Translations

Cosmetic Medicine

Long-term Efficacy and Safety of Liquid AbobotulinumtoxinA Formulation for Moderate-to-Severe Glabellar Lines: A Phase III, Double-Blind, Randomized, Placebo-Controlled and Open-Label Study

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Abstract

Background: A ready-to-use liquid formulation of abobotulinumtoxinA (aboBoNT-A solution) has been developed.
Objectives: The aim of this study was to assess the long-term efficacy and safety of aboBoNT-A solution for the treatment of glabellar lines.
Methods: This was a multicenter, multinational, Phase III study (NCT02493946), with randomized double-blind placebo-controlled (DBPC; 2:1 aboBoNT-A solution 50 U/placebo) and open-label (4 cycles aboBoNT-A solution) periods; additional patients were recruited into the open-label period. Patients were 18 to 65 years old, BoNT-naïve, and dissatisfied/very dissatisfied with moderate/severe glabellar lines at maximum frown. Investigator's live assessment (primary endpoint)/subject's self-assessment of glabellar line severity at maximum frown, patient satisfaction with glabellar line appearance, and FACE-Q patient-reported scales (facial appearance overall, psychological well-being, aging) were assessed. Adverse events were monitored. Analyses were performed on DBPC and long-term analysis (LTA; all patients receiving ≥1 aboBoNT-A solution injection) populations.
Results: Responder rates for the investigator's live assessment, the subject's self-assessment, and patient satisfaction were consistent at Day 29 postinjection across repeat LTA cycles (82.2%-87.8%, 62.8%-80.6%, and 72.2%-87.8%, respectively), with statistically significantly higher responder rates vs placebo (DBPC cycle: 81.6% vs 0.8%, 68.1% vs 2.3%, and 83.1% vs 5.7%, respectively; all $P < 0.0001$). Consistent improvements on FACE-Q scales occurred with repeat cycles (DBPC cycle: aboBoNT-A solution vs placebo, $P < 0.0001$). No new or unexpected adverse events, or neutralizing antibodies, were observed.
Conclusions: These results support the long-term efficacy and safety of aboBoNT-A solution, and its superiority over placebo, for treatment of glabellar lines in adults.

Resumo

Justificativa: Foi desenvolvida uma formulação líquida pronta para uso de abobotulinumtoxinA (solução de aboBoNT-A).
Objetivos: O objetivo deste estudo foi avaliar a eficácia e a segurança em longo prazo da solução aboBoNT-A para o tratamento das linhas glabelares (rugas de expressão).

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Métodos: Este é um estudo multicêntrico, multinacional, de Fase III (NCT02493946), com períodos duplo-cego randomizados controlados por placebo (DBPC; solução 2:1 aboBoNT-A 50 U/placebo) e aberto (quatro ciclos com solução aboNT-A); pacientes adicionais foram recrutados para o período aberto. A faixa etária dos pacientes era de 18 a 65 anos de idade, sem BoNT e insatisfeitos/muito insatisfeitos com linhas glabelares moderadas/graves na região central da testa. Foram analisadas a avaliação ao vivo do investigador (desfecho primário)/autoavaliação do participante da gravidade da linha glabelar na região central da testa, satisfação do paciente com o aspecto da linha glabelar e escalas FACE-Q (aspecto facial geral, bem-estar psicológico, envelhecimento) relatadas pelo paciente. Os eventos adversos foram monitorados. As análises foram realizadas em populações de DBPC e análise de longo prazo (LTA; todos os pacientes recebendo ≥1 injeção de solução de aboBoNT-A).
Resultados: As taxas de resposta da avaliação ao vivo do investigador, a autoavaliação do participantes e a satisfação do paciente foram consistentes no dia 29 após a injeção em ciclos repetidos de LTA (82,2%-87,8%, 62,8%-80,6% e 72,2%-87,8%, respectivamente), com taxas de resposta estatisticamente significativamente mais altas em comparação com o placebo (ciclo de DBPC: 81,6% vs. 0,8%, 68,1% vs. 2,3% e 83,1% vs. 5,7%, respectivamente; todos P <0,0001). Ocorreram melhorias sistemáticas nas escalas FACE-Q com ciclos repetidos (ciclo DBPC: solução aboBoNT-A vs. placebo, P <0,0001). Não foram observados eventos adversos novos ou inesperados ou anticorpos neutralizantes.
Conclusões: Esses resultados apoiam a eficácia e segurança em longo prazo da solução aboBoNT-A, bem como sua superioridade em relação ao placebo, no tratamento de linhas glabelares em adultos.

Level of Evidence: 1

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The safety and efficacy of botulinum neurotoxin type A (BoNT-A) for the treatment of glabellar lines have been well established, with BoNT-A products being administered worldwide for the aesthetic treatment of facial lines.[1,2] The 3 most commonly used BoNT-A products are abobotulinumtoxinA (aboBoNT-A powder; Dysport, Ipsen Ltd, Slough, UK/Azzalure, Galderma SA, Lausanne, Switzerland), incobotulinumtoxinA (Bocouture/Xeomin, Merz Pharmaceuticals, Inc., Frankfurt, Germany), and onabotulinumtoxinA (Vistabel/Botox, Allergan, Inc., Irvine, CA).[3-8] These current, widely used formulations of BoNT-A are provided as a lyophilized or vacuum-dried powder that requires reconstitution before injection.

A unique, ready-to-use solution of aboBoNT-A for injection (aboBoNT-A solution; Alluzience, Ipsen/Galderma, Lausanne, Switzerland) has been developed and investigated in patients with moderate-to-severe glabellar lines.[9-11] This liquid BoNT-A formulation is an important innovation in aesthetic medicine. It may provide benefit over existing powder formulations for both injectors and patients in terms of convenience of injection because there is no need for reconstitution, thereby reducing preparation time and allowing injectors more time to focus on the patient. Additionally, aboBoNT-A solution may provide benefits in terms of consistency and precision of dosing because it is provided at a single, ready-to-use concentration.

In a Phase II, single-cycle, double-blind, placebo- and active comparator–controlled study,[9] and a Phase III, single-cycle, double-blind, placebo-controlled study,[10] aboBoNT-A solution (50 U) provided high levels of efficacy in the treatment of moderate-to-severe glabellar lines, as assessed by both the investigators and patients. At Day 29 postinjection, the proportion of patients who were treatment responders (glabellar line severity rated by investigator as "none" or "mild") following treatment with aboBoNT-A solution was 91.4% and 88.3% in the Phase II and Phase III studies, respectively (both $P < 0.0001$ compared with placebo).[9,10] The Phase III study of aboBoNT-A solution also demonstrated high levels of patient satisfaction with the appearance of glabellar lines following treatment (80.9% at Day 29), as well as significant improvements compared with placebo on the FACE-Q patient-reported outcome measure scales for satisfaction with facial appearance overall, psychological well-being, and aging appearance.[10,11] Furthermore, a long duration of action was demonstrated during the Phase III study of up to 6 months postinjection.[10] AboBoNT-A solution was well-tolerated in both the Phase II and Phase III studies, with no new or unexpected adverse events (AEs) compared with the known profile of BoNT-A products.[9,10] However, data for both these studies were only collected over a single treatment cycle.

The present study aimed to assess the efficacy and safety of aboBoNT-A solution 50 U for improving the appearance of moderate-to-severe glabellar lines in adult patients both during a single double-blind placebo-controlled (DBPC) cycle and over repeat treatment cycles. As per the

previous Phase III study, this study also aimed to evaluate treatment from the patient perspective through the use of multiple patient-reported outcome measures.

