Noninferiority of IncobotulinumtoxinA, Free from Complexing Proteins, Compared with Another Botulinum Toxin Type A in the Treatment of Glabellar Frown Lines

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BACKGROUND Use of botulinum toxin for esthetic purposes has rapidly expanded over the last 20 years. IncobotulinumtoxinA, also known as NT 201, is a new botulinum toxin type A (150 kDa) that is free from complexing proteins.

OBJECTIVES A prospective, multicenter, randomized, rater- and patient-blind, international Phase III trial to investigate the noninferiority of incobotulinumtoxinA to another botulinum toxin type A, onabotulinumtoxinA, in the treatment of glabellar frown lines.

METHODS A total of 381 patients were randomized in a 3:1 (incobotulinumtoxinA:onabotulinumtoxinA) ratio to receive 24 U incobotulinumtoxinA of or onabotulinumtoxinA. Efficacy end points included the percentage of responders (patients with an improvement of $\geq$1 point on a 4-point facial wrinkle scale) at maximum frown at weeks 4 and 12 as assessed by the investigators, and a panel of independent raters based on standardized digital photographs.

RESULTS Four weeks after injection, response rates at maximum frown were 96.4% in the incobotulinumtoxinA group and 95.7% in the onabotulinumtoxinA group as assessed by independent raters. Analysis of the data confirmed the noninferiority of incobotulinumtoxinA. Response rates at rest were lower for both products. The rate of adverse events was low.

CONCLUSION IncobotulinumtoxinA is equally as effective as onabotulinumtoxinA in the treatment of glabellar frown lines. Both preparations were well tolerated.

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IncobotulinumtoxinA (Bocouture/Xeomin, Merz Pharmaceuticals GmbH, Frankfurt, Germany) and onabotulinumtoxinA (Botox cosmetic/Vistabel, Allergan, Irvine, CA) are produced from the same wild-type strain of *Clostridium botulinum*. During fermentation, the neurotoxin is produced as part of a high-molecular-weight complex.[1] The manufacturing process for the final drug incobotulinumtoxinA involves a series of chromatographic purification steps yielding exclusively active neurotoxin, free from inactive or partially active neurotoxin (toxoid) and nonactive complexing proteins present in other commercially available preparations of botulinum toxin type A, including onabotulinumtoxinA.[2,3] IncobotulinumtoxinA has been approved for the treatment of glabellar frown lines in Germany since July 2009.

The aim of this large head-to-head study was to investigate the noninferiority of incobotulinumtoxinA versus onabotulinumtoxinA in the treatment of

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glabellar frown lines when used in a 1:1 dose ratio. This has already been proven in head-to-head studies involving blepharospasm[4] and cervical dystonia.[5] The secondary objectives comprised further evaluation of the treatment effect of incobotulinumtoxinA and onabotulinumtoxinA on the glabellar frown lines at maximum frown or at rest by the independent raters and investigators.

Methods

This study was a prospective, multicenter, randomized, rater- and patient-blind, parallel-group, international Phase III clinical trial performed in 20 active centers in Austria, Germany, and the United Kingdom (www.clinicaltrials.gov number NCT00777803). The study was conducted in accordance with the ethical principles that have their origin in the 1975 Declaration of Helsinki and that are consistent with the Good Clinical Practice principles and the applicable regulatory requirements. Informed consent was obtained from each patient before all study-related procedures.

Eligible study participants were women aged 18 to 50 who had moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on the Facial Wrinkle Scale (FWS)) as assessed by the investigator (0 = none, 1 = mild, 2 = moderate, 3 = severe). Exclusion criteria were severe glabellar frown lines at rest according to investigator rating on the FWS, previous treatment with botulinum toxin of any serotype in the upper third of the face within the prior 6 months and with biodegradable fillers in the glabellar area within the prior 12 months, previous insertion of permanent material in the glabellar area, any surgery or scars in the glabellar area, marked facial asymmetry or ptosis of eyelid or eyebrow, and any medical condition that may put the patient at risk with exposure to botulinum toxins.

Patients were randomized into two groups in a 3:1 (incobotulinumtoxinA:onabotulinumtoxinA) ratio, in a clinical dose-conversion ratio of 1 U:1 U. The duration of the study was 12 weeks, with a 1-week additional screening period. Patients were screened for eligibility during Visit 1 (day −7, screening visit). The randomization and treatment of the patients occurred at Visit 2 (day 0, baseline), when each patient received five intramuscular injections of incobotulinumtoxinA or onabotulinumtoxinA in a blinded manner. The blinding referred to the patients and the independent raters but not to the investigators at the site.

