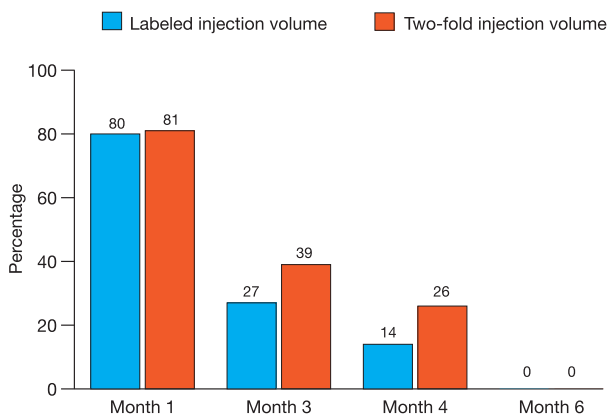


Figure 3. Percentage of subjects who attained a wrinkle severity score of 0 or 1 and an improvement of ≥2 grades.

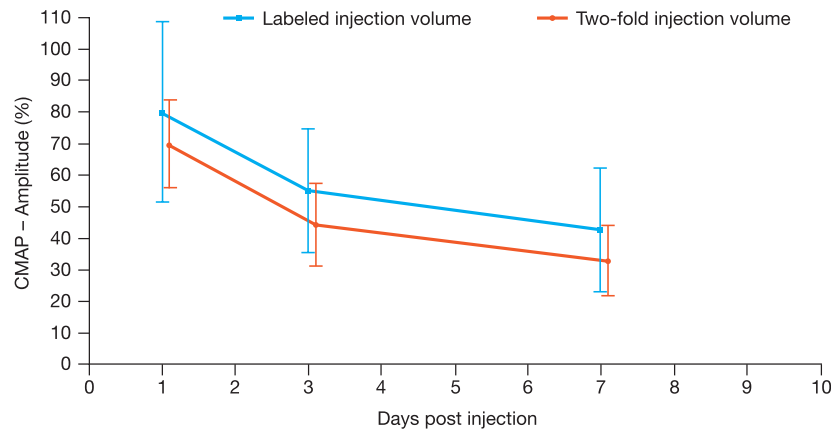


Figure 4. Changes in compound muscle action potential amplitude as a percentage of baseline values from Day 1 to Day 7 (mean ± 1 SD). Baseline values were 100% at Day 0 before treatment.

experienced a response within 7 days. There was no statistically significant difference between the 2 treatment groups in the onset of response.

Safety—No Unanticipated Findings

There were no serious AEs in either treatment group throughout the study. The number of treatment-related AEs was small and all were of mild intensity. There was no difference in the nature or frequency of related AEs between the 2 groups (Table 4). There was one report of subject-reported mild eyelid ptosis with duration of 8 days (not confirmed by the investigator) in a subject who received the labeled injection volume. There was one case of mild bilateral upper eyelid edema that occurred 3 days after treatment and one case of slight lower eyelid edema that occurred 2 days after treatment in the twofold injection volume treatment group; both were of mild intensity and lasted for 3 to 4 days.

Pain associated with the injection was very low, being less than 10 mm on the 100-mm VAS. There was no statistically significant difference between the 2 groups either immediately or at 10 minutes after treatment. The mean pain score for the labeled volume group at 0 minutes post injection was 7.0 mm (range 0–21 mm; median 6.3 mm), compared with 6.9 mm (range 0–35 mm; median 4.7 mm) for the twofold volume group. At 10 minutes post injection, the mean pain score was 3.3 mm (range 0–27 mm; median 1.6 mm) and 4.3 mm (range 0–21 mm; median 3.1 mm), respectively.