METHODS

Study Design

This was a multicenter, multinational, Phase III study of aboBoNT-A solution for the treatment of moderate-to-severe glabellar lines, consisting of a single-treatment, randomized DBPC period, followed by a repeat-cycle open-label period in which all patients received aboBoNT-A solution (NCT02493946; EudraCT: 2014-003841-86). Additional de novo patients were enrolled into the open-label period. The primary objective of this study was to demonstrate the superiority of aboBoNT-A solution over placebo, according to the investigator's live assessment (ILA) of the appearance of glabellar lines at maximum frown on Day 29 of the DBPC period.

This study was conducted at 24 sites across France (6 sites), Germany (16 sites), and the UK (2 sites) between April 2015 and December 2016; 12 of these sites recruited patients for the DBPC period. Recruitment was stopped when approximately 180 patients had been randomized, and enrollment of patients entering open-label Cycle 1 was stopped when approximately 400 additional patients had been enrolled.

Where patient data can be anonymized, Ipsen (Paris, France) will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

Patients

All patients (including de novo patients enrolled into the open-label period) were adults aged between 18 and 65 years, inclusive, with moderate or severe vertical glabellar lines at maximum frown at baseline, as determined by the ILA,[12] and by the subject's self-assessment (SSA) (as defined in the section Assessments and Endpoints). Patients were required to have a patient satisfaction score of dissatisfied or very dissatisfied with their glabellar lines at baseline (as defined in the section Assessments and Endpoints), and to be naïve to treatment with any serotype of botulinum neurotoxin. Patients had to have both the time and the ability to complete the study and comply with study instructions.

Exclusion Criteria

Exclusion criteria were as follows: prior treatment with any serotype of botulinum neurotoxin, or a known allergy or hypersensitivity to any component of aboBoNT-A solution 50 U; prior treatment in the upper face with permanent fillers, dermal fillers (within 3 years of enrollment), skin abrasions/resurfacing (within 5 years), photorejuvenation (within 12 months), eyelid blepharoplasty/brow lift (within 5 years), or any planned facial cosmetic surgery during the study; use of concomitant therapy that, in the investigators' opinion, would have interfered with safety or efficacy evaluations, including medications for bleeding disorders; use of medications affecting neuromuscular transmission (within 30 days); or treatment with an experimental drug or devices (within 30 days); an inability to substantially reduce glabellar lines by physically spreading them, or to frown; an active infection, or other skin problem, affecting the upper face; a history of facial nerve palsy, or marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin, or the presence of any other condition (eg, disorders affecting neuromuscular function), laboratory finding, or circumstance that may have, in the investigators' opinion, increased the risk to the patient or impact upon the study results; a clinically diagnosed anxiety, or other psychiatric, disorder that could have interfered with study participation; a history of drug abuse; female patients who were pregnant, nursing, or planning a pregnancy during the study.

Treatment and Follow-up

Patients entering the DBPC period were randomized 2:1 to receive a single treatment cycle of either aboBoNT-A solution 50 U or placebo. AboBoNT-A solution and matched placebo (liquid containing only the excipients of aboBoNT-A solution) were provided in per-patient vials with each vial containing a volume of 0.625 mL. The concentration of aboBoNT-A solution was 200 U/mL. For injection, aboBoNT-A solution or placebo was evenly distributed across 5 predefined intramuscular sites (procerus, left and right corrugator, left and right lateral corrugator/orbicularis; 0.05 mL per injection site).

Randomization was performed in blocks at a 2:1 ratio of aboBoNT-A/placebo based on computer-generated randomization lists, developed by a statistician independent from the study and managed by an interactive web response system service (IWRS). Randomization numbers were stratified according to gender and baseline glabellar line severity at maximum frown (moderate or severe), as assessed by the ILA.

Eligible patients were assigned a randomization number at baseline and allocated to the associated treatment arm by the IWRS. Once the DBPC period enrollment target for randomized patients was reached, the IWRS continued to

allocate appropriate treatment numbers to de novo patients entering open-label Cycle 1 directly until the overall study enrollment target was reached.

The randomization lists were kept confidential at a secure location, and access was restricted until authorization was given to unblind for analysis. One set of individual sealed code break envelopes was provided to the sponsor's Global Patient Safety Department to allow for emergency code break for individual patients without compromising the blinding of the study. In the event that a medical emergency occurred requiring urgent unblinding of a patient, the investigator and/or the sponsor's Global Patient Safety department could have broken the blinding by asking the IWRS to obtain the patient's treatment identification, and any such event was to be documented in the electronic care report form. However, no emergency unblindings occurred in this study.

Those patients who completed the DBPC period could continue into the open-label period and receive up to 4 additional treatment cycles with aboBoNT-A solution 50 U. De novo patients recruited into the open-label period could also receive up to 4 treatment cycles with aboBoNT-A solution.

Patients were eligible for retreatment if a minimum of 12 weeks had elapsed since prior treatment, glabellar line severity was moderate or severe (as judged by both ILA and SSA at maximum frown), and there were no ongoing treatment-related AEs that would preclude treatment. No retreatment was permitted to be administered after 12 months since first study treatment.

Posttreatment visits occurred at Days 4, 8, 29, 57, and 85 for each treatment cycle. If a patient was not eligible for retreatment at Day 85, they would continue to be evaluated for retreatment every 28 days until eligible, or until study completion. Patients completed the study after 12 months since their first treatment and a minimum of 12 weeks since their last treatment (maximum study duration of 15 months if retreated at 12 months).

Assessments and Endpoints

Investigator-Assessed Outcome Measure

Investigators assessed the appearance of glabellar lines according to a validated 4-point photographic severity scale:[12] none (Grade 0), mild (Grade 1), moderate (Grade 2), and severe (Grade 3). The ILA of glabellar line severity at maximum frown and at rest was performed before treatment on Day 1 of each cycle and at each posttreatment visit to the study center.

The primary efficacy endpoint of this study was response to treatment assessed by the ILA of glabellar line severity at maximum frown on Day 29 of the DBPC cycle. Responders were defined as patients who had a rating of none or mild at a given posttreatment visit. An additional endpoint for the ILA defined responders as patients who achieved an improvement from baseline of at least 1 grade on the photographic severity scale (described above) at a given posttreatment visit.

Patient-Assessed Outcome Measures

The SSA of glabellar line severity at maximum frown was determined according to a 4-point categoric scale: no wrinkles (Grade 0), mild wrinkles (Grade 1), moderate wrinkles (Grade 2), and severe wrinkles (Grade 3). SSA was performed before and independently of the ILA, and responders were defined as patients with no or mild wrinkles at a given posttreatment visit. An additional endpoint for SSA defined responders as patients who achieved an improvement from baseline of at least 1 grade on the categoric scale (described above) at a given posttreatment visit.

A patient's level of satisfaction with the appearance of their glabellar lines was evaluated with a 4-point categoric scale: very satisfied (Grade 0), satisfied (Grade 1), dissatisfied (Grade 2), and very dissatisfied (Grade 3). Responders were defined as having a satisfaction rating of very satisfied or satisfied at a given posttreatment visit.

Three scales from the FACE-Q patient-reported outcome instrument[13,14] were also used to evaluate the patients' perspective of their experience and outcomes of their treatment during this study:

- Satisfaction with facial appearance overall scale: 10 questions were asked about the patients' facial appearance, eg, "How rested does your face look?," and patients responded on a 4-point scale from very dissatisfied (1) to very satisfied (4).
- Psychological well-being scale: patients were asked to indicate their levels of agreement with 10 statements regarding their psychological well-being, eg, "I feel positive about myself," on a 4-point scale from definitely disagree (1) to definitely agree (4).
- Aging appearance appraisal visual analogue scale: patients were asked to indicate how they felt about their appearance with respect to aging on a visual analogue scale ranging from –15 ("I look 15 years younger") to +15 ("I look 15 years older").