During the observation period of 12 weeks (84 days), the patients attended the study site for Visit 3 (week 4, day 28 $\pm$ 3) and Visit 4 (week 12, day 84 $\pm$ 7). At each of these visits, the investigator and the patient performed efficacy and safety assessments. In addition, standardized digital photographs of the treated facial area were taken (six per patient). Each study site was provided with the same equipment (digital camera with 10.0 megapixels, autofocus, and FotoFinder Mediscope Portrait Stand with two metal reflectors) to ensure reproducibility in terms of positioning and lighting. The automatic camera control provided professional illumination by spreading the flashlight evenly on the face of the patient to avoid shadows or reflections on the skin. Three independent raters individually performed the assessment of the photographs according to the FWS. In case of discrepancies in the evaluation between the raters of a patient as a responder or nonresponder, the patient was classified according to the majority.

A total dose of 24 U of incobotulinumtoxinA or onabotulinumtoxinA was administered at baseline. The 0.6-mL total injection volume was divided into five injections: 0.15 mL (6 U) in the procerus muscle, 0.125 mL (5 U) in the medial part of each corrugator muscle, and 0.1 mL (4 U) in the middle part of each corrugator muscle (Figure 1). The primary efficacy end point was the percentage of responders at maximum frown at week 4, as assessed by the panel of three independent raters from standardized digital photographs. Response was defined as an improvement of at least 1 point on a 4-point FWS. Secondary end points included the percentage of responders at

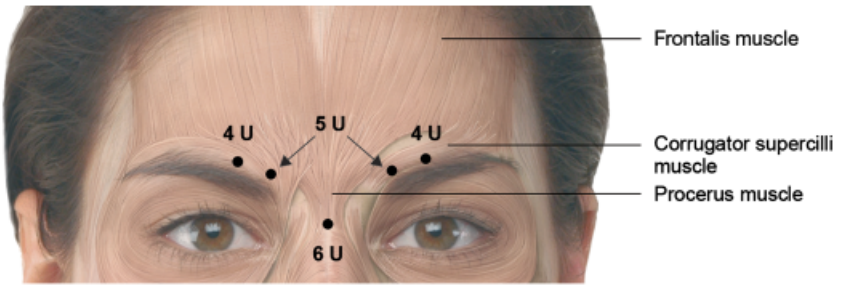

Figure 1. Treatment injection sites.

maximum frown at week 12 (as assessed by the panel of independent raters from standardized digital photographs), the percentage of responders at rest at weeks 4 and 12 (as assessed by the panel of independent raters from standardized digital photographs), and the percentage of responders at weeks 4 and 12 at maximum frown and at rest (as assessed by the investigator and the patient using the FWS). In addition, the patient's global assessment (PGA) of change in appearance after treatment (assessed using a 9-point scale, with a responder defined as a score of at least +2 at weeks 4 and 12 compared with baseline) was recorded.

During the study, adverse events (AEs), AEs of special interest, and signs and symptoms indicating toxin spread were documented. Botulinum toxin type A antibody tests (fluorescence immunoassay, hemidiaphragm assay) were performed.

All randomized and treated patients with an available primary efficacy end point were included in the full analysis set (FAS). The per protocol set (PPS) was the subset of patients of the FAS without major protocol deviations. For the primary efficacy parameter, which was defined as the expected difference in response rates of the two treatment groups, a two-sided 95% Newcombe–Wilson confidence interval (CI) was computed. The interpretation of the CI was based on the null hypothesis that the expected difference in response rates between the treatment groups was smaller than the noninferiority margin of −0.15 (H_0: $p^{incobotulinumtoxinA} - p^{onabotulinumtoxinA} \leq -0.15$). If the lower bound of the estimated CI exceeded the limit of −0.15, noninferiority of incobotulinumtoxinA to onabotulinumtoxinA treatment could be concluded. This confirmatory analysis was based on the PPS. To investigate the robustness of the results, the analysis was repeated on the FAS with observed cases and with missing values imputed. Missing values were imputed as next observation carried backwards or last observation carried forward, depending on which visits the observations were missing from. For the primary efficacy end point, there were no missing values in the PPS expected, because patients without a value for the primary efficacy end point would have been excluded already in the FAS. For all secondary efficacy parameters based on response rates, 95% Newcombe–Wilson CIs were computed.

All patients who had received study medication were part of the safety evaluation set. Safety analyses were based on the safety evaluation set only.

