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AbobotulinumtoxinA Treatment of Glabellar Lines Using a New Reconstitution and Injection Volume: Randomized, Placebo-Controlled Data

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ABSTRACT

Background: Increasing the reconstitution and injection volumes of abobotulinumtoxinA (aboBoNT-A) could provide more options for aesthetic healthcare professionals.

Objective: To evaluate efficacy and safety of aboBoNT-A treatment of moderate-to-severe glabellar lines (GL) versus placebo, using a new reconstitution and injection volume.

Methods & Materials: In this 6-month, Phase III, randomized, double-blind study, subjects 18-64 years were administered aboBoNT-A 50 U (N=224) or placebo (N=77), as five 0.1-mL-injections (10 U) in the glabellar region following reconstitution of a 300-U-vial in 3 mL. Assessments included time to onset of effect, investigator- (ILA) and subject- (SSA) assessed GL severity, subject satisfaction, aesthetic improvement and safety. The primary endpoint was composite 2-grade response at month 1 (a GL severity of none-or-mild at maximum frown and ≥2-grade improvement from baseline concurrently on both ILA and SSA).

Results: Median time to onset was 2 days, 34% of subjects reporting effect on day 1. At month 1, the composite 2-grade responder rate was 65.8% for aboBoNT-A versus 0% for placebo, $P<0.001$, 91–92% had none-or-mild GL severity, and 95–100% had a ≥1-grade GL severity improvement. A ≥1-grade improvement was sustained in 46-56% of aboBoNT-A-treated subjects up to 6 months ($P<0.001$ vs placebo). Aesthetic improvement and subject satisfaction were high throughout 6 months and aboBoNT-A treatment was well tolerated.

Conclusion: Safety and efficacy of GL treatment using 0.1 mL (10 U) aboBoNT-A per injection site were demonstrated, with rapid onset and up to 6 months' duration of effect. Severity improvement was accompanied by sustained aesthetic improvement and subject satisfaction.

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INTRODUCTION

AbobotulinumtoxinA (aboBoNT-A; Dysport®, Ipsen Ltd, Slough, UK) is approved in the US for treatment of moderate to severe glabellar lines (GL) using a total dose of 50 Speywood units (50 U). According to the current US license,[1] a 300-U-vial of this powder formulation is reconstituted with either 1.5 mL or 2.5 mL 0.9% NaCl, and five 10-U-aliquots are then administered to the GL area using corresponding injection volumes of 0.05 mL or 0.08 mL per site.

Increasing the reconstitution volume to obtain a 0.1-mL-volume of injection minimizes the margin of error and is comparable to other botulinum toxin A preparations (onabotulinumtoxinA [Botox®] and incobotulinumtoxinA [Xeomin®]). This volume is also approved for use with aboBoNT-A in some countries, including in the EU.[2] In a prior study, similar efficacy was shown when aboBoNT-A was injected using 0.1 mL as for 0.05 mL per injection, with no safety concerns, following reconstitution of a 125-U-vial.[3]

The present study aimed to further evaluate efficacy and safety of treatment of moderate to severe GL using an injection volume of 0.1 mL with the currently approved 50-U-dose of aboBoNT-A, in a large US study population, following reconstitution of the 300-U-vial with a total reconstitution of 3.0 mL per vial.

MATERIALS AND METHODS

Study Design

This was a Phase III, randomized, double-blind study conducted at 12 US centers between June 2019 and April 2020 (clinicaltrials.gov registration number NCT03960957). Subjects were treated on day 0 with aboBoNT-A 50 U or placebo, and then followed up at day 2, week 2, and monthly from month 1 to month 6.

The primary objective was to evaluate efficacy of aboBoNT-A versus placebo based on the month 1, composite 2-grade response at maximum frown, defined as a GL severity score of 0 or 1 and a ≥2-grade improvement from baseline concurrently on both the Investigator's Live Assessment (ILA) and the Subject's Self-Assessment (SSA) scales. Secondary and exploratory objectives included further assessment of efficac , subject satisfaction, other subject-reported outcomes and safety.

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Consolidated Guideline on Good Clinical Practice and local regulatory requirements, after approval from institutional review boards.