Full details of the FACE-Q scales and associated questions have been published previously.[11,13-15]

For the FACE-Q satisfaction with facial appearance overall and psychological well-being scales, a Rasch transformed score was calculated by adding the scores for the 10 items and converting the score to a scale from 0 to 100.

SSA, patient satisfaction, and FACE-Q scale patient-reported outcome measures were study-specific standardized paper documents that were identifiable only by each patient's number and included instructions for completion associated with the specific tool. They were distributed by

each study center for completion by the patient and were assessed before treatment on Day 1 of each cycle and at all posttreatment visits to the study center.

Onset of treatment response was also recorded by patients on a diary card during the first week postinjection (Days 1-7) of the DBPC cycle. Onset was defined as a positive response to treatment, ie, an answer of "yes" to the question "Since being injected have you noticed any effect on the appearance of your glabellar lines?"

Safety

Treatment-emergent AEs (TEAEs) and vital signs were monitored throughout the study. Blood samples were tested with a mouse protection assay for the presence of neutralizing antibodies to BoNT-A during the study (after initial screening of samples for binding antibodies by radioimmunoprecipitation assay).

Statistical Analyses

The sample size for the DBPC period was driven by the need to provide adequate active treatment and placebo data for the assessment of safety (aboBoNT-A solution, n = 120; placebo, n = 60). Only a relatively small number of patients (n = 27) was required to demonstrate superiority of aboBoNT-A solution compared with placebo, based on an 80% and 10% response rate, respectively (2-sided test powered at 95% with a type I error rate of 0.05) and an expected drop-out of 5%. For the open-label cycles, to allow for appropriate safety assessment of repeat treatment a further 400 de novo patients were planned to be enrolled.

The modified intention-to-treat (mITT) population (DBPC period only) was defined as all randomized patients who received treatment and who had both baseline and at least 1 posttreatment value for the ILA of glabellar lines at maximum frown, and patients were analyzed by allocated treatment at randomization. The safety population (DBPC period only) was defined as all randomized patients who received treatment, and patients were analyzed by treatment actually received. The long-term analysis (LTA) population included all patients (enrolled during the DBPC period and de novo patients enrolled during the open-label period) who received at least 1 injection of aboBoNT-A solution. In the LTA population, Cycle 1 represents the first injection cycle where aboBoNT-A solution 50 U was injected, regardless of whether this was in the DBPC or the open-label period. Therefore, for patients who participated in both study periods and received aboBoNT-A solution in the DBPC period, data are presented for up to 5 aboBoNT-A solution 50 U treatment cycles. Efficacy endpoints from the DBPC period were assessed in the mITT population and safety analyses were based on the safety population. Long-term efficacy and safety analyses were also assessed in the LTA population. All statistical analyses were performed with SAS version 9.4.

The proportion of responders in the DBPC period for the ILA (rated none or mild), the SSA (rated no or mild wrinkles), and the patient's level of satisfaction (rated satisfied or very satisfied) were analyzed by a multivariate logistic regression model controlling for study center and stratification factors (ie, gender and baseline ILA at maximum frown) as fixed effects, and were reported as the adjusted proportion of responders and 95% CI in each treatment group. For the LTA, summary statistics were provided. The proportion (95% CI) of patients with a 1-grade improvement from baseline on the ILA and SSA of glabellar lines at maximum frown is also reported in each treatment group (post-hoc analysis in the DBPC period only), analyzed with a generalized linear model with treatment group, gender, and baseline severity score on the ILA at maximum frown as fixed effects; patients with missing data at a visit are considered as nonresponders.

For the FACE-Q scales (satisfaction with facial appearance overall, psychological well-being, and aging appearance) during the DBPC period, change from baseline in the Rasch transformed scores were analyzed with a linear regression model, controlling for baseline score, center, and stratification factors as fixed effects. Adjusted means (least squares means), standard error, and 95% CI values were provided by treatment group for each FACE-Q scale. For the LTA, descriptive analyses are provided.

Time to onset was analyzed for the DBPC period with a log-rank test and a Cox proportional hazard model including treatment group, center, and stratification factors as fixed effects. Kaplan-Meier estimates (presented with standard error) of the cumulative rate of responses and the median time (with 95% CI) to onset are summarized by treatment group.

Ethics Approvals

This study was conducted in accordance with the Declaration of Helsinki, and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. Approval of the study protocol and informed consent form was obtained from independent ethics committees and IRBs before commencement of the study. The following is a full list of the approving bodies:

- CPP Sud-Mediterranee V CHU de Nice—Hopital de Cimiez, Nice, France
- LEC Landesamt für Gesundheit und Soziales Berlin and Geschäftsstelle der Ethik-Kommission des Landes Berlin, Berlin, Germany
- LEC Ethikkommission der Med. Fakultät der LMU München, München, Germany
- LEC Ethik-Kommission der Ärztekammer Nordrhein, Düsseldorf, Germany

- LEC Ethik-Kommission der Ärztekammer Hamburg, Hamburg, Germany
- CEC Ethik-Kommission der Landesärztekammer in Hessen, Frankfurt, Germany
- LEC Ethik Kommission der Universität Witten-Herdecke, Witten, Germany
- LEC Ethik-Kommission des Fachbereichs Medizin der Johann Wolfgang Goethe-Universität, Frankfurt, Germany
- LEC Ethik-Kommission der Bayerischen Landesärztekammer, München, Germany
- LEC Landesärztekammer Brandenburg Ethikkommission, Cottbus, Germany
- LEC Ethikkommission der Landesärztekammer Rheinland-Pfalz, Mainz, Germany
- LEC Ethik-Kommission bei der Ärztekammer Niedersachsen, Hannover, Germany
- LEC Ethik-Kommission bei der Landesärztekammer Baden-Württemberg, Stuttgart, Germany
- LEC Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität Münster, Münster, Germany
- NRES Committee East Midlands, Nottingham, UK

All patients provided written informed consent at the screening visit prior to study enrollment.

Consolidated Standards of Reporting Trials (CONSORT) Statement

The present study was reported in accordance with CONSORT 2010 guidelines (Appendix A, available online at www.aestheticsurgeryjournal.com).

RESULTS

Baseline Characteristics and Patient Disposition

Baseline characteristics for patients in the DBPC period and LTA population are presented in Table 1. These were similar between treatment groups and for those patients analyzed in the DBPC period and the overall LTA population. The mean [standard deviation] (minimum; maximum) age was 47.8 [9.4] (25; 65) years in the aboBoNT-A solution group and 47.2 [9.0] (24; 64) years in the placebo group for the DBPC period, and 46.6 [10.0] (21; 65) years for the LTA population. The proportion of patients (n/N) who were female was 91.3% (115/126), 90.6% (58/64), and 89.1% (530/595), respectively. Glabellar line severity and patient satisfaction with glabellar lines at baseline of each cycle are presented in Table 2.

Overall, 190 patients were randomly allocated and received treatment in the DBPC period, of whom 126 received aboBoNT-A solution and 64 received placebo (Figure 1A). There were 185 patients from the DBPC period included in the LTA population, and a further 410 de novo patients were enrolled into the open-label period and received at least 1 treatment of aboBoNT-A solution (total, N = 595 patients in the LTA population; Figure 1B). Full details of patient disposition in the DBPC and LTA periods, as well as withdrawals and exclusions through the study, are detailed in Figure 1A,B.