Results

In total, 381 patients were randomized and received an injection and thus constituted the safety evaluation set (Figure 2). These 381 patients had at least an observed baseline value of the primary efficacy variable and were therefore included in the FAS. Eleven patients showed major deviations from the study protocol, so the PPS comprised 370 patients ($n = 277$, incobotulinumtoxinA; $n = 93$, onabotulinumtoxinA). Major deviations were missing efficacy measurements, time schedule deviations such as premature study termination and visits not done or done outside the visit window, taking medication excluded from the study, and deviation of

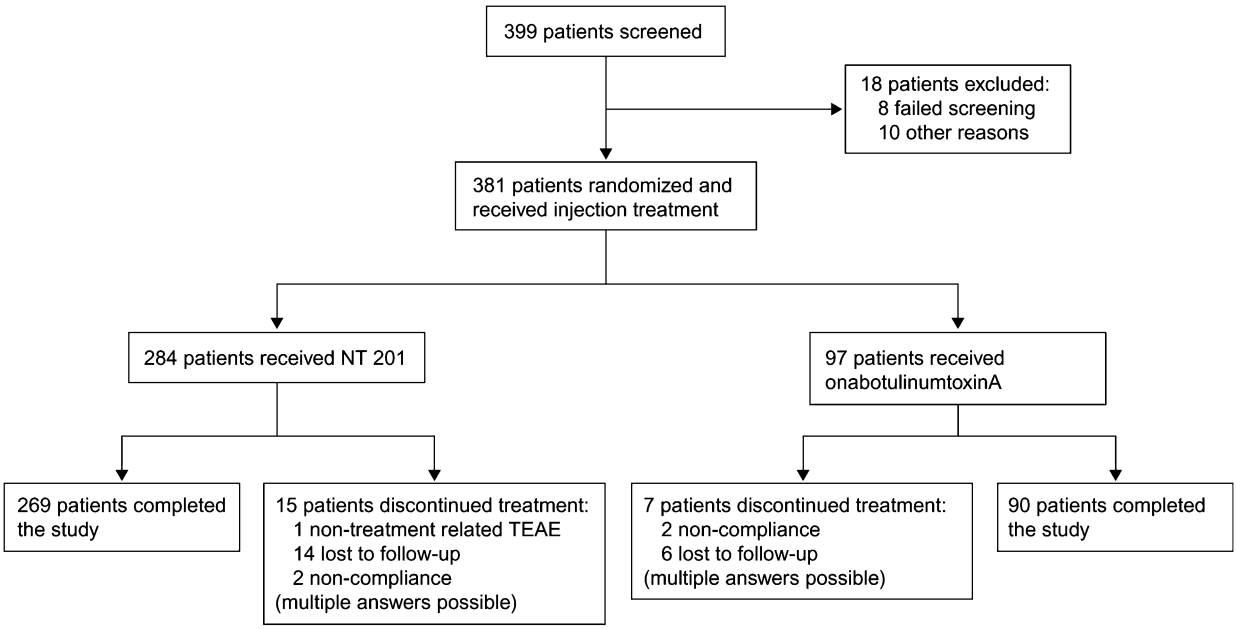

Figure 2. Disposition of patients.

exclusion criteria. The demographics and baseline characteristics of the PPS are shown in Table 1. No relevant differences in demographic and baseline characteristic data were observed between the two treatment groups. According to the investigators' rating at baseline, the majority of

TABLE 1. Summary of Patient Demographics and Baseline Characteristics (Per Protocol Set)

Characteristic	*IncobotulinumtoxinA* (n = *277*)	*OnabotulinumtoxinA* (n = *93*)
Age		
Range	22–50	24–51
Mean ± standard deviation	41.7 ± 5.7	42 ± 6.0
Median	42	42
Race, *n* (%)		
White	275 (99.3)	92 (98.9)
Other	2 (0.7)	1 (1.1)
Facial wrinkle scale score, *n* (%)*		
At rest		
None	11 (4)	5 (5.4)
Mild	92 (33.2)	32 (34.4)
Moderate	174 (62.8)	56 (60.2)
Severe	0	0
Missing	0	0
At maximum frown		
None	0	0
Mild	0	0
Moderate	90 (32.5)	27 (29.0)
Severe	187 (67.5)	66 (71.0)
Missing	0	0
Received at least one previous botulinum toxin treatment for facial lines 6 months prior to study, *n* (%)	84 (30.3)	28 (30.1)