Subjects

Male and female subjects aged 18–64 years, with moderate-to-severe (Grade 2 or 3) GL at maximum frown, as assessed by ILA and SSA, who provided written informed consent were eligible for enrolment. Exclusion criteria included: facial treatment with botulinum toxin in the past 6 months; absorbable (temporary) or non-absorbable (permanent) material inserted in the glabellar region; any facial surgery or aesthetic or other procedures which could interfere with study evaluations; known hypersensitivity to any component of the study product; allergy to cow's milk protein; breastfeeding or planned pregnancy for females during the study; history or presence of eyelid or eyebrow ptosis, amblyopia, cancerous or pre-cancerous lesions in or near the glabellar region, or facial nerve palsy; presence of inflammation active infection or skin disorder in or near the glabellar region; use of medications that affect neuromuscular transmission; and conditions that might interfere with neuromuscular function.

Subjects had to abstain from facial aesthetic procedures and any planned facial surgery or eye surgery during the study.

Treatment

Treatment with aboBoNT-A or placebo was randomized 3:1, stratified by study center. AboBoNT-A, commercially available Dysport, was provided as a lyophilized powder in single-use 300-U-vials. Placebo vials contained excipients identical in appearance to aboBoNT-A powder. Before injection, each vial was reconstituted with 3.0 mL sterile preservative-free 0.9% NaCl USP for injection. A total volume of 0.5 mL reconstituted aboBoNT-A (50 U) or placebo was injected in the glabellar area, divided into five aliquots of 0.1 mL (10 U). One injection was placed in the procerus muscle, and two into each corrugator muscle.

Efficacy Assessments

GL severity was evaluated at maximum frown and at rest by investigators, using the validated 4-grade photographic ILA scale ranging from 'none' (Grade 0), 'mild' (Grade 1), 'moderate' (Grade 2) to 'severe' (Grade 3). GL severity was also graded at maximum frown by subjects, using the 4-grade categorical SSA scale ranging from 'no wrinkles' (Grade 0), 'mild wrinkles' (Grade 1), 'moderate wrinkles' (Grade 2), to 'severe wrinkles' (Grade 3).

The primary endpoint was the composite 2-grade GL response at maximum frown at month 1, which is defined ab ve.

Other GL severity endpoints included ILA response at maximum frown and at rest, defined as achievement of a 0 or 1 score, or defined as a ≥1-grade improvement from baseline. Similar definitions were used to assess SSA response at maximum frown.

Time to loss of a score of 0 or 1 (ie, return to a score of 2 or 3) and time to return to baseline scores were calculated based on concurrent evaluations on both ILA and SSA at maximum frown.

Subject-reported time to onset of response, was assessed using a 7-day subject diary. Subjects responded 'yes' or 'no' to the question 'Since being injected, have you noticed an improvement in the appearance of your glabellar lines (lines between your eyebrows)?'

Aesthetic improvement of GL at maximum frown was rated by the subjects using the 7-graded Global aesthetic improvement scale (GAIS) from 'very much worse' to 'very much improved'.
Other subject-reported outcomes included a subject satisfaction questionnaire consisting of 10 questions, capturing satisfaction with appearance and treatment outcome, and three validated FACE-Q© scales: Appraisal of Lines Between the Eyebrows, comprising 7 questions relating to how bothered the subject was by their GL, rated on a 4-point scale from 'not at all' (1) to 'extremely' (4),[4] Psychological Function, comprising 10 items, rated on a 4-point scale from 'definitely disagree' (1) to 'definitely agree' (4),[5] and Subject-perceived Age Visual Analog Scale (VAS) capturing how old the subject thinks that they look compared to their actual age (±15 years).[6]

Safety Assessments

Safety assessments included collection of treatment-emergent adverse events (TEAEs) throughout the study, and physical examination of the face, head, and neck at baseline, day 2, week 2, month 1, and month 6 after treatment.

Statistics

Statistical calculations were done using SAS® version 9.4. Efficacy analyses were based on the intent-to-treat (ITT) population, defined as all subjects who were randomized, or on the per-protocol (PP) population, defined as an ITT subject with no protocol deviations with substantial impact on primary efficacy outcome. The safety population consisted of all subjects administered study drug.

Primary endpoint: the composite 2-grade responder rate at maximum frown at month 1 for aboBoNT-A and placebo were compared using Cochran-Mantel-Haenszel test stratified by center at a 5% significance level (2-sided). Pooling of centers was done based on geographical location, until the pooled center had at least 16 subjects, and at least one responder and one non-responder for the primary endpoint. Missing data were handled by multiple imputation. The secondary and exploratory ILA and SSA responder rates were compared using Cochran-Mantel-Haenszel test stratified by pooled cente .