Across all patients included in the study (N = 600, DPBC period and/or open-label period), the mean duration of follow-up was 377.2 [96.4] days (range, 5-479 days).

Investigator-Reported Assessments

The proportion of responders by the ILA of glabellar lines at maximum frown at Day 29 of the DBPC period (primary endpoint) demonstrated the statistically significant superiority of aboBoNT-A solution over placebo ($P < 0.0001$; Figure 2). Across the repeated aboBoNT-A solution treatment cycles (LTA population), the proportion of responders at Day 29 was consistent, with between 82.2% and 87.8% of patients reported as responders to treatment across Cycles 1 to 5 (Figure 2).

Responder rates at all visits up to Day 85 are presented in Supplemental Table 1, available online at www.aestheticsurgeryjournal.com. The overall proportion of responders in Cycles 2 to 4 (LTA population) was consistently higher than in Cycle 1 at all visits through to Day 57.

In a post-hoc analysis, 94.3% of patients who received aboBoNT-A solution showed an improvement from baseline of at least 1 severity grade by the ILA of glabellar lines at maximum frown on Day 29 postinjection, compared with 11.2% in the placebo group ($P < 0.0001$; Supplemental Figure 1A, available online at www.aestheticsurgeryjournal.com).

The proportion of responders by the ILA of glabellar lines at rest at Day 29 postinjection was also consistent across repeated aboBoNT-A solution treatment cycles, with responder rates of between 78.0% and 84.2% (LTA population; Supplemental Figure 2, available online at www.aestheticsurgeryjournal.com). The proportion of responders at rest was slightly higher at Day 29 of all LTA cycles compared with the DBPC cycle, where the proportion of responders at rest was 62.2% compared with 5.4% in the placebo group ($P < 0.0001$).

Patient-Reported Assessments

The proportion of responders by the SSA of glabellar lines at maximum frown (Figure 3A) was consistent across repeated aboBoNT-A solution treatment cycles (between 62.8% and 80.6% at Day 29; LTA population). The SSA responder rates at maximum frown were also statistically significantly higher

Table 1. Baseline Patient Characteristics for the DBPC (Randomized Population) and LTA Cycles (LTA Population)

Patient characteristic	DBPC period		LTA period[a]
	AboBoNT-A solution 50 U (N = 126)	Placebo (N = 64)	AboBoNT-A solution 50 U (N = 595)
Gender			
Female, n (%)	115 (91.3)	58 (90.6)	530 (89.1)
Male, n (%)	11 (8.7)	6 (9.4)	65 (10.9)
Mean age, years [SD] (min; max)	47.8 [9.4] (25; 65)	47.2 [9.0] (24; 64)	46.6 [10.0] (21; 65)
Race, n (%)			
Asian	0	0	1 (0.2)
Black or African American	1 (0.8)	0	1 (0.2)
Caucasian/White	125 (99.2)	64 (100.0)	589 (99.0)
American Indian	0	0	1 (0.2)
Other	0	0	3 (0.5)

AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; LTA, long-term analysis; SD, standard deviation. [a]This population of 595 patients consisted of 185 patients from the DBPC period and 410 additional patients recruited directly into open-label period.

Table 2. Glabellar Line Assessments at Baseline of the DBPC (Randomized Population) and LTA Cycles (LTA Population)

Glabellar line assessments	DBPC period		LTA period[a]				
	AboBoNT-A solution 50 U (N = 125)	Placebo (N = 63)	Cycle 1 (N = 595)	Cycle 2 (N = 558)	Cycle 3 (N = 486)	Cycle 4 (N = 319)	Cycle 5 (N = 89)
ILA at maximum frown, n (%)							
None	0	0	0	0	0	0	0
Mild	0	0	0	0	1 (0.2)	1 (0.3)	0
Moderate	58 (46.4)	29 (46.0)	260 (43.7)	413 (74.0)	395 (81.3)	263 (82.4)	74 (83.1)
Severe	67 (53.6)	34 (54.0)	335 (56.3)	145 (26.0)	90 (18.5)	55 (17.2)	15 (16.9)
SSA at maximum frown, n (%)							
No wrinkles	0	0	0	2 (0.4)	0	1 (0.3)	0
Mild wrinkles	0	0	1 (0.2)	26 (4.7)	8 (1.6)	3 (0.9)	1 (1.1)
Moderate wrinkles	63 (50.4)	22 (34.9)	277 (46.6)	398 (71.3)	383 (78.8)	260 (81.5)	69 (77.5)
Severe wrinkles	62 (49.6)	41 (65.1)	317 (53.3)	132 (23.7)	95 (19.5)	55 (17.2)	19 (21.3)
Patients' level of satisfaction with glabellar lines, n (%)							
Very satisfied	0	0	0	11 (2.0)	10 (2.1)	2 (0.6)	1 (1.1)
Satisfied	0	0	0	94 (16.8)	73 (15.0)	50 (15.7)	14 (15.7)
Dissatisfied	81 (64.8)	40 (63.5)	364 (61.2)	395 (70.8)	362 (74.5)	243 (76.2)	62 (69.7)
Very dissatisfied	44 (35.2)	23 (36.5)	231 (38.8)	58 (10.4)	41 (8.4)	24 (7.5)	12 (13.5)

AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; ILA, investigator's live assessment; LTA, long-term analysis; SSA, subject's self-assessment. [a]This population of 595 patients consisted of 185 patients from the DBPC period and 410 additional patients recruited directly into open-label period.