*Glabellar frown lines according to investigators' assessment

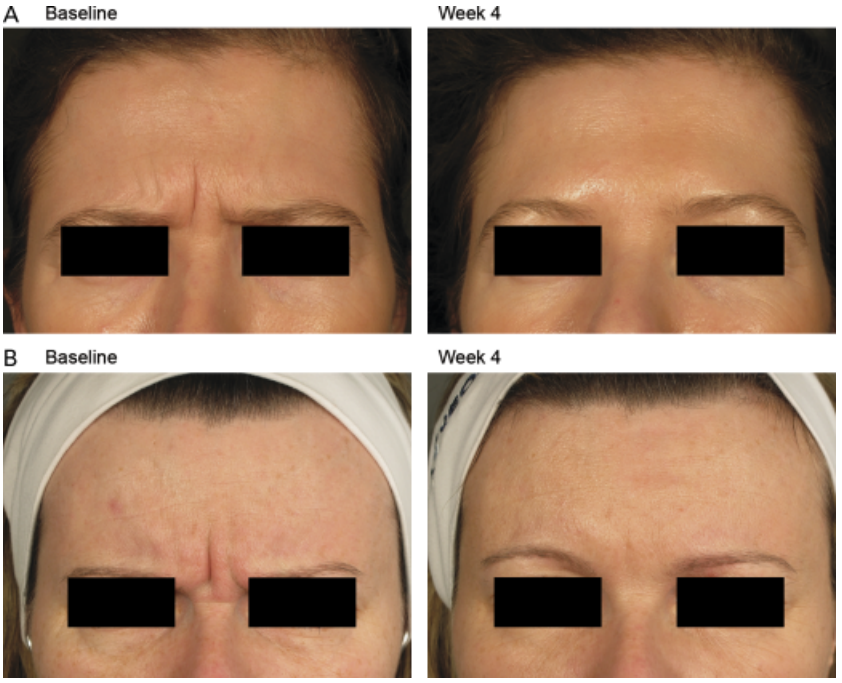

Figure 3. Clinical photographs showing patients at maximum frown: (A) patient treated with incobotulinumtoxinA; (B) patient treated with onabotulinumtoxinA.

patients had moderate glabellar frown lines at rest (62.8% incobotulinumtoxinA; 60.2% onabotulinumtoxinA) and severe glabellar frown lines at maximum frown (67.5% incobotulinumtoxinA; 71.0% onabotulinumtoxinA) (Table 1).

The results of the primary efficacy analysis showed high response rates in both treatment groups. Four weeks after injection, the response rate with respect to the FWS at maximum frown for the PPS was 96.4% in the incobotulinumtoxinA group and 95.7% in the onabotulinumtoxinA group, as assessed by the panel of independent raters from standardized digital photographs (Figures 3 and 4A). Twelve weeks after injection (imputed values, PPS), the response rate at maximum frown was still high: 80.1% in the incobotulinumtoxinA group and 78.5% in the onabotulinumtoxinA group as assessed on the FWS (Figure 4A). The 95% CIs for the difference in response rates between treatment groups (week 4, −3.2–7.1%; week 12, −7.1–12%) clearly support noninferiority of incobotulinumtoxinA to onabotulinumtoxinA, because the lower bound of the CI exceeds the predefined noninferiority margin of −15%. Similar results were obtained for the FAS with observed cases and worst case imputation of missing values.

The assessments of the non-blinded investigators at maximum frown showed comparable results (Figure 4B). After 4 weeks, 98.9% of the patients treated with incobotulinumtoxinA and 95.7% of those treated with onabotulinumtoxinA were responders (PPS). After 12 weeks (imputed values), responder rates had decreased to 79.4% in the incobotulinumtoxinA group and 81.7% in the onabotulinumtoxinA group. Noninferiority of incobotulinumtoxinA to onabotulinumtoxinA was confirmed at both time points. Similar results were observed for the FAS.