For analysis of duration of effect and time to onset of treatment response, Kaplan-Meier estimates of the median event times were used.

For the two FACE-Q scales containing multiple items, the subjects' scores for the individual items were converted to a single Rasch-transformed total score from 0 to 100 for each scale as per the FACE-Q manual. Higher total scores indicated greater psychological function or that subjects were less bothered by their GL appearance. No statistical comparisons were performed for FACE-Q data.

RESULTS

Subject Disposition and Demographics

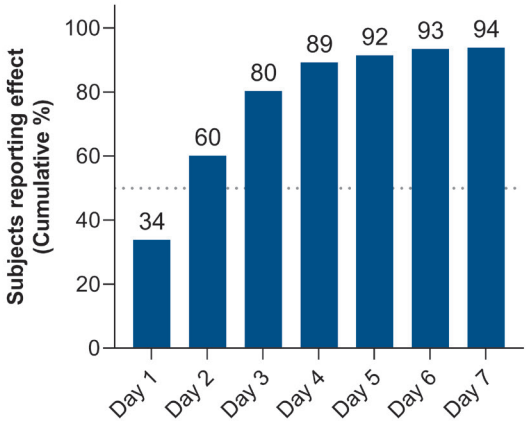
In total, 301 subjects were randomized, comprising the ITT population, 300 were treated, comprising the safety population, and 287 subjects (95%) completed the study. Most non-completers were lost to follow-up. No subjects discontinued due to adverse events. One subject in the aboBoNT-A group was randomized in violation of the age criteria (aged 65) and was therefore withdrawn before receiving treatment.

TABLE 1.

Demographics and Baseline Characteristics (ITT Population)			
	aboBoNT-A N=224	Placebo N=77	Overall N=301
Demographics			
Age, years			
Mean (SD)	44.7 (11.43)	42.5 (11.86)	**44.1 (11.56)**
Range	21–65	21–66	**21–66**
Sex, n (%)			
Men	29 (12.9)	8 (10.4)	**37 (12.3)**
Women	195 (87.1)	69 (89.6)	**264 (87.7)**
Baseline glabellar line severity at maximum frown			
ILA, n (%)			
Moderate	57 (25.6)	15 (19.5)	--
Severe	166 (74.4)	62 (80.5)	--
SSA, n (%)			
Mild wrinkles	1 (0.4)	0	--
Moderate wrinkles	114 (50.9)	35 (45.5)	--
Severe wrinkles	109 (48.7)	42 (54.5)	--
Baseline glabellar line severity at rest			
ILA, n (%)			
None	35 (15.7)	14 (18.2)	--
Mild	71 (31.8)	21 (27.3)	--
Moderate	87 (39.0)	27 (35.1)	--
Severe	30 (13.5)	15 (19.5)	--

aboBoNT-A=AbobotulinumtoxinA, ILA=Investigator's live assessment, ITT=intent-to-treat, n=number of subjects, SD=standard deviation, SSA=Subject's self-assessment

FIGURE 1. Subject-reported onset of effect in the subject diary, aboBoNT-A group.



The study population consisted of 88% women and 92% White subjects. Randomized subjects were aged between 21 and 66 years, mean, 44.1 years, and 52% were toxin naive. More details are provided in Table 1.