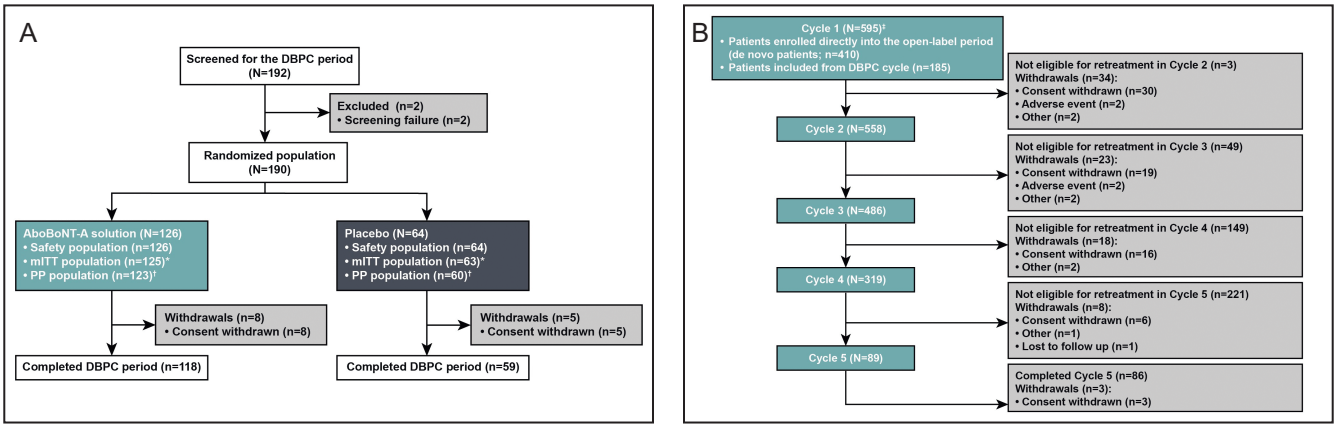

Figure 1. Patient disposition flow diagram. (A) DBPC period. (B) LTA cycles (LTA population). Patients were eligible for injection at the subsequent treatment cycle if: glabellar lines were assessed as moderate or severe by the ILA and SSA at maximum frown; at least 12 weeks had elapsed since previous treatment; and there were no ongoing treatment-related adverse events that would preclude the patient from retreatment. In total, 37 patients received a single injection cycle, 72 received 2 cycles, 167 received 3 cycles, 230 received 4 cycles, and 89 received 5 cycles of aboBoNT-A solution. *Exclusion for lack of posttreatment evaluation of ILA at maximum frown (aboBoNT-A solution, n = 1; placebo, n = 1). †Exclusion for protocol deviations: received facial aesthetic treatment (Acnatac) in violation of the protocol (aboBoNT-A solution, n = 1); no evaluation of primary efficacy endpoint at Day 29 (aboBoNT-A solution, n = 2; placebo, n = 3); significant deviations from time windows at Day 29 ± 1 week (placebo, n = 1). ‡LTA Cycle 1 included the first injection cycle of aboBoNT-A solution for all patients during the study. For de novo patients, this is Cycle 1 of the open-label period; for patients included in the DBPC period, this is the DBPC cycle treatment for those who received aboBoNT-A solution; and the first open-label aboBoNT-A solution treatment for those who received placebo (n = 5 patients in the DPBC placebo group did not continue to the open-label period). Thus data for the DBPC mITT population and LTA population overlapped at Cycle 1 for n = 126 patients. From Cycle 2, all treatments were open-label; for those patients who received aboBoNT-A solution during the DBPC period, Cycle 2 was their first open-label injection. AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; ILA, investigator's live assessment; LTA, long-term analysis; mITT, modified intention-to-treat; PP, per protocol; SSA, subject's self-assessment.

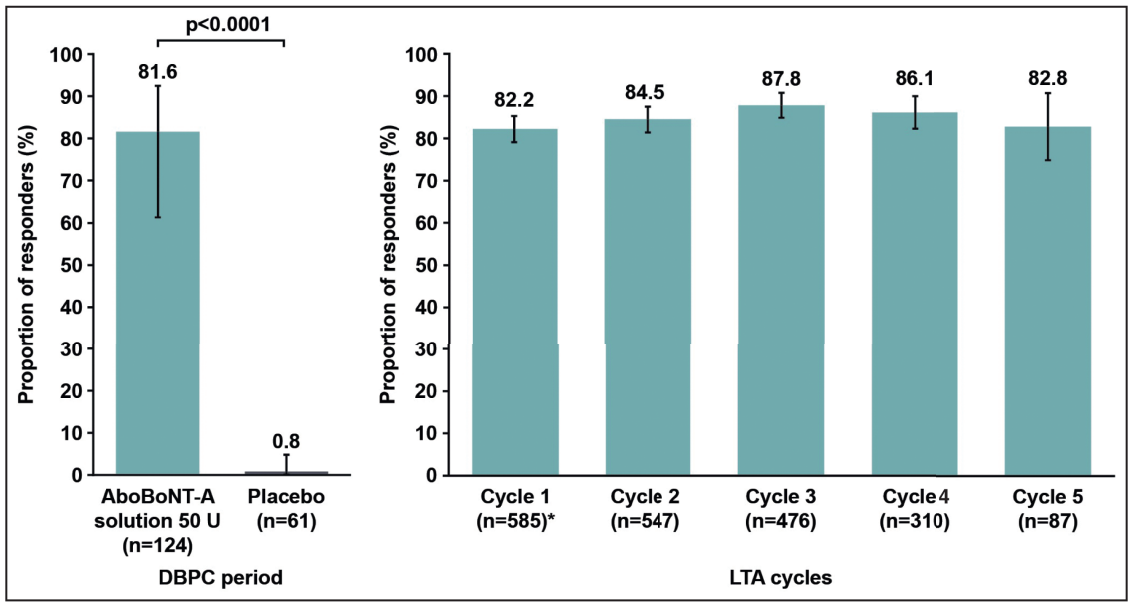

Figure 2. Proportion of responders on Day 29 of each treatment cycle (DBPC period, mITT population; LTA population), by the ILA of glabellar line severity at maximum frown. Responders were defined as patients who had a severity grade of none or mild at a given posttreatment visit. *LTA Cycle 1 includes DBPC period data for patients who received aboBoNT-A solution 50 U during the DBPC period. Error bars represent the 95% CI. n = number of patients with data at a given time point. AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; ILA, investigator's live assessment; LTA, long-term analysis; mITT, modified intention-to-treat.

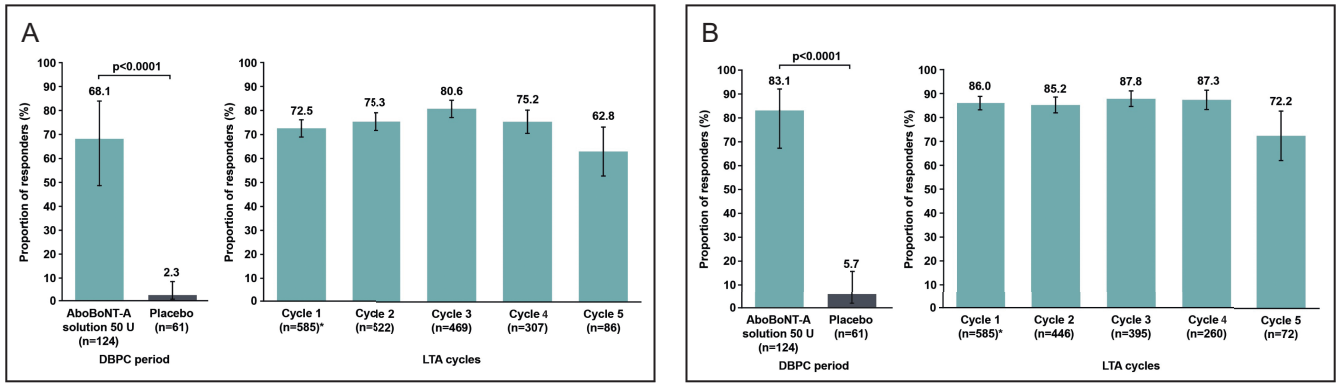

Figure 3. Proportion of responders on Day 29 across treatment cycles (DBPC Period, mITT population; LTA population). (A) The SSA of glabellar lines at maximum frown. (B) Patient's level of satisfaction with the appearance of their glabellar lines. Responders were defined as: (1) patients who had no or mild wrinkles by the SSA; or (2) who had a satisfaction rating of very satisfied or satisfied. *LTA Cycle 1 includes DBPC period data for patients who received aboBoNT-A solution 50 U during the DBPC period. Error bars represent the 95% CI. n = number of patients with data at a given time point. AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; LTA, long-term analysis; mITT, modified intention-to-treat; SSA, subject's self-assessment.

for aboBoNT-A solution compared with placebo during the DBPC period ($P < 0.0001$; Figure 3A). Additionally, in a post-hoc analysis (DBPC period), 91.9% of patients in the aboBoNT-A solution group had an improvement from baseline of at least 1 severity grade by the SSA of glabellar lines at maximum frown on Day 29 postinjection, compared with 30.3% in the placebo group ($P < 0.0001$; Supplemental Figure 1B, available online at www.aestheticsurgeryjournal.com).