A further objective of the trial was to evaluate patients' self-assessment of treatment success. At maximum frown, 93.9% of the patients treated with incobotulinumtoxinA and 93.5% of those treated with onabotulinumtoxinA were responders

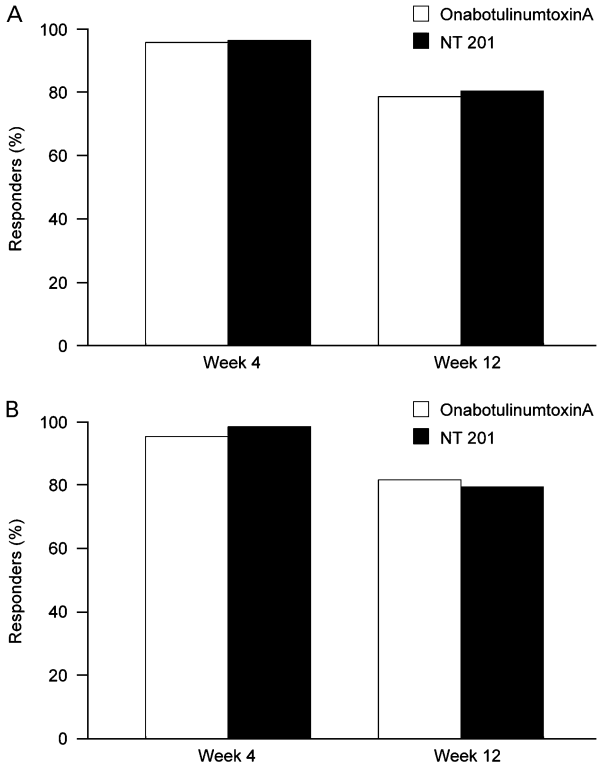

Figure 4. Percentage of responders at maximum frown at weeks 4 and 12 according to the facial wrinkle scale for the per protocol set: (A) independent rater assessment based on digital photographs; (B) investigator assessment based on the live patient.

at week 4, with respect to the FWS. Additionally, the PGA of change in appearance of glabellar frown lines compared with the situation immediately before the injection was evaluated. At week 4, 93.5% of the patients treated with incobotulinumtoxinA and 92.5% of those treated with onabotulinumtoxinA were responders (Figure 5). The response rates were still high at week 12: 85.4% in the incobotulinumtoxinA group and 85.2% in the onabotulinumtoxinA group (Figure 5). The CIs again confirmed the noninferiority of incobotulinumtoxinA.

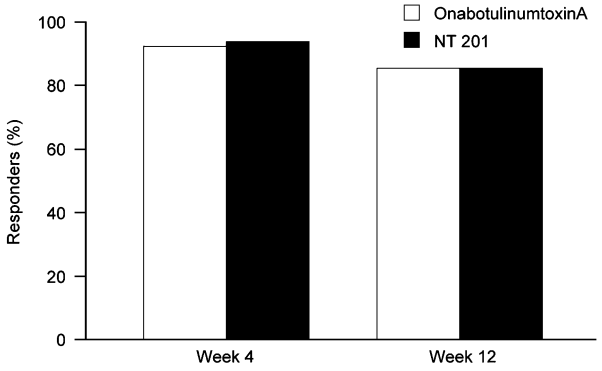

Figure 5. Percentage of responders according to the patient's global assessment at weeks 4 and 12 at maximum frown.

The response rates at rest according to the FWS were lower than at maximum frown for all assessors at both time points. In addition, response rates of each assessor at rest at week 12 were lower than the corresponding rate at week 4. Responder rates at rest, as assessed by the independent panel and investigators according to the FWS, are shown in Table 2. Furthermore, the investigators observed higher response rates than the independent panel for both treatment groups at rest (Table 2).

Safety of incobotulinumtoxinA and onabotulinumtoxinA was evaluated in 381 patients (284 in the incobotulinumtoxinA group and 97 in the onabotulinumtoxinA group). Overall, the incidence of AEs in this study was low (Table 3). Treatment-emergent AEs (TEAEs) occurred in 19.4% of patients treated with incobotulinumtoxinA and 26.8% of those treated with onabotulinumtoxinA. TEAEs that were considered "related to treatment" occurred in 3.2% of patients in the incobotulinumtoxinA group and 5.2% in the onabotulinumtoxinA group. The most frequent TEAE that was considered to be related to treatment was headache and was documented for 1.8% of the patients in the incobotulinumtoxinA group and 2.1% of those in the onabotulinumtoxinA group. All other related TEAEs (pruritus, contusion, hematoma, eyelid edema, and eyelid ptosis) had a total incidence of 0.8% or less. Eyelid ptosis, a TEAE of special interest that was considered to be related to treatment, occurred in one (1.0%) patient in the onabotulinumtoxinA group and resolved. There were no TEAEs related to treatment that resulted in discontinuation in either treatment group. No patient developed neutralizing antibodies during the course of the study.