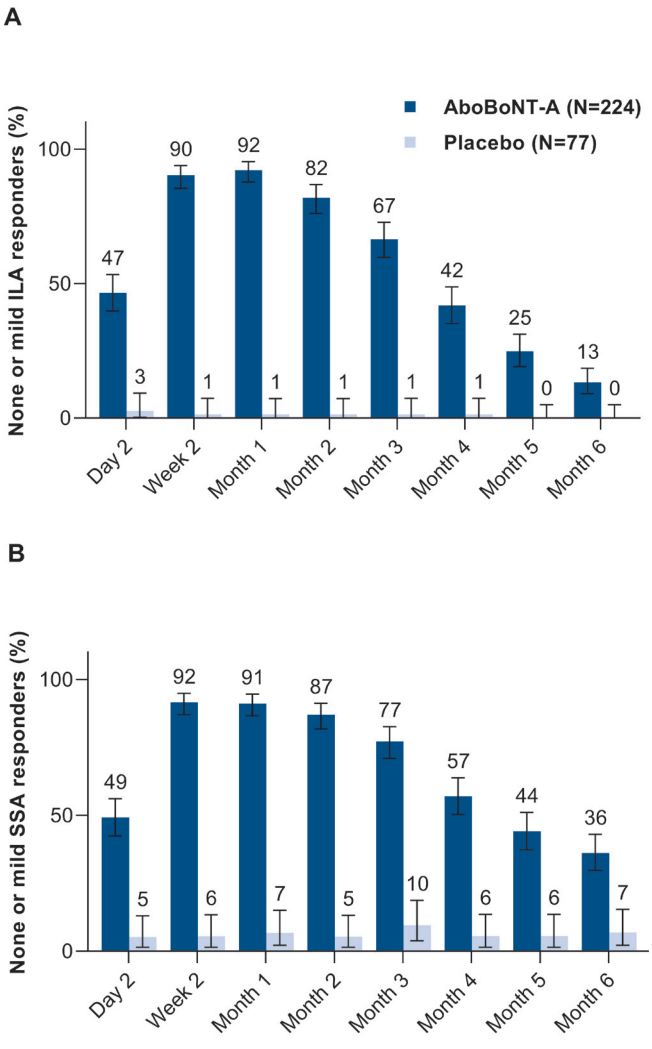
Efficacy

Time to Onset of Response

The median subject-reported time to onset of effect was 2.0 days after aboBoNT-A treatment based on the subject diary, with 34% reporting onset on day 1 and 60% by day 2 (Figure 1). For placebo, no median time to onset could be calculated due to few subjects reporting an effect (11 of 77).

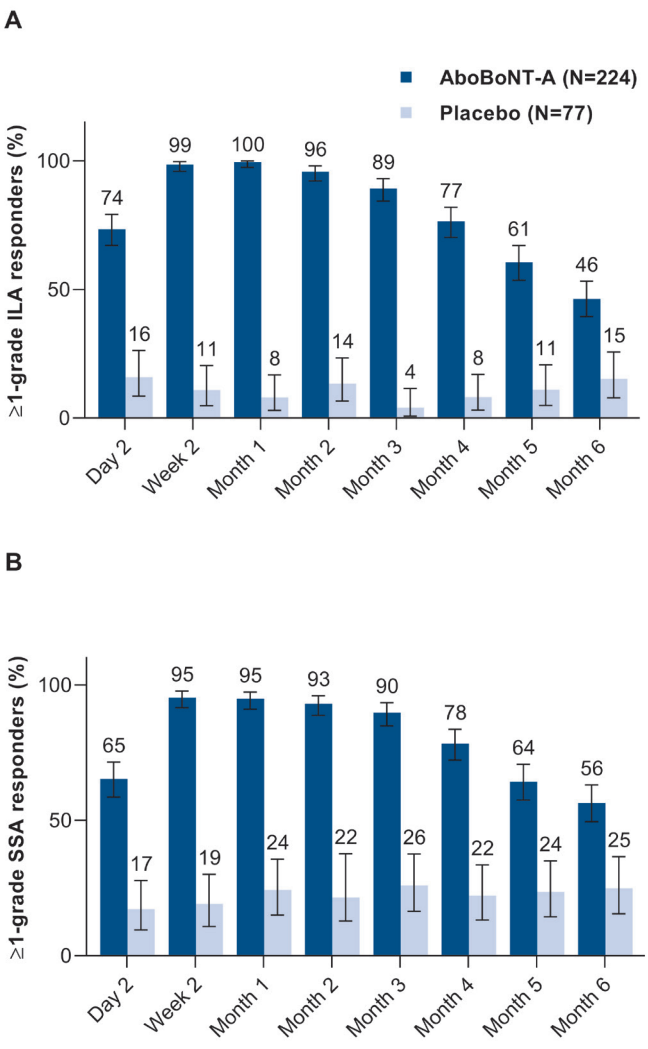
The investigator assessments of GL severity (ILA) at day 2 showed 47% of subjects with none or mild GL severity and

FIGURE 2. None or mild glabellar line severity response at maximum frown on the Investigator's live assessment scale (A) and Subject's self-assessment scale (B), ITT population, observed cases.



Error bars show 95% Clopper-Pearson Confidence Interval.
p<0.001 for aboBoNT-A vs. placebo at each visit.