Similarly, a consistently high rate of responders for patient satisfaction with glabellar line appearance (rated satisfied or very satisfied) was observed with repeated aboBoNT-A solution treatment (between 72.2% and 87.8% at Day 29; LTA population), with statistically significantly higher responder rates for aboBoNT-A solution compared with placebo observed during the DBPC period ($P < 0.0001$; Figure 3B).

Responder rates for the SSA and patient satisfaction with glabellar line appearance at time points up to Day 85 are presented in Supplemental Tables 2 and 3, available online at www.aestheticsurgeryjournal.com, respectively. For the FACE-Q outcome measures, statistically significant improvements were observed on all 3 scales for aboBoNT-A solution compared with placebo at Day 29 during the DBPC period (all $P < 0.0001$). Improvements in the satisfaction with facial appearance overall were consistent across repeat aboBoNT-A solution cycles (Figure 4A). On the psychological well-being scale, a stable improvement from baseline was also observed with each repeat aboBoNT-A solution cycle (Figure 4B). These scores across repeat cycles showed a slightly greater change from cycle baseline than that of the already notable difference in psychological well-being observed with aboBoNT-A solution during the DBPC period compared with the placebo group (Figure 4B). In terms of the aging appraisal, over repeat aboBoNT-A solution cycles patients consistently rated themselves a mean of between 0.9 and 1.3 years younger at Day 29 postinjection than at cycle baseline (Figure 4C).

Time to Onset (DBPC Period Only)

Overall, the median time to onset of treatment response in the DBPC cycle, as assessed by patients during their first week postinjection, was 2.0 days in the aboBoNT-A solution group, and was not calculable in the placebo group because of the small number of responders.

On Day 1 postinjection 25% of patients detected a response following treatment with aboBoNT-A solution, compared with only 3% in the placebo group (Figure 5). By Day 7, 93% of patients in the aboBoNT-A solution group were responders compared with 13% in the placebo group.

Safety

An overall summary of TEAEs is presented in Table 3. During the DBPC period, the proportion of patients with at least 1 TEAE was similar for patients who received aboBoNT-A solution compared with those who received placebo (40.5% vs 37.5%, respectively). The proportion of subjects experiencing TEAEs per aboBoNT-A solution cycle (LTA population) ranged from 45.4% in Cycle 1 to 21.3% in Cycle 5. Overall, the most frequently reported TEAEs following aboBoNT-A solution treatment during the DBPC period and for the overall LTA population were nasopharyngitis and headache (Table 3).

Treatment-related TEAEs were reported for 11.9% of patients in the aboBoNT-A solution group and 6.3% in the placebo group in the DBPC period. For the LTA population,

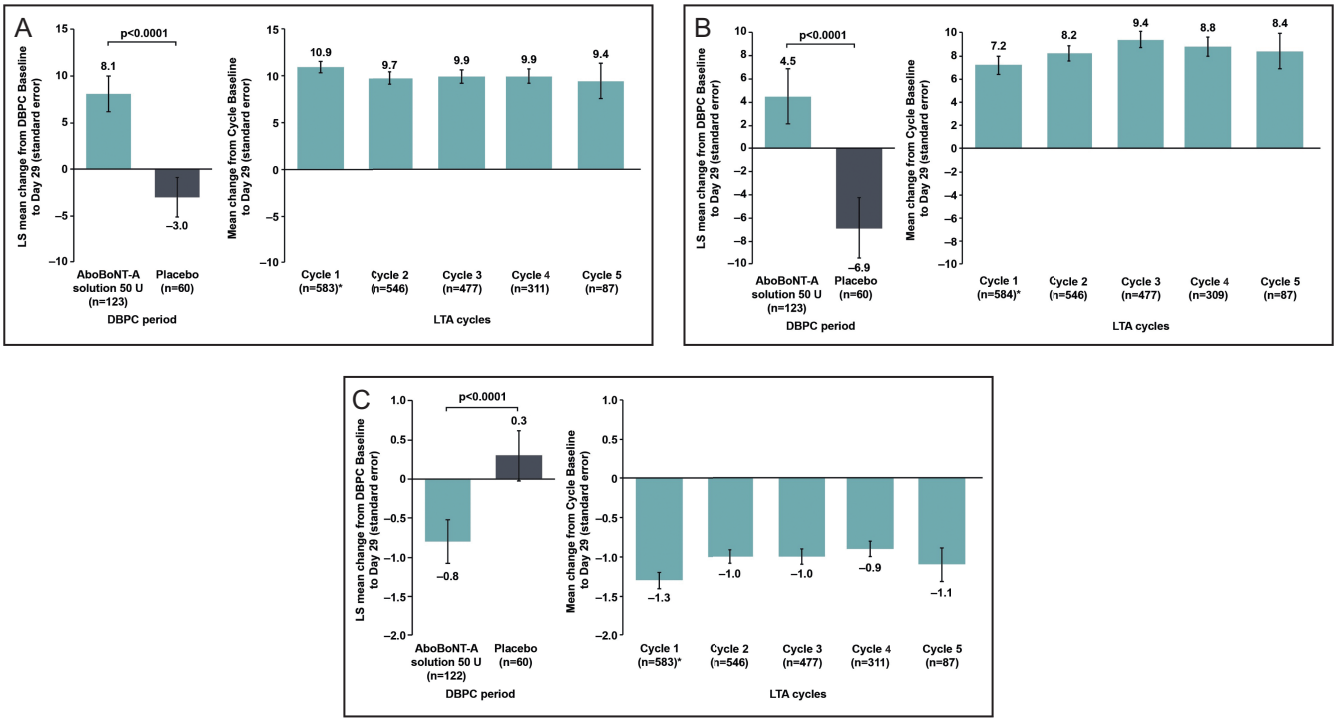

Figure 4. FACE-Q scales. (A) Satisfaction with facial appearance overall (Rasch transformed score). (B) Psychological well-being (Rasch transformed score). (C) Aging appraisal during the DBPC period (mITT population) and LTA cycles (LTA population). *LTA Cycle 1 included DBPC cycle data for patients who received aboBoNT-A solution 50 U during the DBPC period. Data presented are the mean or LS mean change (see *y*-axis labels) from the baseline value of each cycle. Error bars represent the standard error. n = number of patients with data at a given time point. AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; LS, least squares; LTA, long-term analysis; mITT, modified intention-to-treat; SSA, subject's self-assessment.

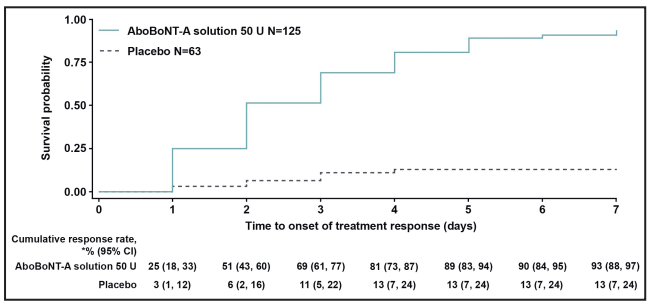

Figure 5. Kaplan-Meier estimate of time to onset of treatment response by treatment group (DBPC period, mITT population). *Percentage of patients who had responded to treatment by each day in the first week postinjection, determined by Kaplan-Meier estimates. AboBoNT-A, abobotulinumtoxinA; DBPC, double-blind placebo-controlled; mITT, modified intention-to-treat.

the proportion of patients with treatment-related TEAEs was 12.6% at Cycle 1, decreasing with each cycle to 2.5% at Cycle 4 and then 4.5% at Cycle 5 (Table 3). The most frequent treatment-related TEAEs with aboBoNT-A solution during the DBPC period were headache and hematoma, and in the LTA population was headache (Table 3).