TABLE 2. Response Rates at Rest Assessed by the Independent Panel from Digital Photographs and Assessed Live by the Investigators (Per Protocol Set)

	%			
	Week 4		*Week 12*	
Assessor	*IncobotulinumtoxinA*	*OnabotulinumtoxinA*	*IncobotulinumtoxinA*	*OnabotulinumtoxinA*
Independent panel	41.5	39.8	36.1	35.5
Investigator	75.8	71.0	59.9	54.8

All values include worst case imputation except those for the investigator at week 4, to which no imputation was applicable.

Discussion

In this large head-to-head comparison study, incobotulinumtoxinA and onabotulinumtoxinA had similarly high and comparable response rates at maximum frown at week 4 and week 12 post-treatment whether assessed by an independent panel, the investigator, or the patient. Noninferiority of incobotulinumtoxinA to onabotulinumtoxinA was confirmed at maximum frown and at rest as assessed by the independent panel and the investigator over a period of at least 12 weeks. These results demonstrating clinical equipotency were expected because this has been shown in previous clinical trials using a clinical dose conversion ratio of 1:1.[4,5] In addition, botulinum toxins have proven efficacy in the treatment of glabellar frown lines since the U.S. Food and Drug Administration approved the first representative of this class of drugs in 2002.[6–12]

TABLE 3. Incidence of Treatment Emergent Adverse Events (TEAEs) According to System Organ Class (SOC) and Preferred Term (Total Incidence $\geq$ 0.8% of SOC or Preferred Term)–Safety Evaluation Set

	%	
Medical Dictionary for Regulatory Activities SOC Preferred Term	*IncobotulinumtoxinA (n = 284)*	*OnabotulinumtoxinA (n = 97)*
Patients with at least one TEAE	19.4	26.8
Infections and infestations	8.5	11.3
Nasopharyngitis	3.9	4.1
Influenza	1.1	1.0
Sinusitis	1.1	1.0
Gastrointestinal infection	0.4	2.1
Nervous system disorders	4.2	8.2
Headache	4.2	7.2
Gastrointestinal disorders	2.5	1.0
Skin and subcutaneous tissue disorders	1.1	4.1
Injury, poisoning, and procedural complications	1.8	1.0
Musculoskeletal and connective tissue disorders	1.4	1.0
Respiratory, thoracic, and mediastinal disorders	1.1	1.0
Vascular disorders	0.7	2.1
Hematoma	0.7	1.0
Eye disorders	0.4	2.1
Neoplasms benign, malignant and unspecified (inclusive of cysts and polyps)	0.7	1.0

Both products achieved good patient assessment of improvement and high patient satisfaction, which are important outcome measures in facial esthetics.

Studies may differ in terms of patient demographics, the time point taken to measure efficacy, and the definition of "responder," so care must be taken when comparing the response rates to those of different products reported in different studies.

In the current study, the response rates were similar for the incobotulinumtoxinA and onabotulinumtoxinA groups. At rest, the response rates were lower than those observed at maximum frown. This was expected because wrinkles at rest have a non-muscle-related component to them. The response rates according to the independent panel's assessments of the FWS score from photographs at rest were lower than those that the investigators observed (Table 2). This difference may reflect the greater difficulty in assessing the wrinkle depth, especially fine wrinkles at rest, from photographs than in person. Similar differences between assessment "live" and from standardized photographs have been noted in a recent study on lateral periorbital wrinkles.[13]

The incidence of AEs was low in both groups. incobotulinumtoxinA and onabotulinumtoxinA displayed similar AE profiles, which were also similar to reported safety profiles of botulinum toxins used for the treatment of glabellar frown lines.[6,7] A low incidence of expected side effects, such as eyelid ptosis, occurred only in the onabotulinumtoxinA group and were resolved.

Limitations of this study are the inclusion of patients with a maximum age of 50 rather than 65, which is often used, and inclusion of only a small number of patients of different ethnicities, restricting the breadth of patient demographics. Comparison to different published clinical trials is difficult because trials may have slightly different end points (for instance, response defined as an improvement of ≥ 2 or ≥ 1 points). For this reason, direct comparative trials such as this, in which two products are tested using identical end points in the same trial, are needed to compare the efficacy and tolerability of different products.

In conclusion, incobotulinumtoxinA is as effective as onabotulinumtoxinA in the treatment of glabellar frown lines over at least 12 weeks. These data confirm the results observed in the treatment of blepharospasm and cervical dystonia.[4,5] The high satisfaction rates that the treated patients themselves reported supported the independent panel's and investigators' assessments of the high treatment success. Both preparations were well tolerated.

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