FIGURE 3. At least 1 grade glabellar line severity improvement at maximum frown on the Investigator's live assessment scale (A) and Subject's self-assessment scale (B), ITT population, observed cases.



Error bars represent 95% Clopper-Pearson Confidence Interval.
p<0.001 for aboBoNT-A vs. placebo at each visit.

74% with a ≥1-grade improvement at maximum frown. Subject assessments (SSA) showed comparable results (Figure 2 and Figure 3).

Glabellar Line Severity Improvement

The composite 2-grade GL responder rate at maximum frown at month 1 (primary endpoint) was significantly higher in the aboBoNT-A group, 65.8% (95% CI: 59.49–72.03), than in the placebo group, 0.0% (95% CI: 0.00–4.68), P<0.001 in the ITT population. Results were similar in the PP population (data not shown).

The highest none-or-mild GL responder rate at maximum frown was 92% of subjects, reached at week 2 in the subject assessments (SSA) and at month 1 in the investigator assessments (ILA). Both scales showed statistically significant, higher none-or-mild severity responder rates for aboBoNT-A compared to placebo from day 2 through month 6 (P<0.001) (Figure 2). In the placebo group, none-or-mild rates were ≤3% on the ILA scale and ≤10% on the SSA scale throughout the 6 month study.

A ≥1-grade improvement from baseline in GL severity at maximum frown was achieved in all subjects treated with aboBoNT-A at month 1 in the investigator assessments (ILA) and in 95% in the subject assessments (SSA). The ≥1-grade responder rates at maximum frown remained significantl higher for the aboBoNT-A group than placebo (P<0.001) throughout 6 months after treatment, both in the ILA and SSA assessments (Figure 3). At month 6, a ≥1-grade improvement in GL severity was reported in 46% of subjects on the ILA scale and 56% of subjects on the SSA scale in the aboBoNT-A group, compared to 15% (ILA) and 25% (SSA) for placebo.

Figure 4 shows treatment results at maximum frown at 1 and 6 months after treatment with aboBoNT-A.

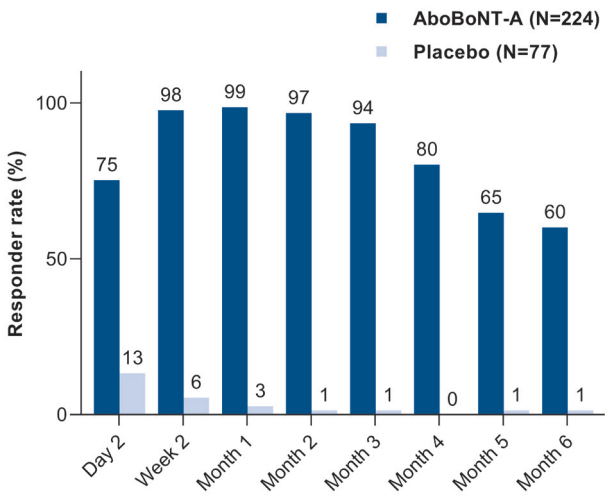
GL severity at rest was improved in 72% of subjects at 1 month after aboBoNT-A treatment versus in 16% for placebo, as assessed by the investigators (ILA). The ≥1-grade improvement responder rates at rest were significantly higher for aboBoNT-A than placebo at all post-treatment visits through month 6 (P<0.001, data not shown). At month 6, 51% (aboBoNT-A) versus 24% (placebo) had a ≥1-grade improvement from baseline at rest.

Duration of Severity Improvement

For subjects who achieved a score of 0 or 1 on both the ILA and the SSA scales concurrently at maximum frown after aboBoNT-A-treatment, the median time to loss of this score on both scales was 163 days (5.4 months) after injection, based on the Kaplan-Meier analyses. At 6 months after injection, >50% of the subjects who achieved a score of 0 or 1 had still not returned to baseline scores, ie, retained at least a 1-grade improvement on one or both scales.

FIGURE 4. Photographs of a 47-year-old female subject at baseline and 1 and 6 months after treatment with 50 U aboBoNT-A.

FIGURE 5. Global aesthetic improvement scale responder rate reported by subjects (mITT population).



Responders include subjects who responded "Improved", "Much improved", or "Very much improved" on the GAIS.