Discussion

This clinical study was designed to evaluate whether using a twofold increase in injection volume to deliver the same unit dose of abobotulinumtoxinA had any impact on the treatment results or safety compared with the labeled injection volume. The results indicate

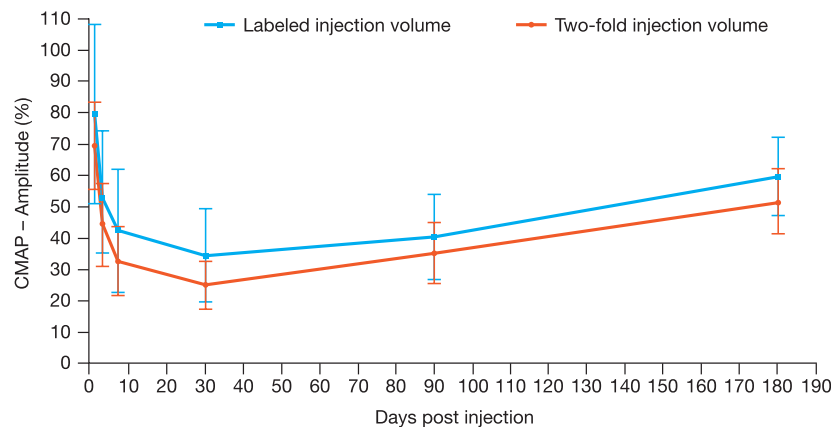


Figure 5. Changes in compound muscle action potential amplitude as a percentage of baseline values over 6 months (mean ± 1 SD), with statistically significant difference between groups at 1 month ($p = .031$).

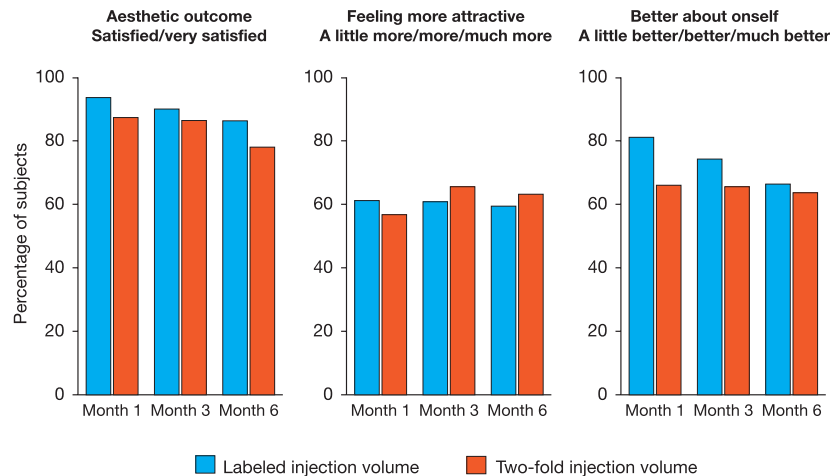


Figure 6. Subject satisfaction with aesthetic outcome, attractiveness, and feelings about themselves.

that both efficacy and safety are maintained when using the larger injection volume of 0.1 mL per injection point to deliver 10 sU of abobotulinumtoxinA.

A search of the published literature identified few clinical trials comparing the effect and safety of different reconstitution volumes to deliver a fixed unit dose of botulinum toxin to treat facial muscles. Comparisons with and between these studies are difficult because they investigated different products and involved the use of unit dose and reconstitution volume that are different from the respective product labels. One study on 20 patients comparing 2 reconstitution volumes used single injection of 5 U onabotulinumtoxinA in either 0.05 mL or 0.25 mL to treat lateral orbital rhytides and concluded no statistically significant difference in effect between the 2 injection volumes. There were no study-related AEs in either group. Another study of 80 patients used a total of 30 U onabotulinumtoxinA reconstituted as 10 U, 3.3 U, 2.0 U, and 1.0 U per 0.1 mL given as 7 intramuscular injections to treat glabellar rhytides. This study did not show any significant differences in wrinkle assessment by trained observers or in the number of subjects reporting AEs.^{8,9} Another comparative study involving 40 patients used 5 injection points of 5 U incobotulinumtoxinA in either 0.125 or 0.2 mL per injection point to treat glabellar lines and found no difference in response rate between the 2 treatment groups.¹⁰