No patient experienced an event associated with remote spread of toxin during any treatment cycle. Similarly, no hypersensitivity reactions occurred that were assessed by the investigator as related to the study; events of eye allergy (n = 1, 2 events) and rash (n = 1) occurred in the LTA population but were not considered treatment related. Eyelid ptosis occurred in between 0.0% and 1.3% of patients, across the LTA cycles (0.0% in the DBPC cycle), decreasing with each cycle; all except 1 event were considered treatment related. Eyelid edema occurred in 1.6% of patients receiving aboBoNT-A solution in the DBPC cycle (compared with 0.0% in the placebo group), and occurred in between 0.3% and 1.3% of patients across LTA cycles; all except 1 event of eyelid edema was considered treatment-related. The only treatment-related TEAE that led to study withdrawal was eyelid ptosis (aboBoNT-A solution Cycle 1 Day 10, lasting 49 days).

All injection site reactions were nonserious and mild or moderate in intensity. The most frequent was hematoma (LTA population), reported as injection site bruising (0.0%-0.2%, across cycles), injection site hematoma (0.2%-1.1%), hematoma (0.3%-1.3%), and periorbital hematoma (0.0%-0.3%). Injection site pain occurred in just 2 patients (0.0%-1.1%) in the LTA population. The majority of injection site

Table 3. Summary of AEs in the DBPC Period (Safety Population) and LTA Cycles (LTA Population)

n (%)	DBPC period		LTA period[a]				
	AboBoNT-A solution 50 U (N = 126)	Placebo (N = 64)	Cycle 1 (N = 595)	Cycle 2 (N = 558)	Cycle 3 (N = 486)	Cycle 4 (N = 319)	Cycle 5 (N = 89)
Any TEAEs	51 (40.5)	24 (37.5)	270 (45.4)	211 (37.8)	162 (33.3)	70 (21.9)	19 (21.3)
Nasopharyngitis	13 (10.3)	8 (12.5)	70 (11.8)	79 (14.2)	53 (10.9)	18 (5.6)	8 (9.0)
Headache	13 (10.3)	4 (6.3)	78 (13.1)	39 (7.0)	27 (5.6)	15 (4.7)	2 (2.2)
Hematoma	5 (4.0)	0	8 (1.3)	2 (0.4)	5 (1.0)	1 (0.3)	1 (1.1)
Pharyngitis	3 (2.4)	0	6 (1.0)	0	0	1 (0.3)	0
Vertigo	3 (2.4)	0	5 (0.8)	1 (0.2)	0	0	0
Back pain	2 (1.6)	1 (1.6)	13 (2.2)	7 (1.3)	4 (0.8)	2 (0.6)	0
Any severe TEAEs	0	1 (1.6)	12 (2.0)	17 (3.0)	9 (1.9)	4 (1.3)	0
Any related TEAEs	15 (11.9)	4 (6.3)	75 (12.6)	34 (6.1)	22 (4.5)	8 (2.5)	4 (4.5)
Headache	5 (4.0)	3 (4.7)	32 (5.4)	16 (2.9)	8 (1.6)	3 (0.9)	0
Hematoma	5 (4.0)	0	7 (1.2)	2 (0.4)	4 (0.8)	0	1 (1.1)
Eyelid edema	2 (1.6)	0	7 (1.2)	3 (0.5)	2 (0.4)	1 (0.3)	1 (1.1)
Eyelid ptosis	0	0	8 (1.3)	4 (0.7)	2 (0.4)	1 (0.3)	0
Any TEAEs leading to withdrawal	0	0	2 (0.3)	2 (0.4)	0	0	0
Any serious AEs	1 (0.8)	2 (3.1)	9 (1.5)	13 (2.3)	5 (1.0)	7 (2.2)	0

AboBoNT-A, abobotulinumtoxinA; AE, adverse event; DBPC, double-blind placebo-controlled; LTA, long-term analysis; TEAE, treatment-emergent adverse event (TEAEs are reported for any events that occurred in ≥2% of patients at any treatment cycle; related TEAEs are reported for any events that occurred in ≥1% of patients at any treatment cycle). [a]This population of 595 patients consisted of 185 patients from the DBPC period (n = 126 treated with aboBoNT-A solution; n = 59 receiving placebo) and 410 additional patients recruited into open-label Cycle 1.

reactions were assessed by the investigator as treatment-related, and no events of hematoma were observed in the placebo group during the DBPC period.

No deaths, treatment-related severe TEAEs, or treatment-related serious AEs occurred during the course of the study. Furthermore, no patient tested positive for BoNT-A-neutralizing antibodies following treatment with aboBoNT-A solution.

DISCUSSION

The present study is the first to demonstrate the long-term efficacy and safety (up to 5 treatments) of a novel aboBoNT-A solution 50 U for the improvement of moderate-to-severe glabellar lines, confirming the efficacy observed after a placebo-controlled single treatment. Thus, these data suggest that aboBoNT-A solution may provide a suitable addition to the portfolio of current BoNT-A products for the treatment of glabellar lines in adult patients. Furthermore, this innovative liquid formulation of aboBoNT-A may provide added convenience and precision over existing BoNT-A powder formulation products because it is ready-to-use (does not require reconstitution) and provided at a single concentration, thus simplifying the procedure in a time-efficient manner, which in turn may improve efficiency for clinicians and allow more time for injector-patient interaction.

Across all outcomes reported in the present study, the response to aboBoNT-A solution treatment postinjection was consistent over repeated treatment cycles, and was statistically significant compared with placebo during the DBPC period. Over 80% of patients were responders to treatment on Day 29 of each treatment cycle, as assessed by ILA of glabellar line severity at maximum frown (rated as none or mild), peaking at 87.8% in Cycle 3. This is consistent with the results observed in single-cycle studies of aboBoNT-A solution 50 U, albeit in much smaller populations (91.4% [n = 35] and 88.3% [n = 125] in the Phase II and Phase III studies, respectively).[9,10] Similarly, this proportion of treatment responders at 1 month postinjection is consistent with what has been observed across numerous

studies of aboBoNT-A powder formulation.[16] Furthermore, in the present study an even higher proportion of patients had at least a 1-grade improvement in glabellar line severity as assessed by both the ILA (94.3%) and the SSA (91.9%).

In terms of patient-reported outcomes, other than the SSA, patients' level of satisfaction with their glabellar line appearance on Day 29 following injection was consistently high across repeated treatment cycles with aboBoNT-A solution (>85% LTA Cycles 1-4). These high levels of patient satisfaction with glabellar line appearance were consistent with those observed at Day 29 following injection with aboBoNT-A solution during another Phase III study (80.9%),[10] and similar to the results of studies with aboBoNT-A powder formulation.[16-18] Patients also reported statistically significant improvements on the FACE-Q satisfaction with facial appearance overall, psychological well-being, and aging appearance scales after a single treatment cycle with aboBoNT-A solution compared with placebo. The results from the DBPC period were similar to those observed with the same 3 FACE-Q outcome measures during the previously mentioned single-cycle Phase III aboBoNT-A solution study.[11] Furthermore, in the present study, the magnitude of change observed compared with cycle baseline was consistent across repeated treatment cycles for each of the 3 FACE-Q scales. To the authors' knowledge, this is the first study to report the impact of aboBoNT-A treatment on satisfaction as assessed by FACE-Q over repeat cycles in a prospective clinical study. It should also be noted when considering the FACE-Q results that benefits in a patient's perception of their overall facial appearance, psychological well-being, and age appearance were observed even though only the glabellar lines were treated in this study.