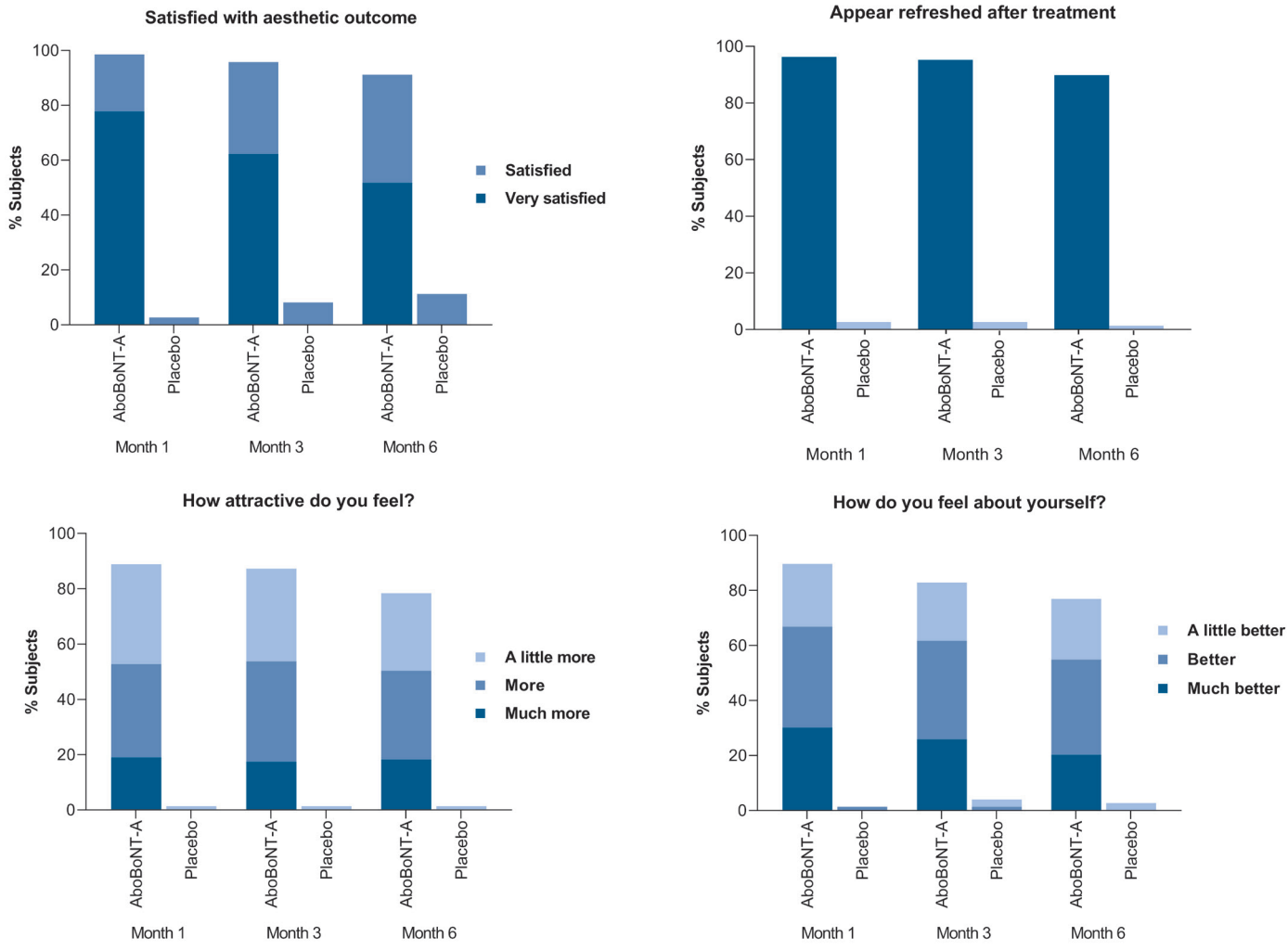
Global Aesthetic Improvement

At peak response (month 1), 99% of subjects in the aboBoNT-A group assessed themselves as aesthetically improved in the GL area in the GAIS assessments. Aesthetic improvement was sustained in 94% through month 3, 80% through month 4 and 60% through month 6. In the placebo group, the GAIS responder rate was ≤13% throughout month 6 (Figure 5).