To our knowledge, this study represents the first randomized controlled study comparing 2 reconstitution

schemes for delivering a fixed unit dose of abobotulinumtoxin where one of the treatment arms used the labeled recommendation for injection volume. In this study population, no increase in pain on injection, as measured by VAS, was observed for the larger volume. No difference in safety profile was observed for the different injection volumes, and the types of AEs for both groups were in line with those described in the abobotulinumtoxinA SmPC.¹ No serious AEs were reported. This suggests that for the injection volume of 0.1 mL per injection point (10 sU per point), the spread, if any, of abobotulinumtoxinA to surrounding muscles has not resulted in any clinically significant AEs. Assessment of wrinkle severity showed rapid onset, high maximum effect, and long duration of effect with both injection volumes. No decrease in clinical efficacy at the target muscle was observed despite an increase in reconstitution volume. Subjects in both treatment groups showed a high degree of satisfaction with both the aesthetic outcome and the onset of effect.

CMAP results provide objective support to the clinical findings, as the muscle paralysis response of the corrugator muscles to abobotulinumtoxinA treatment very closely reflects the wrinkle severity assessments. The CMAP amplitude has previously been reported to be an appropriate neurophysiological parameter for evaluation of the dose–response effect of botulinum toxin injections in the facial muscles of the glabellar area.¹¹ In our study, CMAP results also demonstrate that the twofold injection volume of 0.1 mL of

TABLE 4. Treatment-Related Adverse Events by Medical Dictionary for Regulatory Activities, System Organ Class, and Preferred Term

MedRA SOC	MedRA Preferred Term	Labeled Injection Volume (10 µ/0.05 mL) (N = 30)		Twofold Injection Volume (10 µ/0.1 mL) (N = 32)		Total (N = 62)	
		Subjects	Events	Subjects	Events	Subjects	Events
		n (%)	n	n (%)	n	n (%)	n
Eye disorders	Eyelid edema	0 (0.0)	0	2 (6.3)	2	2 (3.2)	2
	Eyelid ptosis	1 (3.3)	1	0 (0.0)	0	1 (1.6)	1
General disorders and administration site conditions	Face edema	0 (0.0)	0	1 (3.1)	1	1 (1.6)	1
	Sensation of pressure	1 (3.3)	1	0 (0.0)	0	1 (1.6)	1
	Tenderness	1 (3.3)	1	0 (0.0)	0	1 (1.6)	1
Nervous system disorders	Headache	2 (6.7)	2	4 (12.5)	4	6 (9.7)	6
	Tension headache	2 (6.7)	2	0 (0.0)	0	2 (3.2)	2
Skin and subcutaneous tissue disorders	Pruritus	0 (0.0)	0	1 (3.1)	1	1 (1.6)	1
Total		7 (23.3)	7	6 (18.8)	8	13 (21.0)	15

MedRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

abobotulinumtoxinA is noninferior to the 0.05 mL labeled injection volume in delivering the 10 sU fixed dose.

In comparing the 2 groups, although not statistically significant, there is a numerical difference both in wrinkle severity and in CMAP results, suggesting higher efficacy and longer duration of effect when the twofold injection volume is used. Similar observations have been reported previously, when an increase in wrinkle reduction or hypohidrotic effect has been shown when a higher injection volume is used for a fixed dose.¹²⁻¹⁴ The increased effect of the twofold increase in injection volume might be explained by a greater coverage of nerve terminals, thus resulting in a faster onset of effect and a slightly improved efficacy. These findings need to be studied further. Furthermore, there was still measurable impact on CMAP at 6 months, and this might partly explain the observed continuation of patients' satisfaction at 6 months despite attenuation in the wrinkle severity response.

Conclusion

Both the twofold injection volume of abobotulinumtoxinA and the labeled injection volume provide excellent efficacy with early onset of effect, high effectiveness, and duration of effect lasting up to 6 months. The study results were consistent for improvements in wrinkle severity, reductions in CMAP amplitudes, and subject satisfaction. The safety profile was comparable for the 2 different injection volumes in the nature, frequency, and severity of AEs, and the low level of pain on injection was similar in both study groups. Additionally, the objective neurophysiological measurement of CMAP supported the noninferiority of the twofold injection volume to the labeled injection volume.

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