This is one of the few studies that has evaluated time to onset in a detailed manner over the 7 days immediately following injection. In the literature, the median time to onset of response is reported to be between 2 and 3 days. However, in the present study a treatment response was reported within the first day posttreatment in a quarter of patients, consistent with the results observed in the previous Phase III study of aboBoNT-A solution.[10,19,20]

Single and repeated treatments with aboBoNT-A solution were well-tolerated, with no new or unexpected events compared with the known profile of aboBoNT-A powder formulation,[21] or previous studies of aboBoNT-A solution.[9,10] Similarly, there were no events that were indicative of a spread of toxin effect, which is consistent with evidence for BoNT-A powder formulations that are reconstituted.[22] Furthermore, there was no evidence for the presence of BoNT-A-neutralizing antibodies, which is consistent with the reported low neutralizing antibody incidence with BoNT-A powder formulations in this indication.[22] The similarity of the safety profile of aboBoNT-A solution to powder formulations, and the lack of unexpected events in this study, is reassuring because it was not assumed that this would be the case.

In terms of limitations, due to the lower patient numbers in LTA Cycle 5 compared with Cycles 1 to 4, the results from patients receiving 5 aboBoNT-A solution treatment cycles may not be representative of the overall study population. In addition, although the study design was focused on the safety of repeated cycles, this was limited because of the variation in response; for example, some patients may not have required reinjection until 6 months. However, overall, this study provides evidence from a considerably larger population than that of the single-cycle Phase II and Phase III studies, thus providing the best current level of evidence for the benefits of aboBoNT-A solution in patients receiving treatment for glabellar lines. A further strength of this study is the focus on patient-reported outcome measures for determining the effectiveness of treatment; in the field of aesthetic medicine it is increasingly accepted that assessments from the patient's perspective should be considered the most important indicator of treatment success.[23]

CONCLUSIONS

The results of this study support the efficacy and safety of this unique, ready-to-use aboBoNT-A solution for the treatment of moderate-to-severe glabellar lines in adult patients. Of note, the high proportion of responders for both investigator- and patient-reported efficacy and satisfaction outcomes from this study were highly consistent across treatment cycles, and a fast onset of action was observed. AboBoNT-A solution may provide benefits to both injectors and patients because it is convenient to use and allows for consistent and precise dosing with every injection.

Supplemental Material

This article contains supplemental material located online at www.aestheticsurgeryjournal.com.

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REFERENCES

1. De Boulle K, Fagien S, Sommer B, Glogau R. Treating glabellar lines with botulinum toxin type A-hemagglutinin complex: a review of the science, the clinical data, and patient satisfaction. *Clin Interv Aging.* 2010;5:101-118.
2. Sundaram H, Signorini M, Liew S, et al. Global aesthetics consensus: botulinum toxin type A—evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. *Plast Reconstr Surg.* 2016;137:518e-529e.
3. Gart MS, Gutowski KA. Overview of botulinum toxins for aesthetic uses. *Clin Plast Surg.* 2016;43(3):459-471.
4. Allergan, Inc. Highlights of prescribing information: Botox®. 2018. Accessed July 22, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf.
5. Merz Pharmaceuticals, LLC. Highlights of prescribing information: Xeomin®. 2018. Accessed July 22, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125360s073lbl.pdf.
6. Ipsen Biopharm Ltd. Dysport full prescribing information. 2020. Accessed July 22, 2020. https://www.ipsen.com/websites/Ipsen_Online/wp-content/uploads/2020/07/10002305/DYS-US-004998_Dysport-PI-July-2020.pdf.
7. Electronic Medicines Compendium. Azzalure summary of product characteristics. 2019. Accessed July 22, 2020. https://www.medicines.org.uk/emc/product/6584/smpc.
8. Electronic Medicines Compendium. Dysport 300 units summary of product characteristics. 2020. Accessed July 22, 2020. https://www.medicines.org.uk/emc/medicine/870/SPC/Dysport+300+units,+Dysport+500+units/.
9. Ascher B, Kestemont P, Boineau D, et al. Liquid formulation of abobotulinumtoxinA exhibits a favorable efficacy and safety profile in moderate to severe glabellar lines: a randomized, double-blind, placebo- and active comparator-controlled trial. *Aesthet Surg J.* 2018;38(2):183-191.
10. Ascher B, Rzany B, Kestemont P, et al. Liquid formulation of abobotulinumtoxinA: a 6-month, phase 3, double-blind, randomized, placebo-controlled study of a single treatment, ready-to-use toxin for moderate-to-severe glabellar lines. *Aesthet Surg J.* 2020;40(1):93-104.
11. Ascher B, Rzany B, Kestemont P, et al. Significantly increased patient satisfaction following liquid formulation abobotulinumtoxinA treatment in glabellar lines: FACE-Q outcomes from a phase 3 clinical trial. *Aesthet Surg J.* 2020;40(9):1000-1008.
12. Honeck P, Weiss C, Sterry W, Rzany B; Gladys study group. Reproducibility of a four-point clinical severity score for glabellar frown lines. *Br J Dermatol.* 2003;149(2):306-310.
13. Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetics patients. *Clin Plast Surg.* 2013;40(2):249-260.
14. Klassen AF, Cano SJ, Schwitzer JA, Scott AM, Pusic AL. FACE-Q scales for health-related quality of life, early life impact, satisfaction with outcomes, and decision to have treatment: development and validation. *Plast Reconstr Surg.* 2015;135(2):375-386.
15. Panchapakesan V, Klassen AF, Cano SJ, Scott AM, Pusic AL. Development and psychometric evaluation of the FACE-Q aging appraisal scale and patient-perceived age visual analog scale. *Aesthet Surg J.* 2013;33(8):1099-1109.
16. Rzany B, Ascher B, Monheit G. Treatment of glabellar lines with botulinum toxin type A (Speywood Unit): a clinical overview. *J Eur Acad Dermatol Venereol.* 2010;24(Suppl 1):1-14.
17. Ascher B, Zakine B, Kestemont P, Baspeyras M, Bougara A, Santini J. A multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety of 3 doses of botulinum toxin A in the treatment of glabellar lines. *J Am Acad Dermatol.* 2004;51(2):223-233.
18. Ascher B, Zakine B, Kestemont P, et al. Botulinum toxin A in the treatment of glabellar lines: scheduling the next injection. *Aesthet Surg J.* 2005;25(4):365-375.
19. Nestor M, Cohen JL, Landau M, et al. Onset and duration of abobotulinumtoxinA for aesthetic use in the upper face: a systematic literature review. *J Clin Aesthet Dermatol.* 2020;13(12):E56-E83.
20. Monheit GD, Baumann L, Maas C, Rand R, Down R. Efficacy, safety, and subject satisfaction after abobotulinumtoxinA treatment for moderate to severe glabellar lines. *Dermatol Surg.* 2020;46(1):61-69.
21. Cohen JL, Scuderi N. Safety and patient satisfaction of abobotulinumtoxinA for aesthetic use: a systematic review. *Aesthet Surg J.* 2017;37(suppl_1):S32-S44.
22. Dover JS, Monheit G, Greener M, Pickett A. Botulinum toxin in aesthetic medicine: myths and realities. *Dermatol Surg.* 2018;44(2):249-260.
23. Mori S, Lee EH. Beyond the physician's perspective: a review of patient-reported outcomes in dermatologic surgery and cosmetic dermatology. *Int J Womens Dermatol.* 2019;5(1):21-26.