Subject Satisfaction Questionnaire

From month 1 to month 6, ≥91% of subjects in the aboBoNT-A group were satisfied with the aesthetic outcome of their treatment, ≥90% responded that they appeared refreshed, ≥84% were

FIGURE 6. Subject satisfaction questionnaire (mITT population).



satisfied with their appearance, ≥78% felt more attractive, ≥77% felt better about themselves, ≥68% felt the treatment brought them a less tired look, and ≥60% a more youthful appearance, and almost all subjects in the aboBoNT-A group (≥98%) considered their treatment results to look natural (Figure 6).

A majority of subjects (73%) felt that they looked younger than their age, 1 month after treatment.

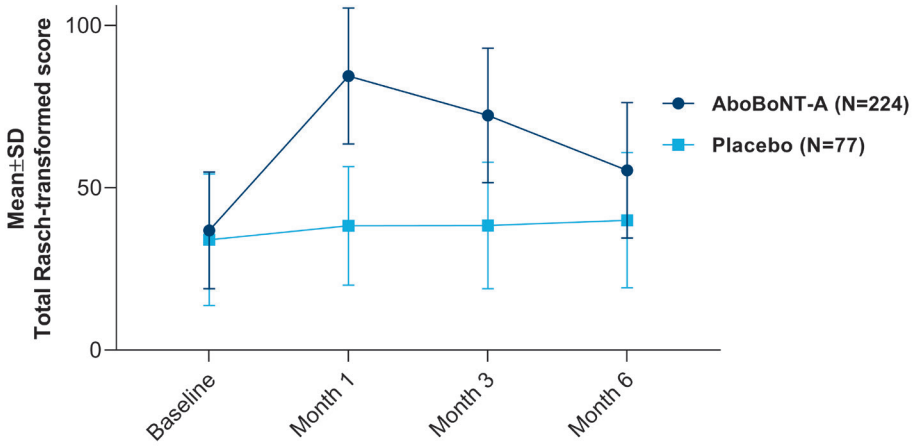
At month 6, 99% of subjects treated with aboBoNT-A responded that they would recommend this treatment to family and 96% that they would like to receive the same treatment again.

Subject-reported FACE-Q Scales

The subject-reported FACE-Q Appraisal of Lines Between the Eyebrows total score increased after treatment with aboBoNT-A, indicating that subjects were less bothered by their GL appearance post-treatment. Mean scores remained higher for aboBoNT-A than placebo from month 1 to month 6, with a peak at month 1 (Figure 7).

In the FACE-Q Psychological Function assessments, measuring concepts such as feeling happiness, confidence, and self-acceptance, the mean total scores showed an improvement in overall subject well-being in the aboBoNT-A group after treatment compared to placebo. Mean scores in the aboBoNT-A group improved after treatment (+9.1 at month 1) and remained higher than baseline throughout the study (+5.5 at month 6). Meanwhile, in the placebo group, there was a consistent decrease in the mean score after treatment (-1.2 at month 1; -3.5 at month 6 compared to baseline).

FIGURE 7. FACE-Q Appraisal of lines between the eyebrows, mITT population.



Subjects tended to perceive themselves as younger after treatment with aboBoNT-A. The largest improvement was at month 1, when subjects reported looking 2.1 years younger than before aboBoNT-A treatment (mean value), while the placebo group increased their perceived age by a mean of 0.4 year at month 1 after treatment.

Safety

An overview of TEAEs is presented in Table 2. Serious events occurred in 4 subjects (1.8%) in the aboBoNT-A group and in no subjects in the placebo group. None of these events were related to treatment.

Treatment-related TEAEs occurred in 10.8% of subjects in the aboBoNT-A group and 7.8% in the placebo group, all were of mild or moderate intensity. The most common treatment-related TEAEs during the study, occurring in >1 subject in total, were headache, eyelid ptosis and injection-site pain (Table 2). Three subjects (1.3%) developed eyelid ptosis after injection of aboBoNT-A. All ptosis events were mild in intensity and resolved without intervention. No new safety signals were identified

TABLE 2.

Treatment-Emergent Adverse Events		
	aboBoNT-A N=223 n (%)	Placebo N=77 n (%)
Any TEAE	55 (24.7)	19 (24.7)
Any treatment-related TEAE	24 (10.8)	6 (7.8)
Most common treatment-related TEAEs (>1 subject in total)		
Headache	19 (8.5)	3 (3.9)
Eyelid ptosis	3 (1.3)	0
Injection-site pain	1 (0.4)	2 (2.6)

aboBoNT-A=AbobotulinumtoxinA, n=number of subjects

DISCUSSION

The aim of this study was to evaluate GL treatment using a new higher dilution of the 300-U-vial of aboBoNT-A powder, and a volume of injection of 0.1 mL. The safety results for this injection volume were consistent with the well-known safety profile of aboBoNT-A and in-line with the current prescribing information.[1,7-9] No new safety signals were identified. Treatment with aboBoNT-A was well tolerated and there was a low rate of injection site pain (0.4% in the aboBoNT-A group). All treatment-related TEAEs were non-serious and mild or moderate in intensity. Eyelid ptosis, all of mild intensity, was reported in 1.3% of subjects, which is lower than in the prescribing information for aboBoNT-A,[1] and for other toxin products used in glabellar line treatment including onabotulinumtoxinA[10] and prabotulinumtoxinA-xvfs,[11] indicating no increase in local spread of toxin with the larger injection volume of aboBoNT-A.

The present study confirmed efficacy also for this dilution and injection volume, including a rapid onset of effect, with a median time to onset of 2 days reported in the subject diary, and a ≥1-grade improvement in GL severity on day 2 reported for 74% and 65% of subjects in the investigator- and subject-assessments, respectively. This is similar to the onset time for aboBoNT-A demonstrated in prior studies.[3,8,12-14]

In line with previously reported data on aboBoNT-A,[7,13] high responder rates were attained on both GL severity scales at 2–4 weeks after treatment with the 0.1-mL-injection volume, including a none-or-mild response in 92% of subjects and a ≥1-grade response in 95%–100% of subjects. The GL severity improvement was sustained up to 6 months after aboBoNT-A treatment, with statistically significant higher responder rates over placebo both in the investigator and subject assessments. Approximately half of the subjects (46% based on ILA; 56%

based on SSA) maintained a ≥1-grade improvement at 6 months after aboBoNT-A treatment, similar to in prior aboBoNT-A studies with the 0.05-mL-volume of injection (Joseph et al, *manuscript in preparation*).[7,8] GAIS results also showed maintained aesthetic improvement in a large proportion of subjects (60%) in the aboBoNT-A group at 6 months, further supporting a long duration of effect also with this dilution.

Importantly, the treatment effects of aboBoNT-A in this study translated into high rates of subject satisfaction, persisting for up to 6 months; ≥91% were satisfied with the aesthetic outcome of their treatment, ≥98% found the results natural-looking, and ≥77% reported broader positive effects of treatment such as feeling more attractive and feeling better about themselves. The FACE-Q scale results confirmed improvement in both satisfaction with GL appearance and psychological well-being, which has also been shown in prior studies with different dilutions of aboBoNT-A.[15]

Overall, the results from this new dilution study confirme those obtained in the previously published Phase IV study[3] comparing GL treatment with aboBoNT-A using the 0.1 mL versus 0.05 mL injection volume. By this study, we have even more data showing the safety and efficacy of treatment with aboBoNT-A, confirming the rapid onset, long duration, and high subject satisfaction. The safety profile was maintained and there were no signs of increased local spread of toxin with the higher dilution and larger injection volume.

CONCLUSION

In summary, injections with 50 U of aboBoNT-A, using the new dilution resulting in 0.1 mL injection volume per 10 U, was a safe and highly effective treatment of moderate-to-severe GL, with rapid onset and effects persisting for up to 6 months. Aesthetic improvement and subject satisfaction were sustained throughout 6 months.

DISCLOSURES

J. Schlessinger is a clinical trial investigator and paid consultant for Galderma, Merz and Allergan and a shareholder of Allergan and Evolus. D.P. Friedmann is a clinical trial investigator for Galderma. F. Mayoral is a clinical trial investigator for Galderma. D. Mraz Robinson is a clinical trial investigator for Galderma. D.A. Glaser is a clinical trial investigator for Galderma. D. Wu is a clinical trial investigator for Galderma. Dr. Marcus is a clinical trial investigator for Galderma, a speaker for Galderma, Allergan, and Evolus, a trainer for Galderma, and Merz, and an advisory board member for Galderma, Allergan, Merz, and Evolus. Dr. Somenek is a clinical trial investigator for Galderma, a speaker for Galderma, Cutera, Lutronic, and Aesthetics Biomedical, a trainer for Galderma and Allergan, and an advisory board member for Galderma. X. Lin is an employee at Galderma.

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