A Randomized, Double-Blind Trial to Investigate the Equivalence of IncobotulinumtoxinA and OnabotulinumtoxinA for Glabellar Frown Lines

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BACKGROUND IncobotulinumtoxinA and onabotulinumtoxinA are indicated for the temporary improvement in the appearance of glabellar frown lines (GFL). This is the first randomized direct comparator study to date, at the Food and Drug Administration–recommended dose of 20 units (U), for the treatment of GFL.

OBJECTIVE To investigate the dose equivalence of incobotulinumtoxinA (20 U) and onabotulinumtoxinA (20 U) for the treatment of moderate-to-severe GFL.

MATERIALS AND METHODS Prospective, randomized (1:1), double-blinded, parallel-group study in 250 females (18–50 years), employing a single treatment with incobotulinumtoxinA or onabotulinumtoxinA, followed by a 4-month observational period.

RESULTS At the primary efficacy endpoint (1 month after treatment), incobotulinumtoxinA was equivalent to onabotulinumtoxinA in the treatment of GFL at the 20 U dose within the prespecified ±15% margin of equivalence. Efficacy remained similar between treatment groups through 4 months after treatment as assessed by the independent masked panel and the masked treating physicians. Patient satisfaction ratings were similar between groups and favorable (>90%) throughout. Both treatments were well tolerated.

CONCLUSION Equivalence was demonstrated at the primary endpoint between incobotulinumtoxinA and onabotulinumtoxinA in the treatment of GFL at the 20 U dose at 1 month. Similar efficacy and tolerability profiles were observed through 4 months after treatment.

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IncobotulinumtoxinA (Xeomin; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) is a purified preparation of botulinum neurotoxin type A (BoNT/A), which is free from complexing proteins.[1] IncobotulinumtoxinA has been approved in the United States for the treatment of cervical dystonia and blepharospasm since 2010.[2] In 2011, the Food and Drug Administration (FDA) approved incobotulinumtoxinA for the temporary improvement in the appearance of moderate-to-severe glabellar frown lines (GFL) associated with corrugator and/or procerus muscle activity in adults, with a recommended dose of 20 units (U).[2] OnabotulinumtoxinA (Botox; Allergan, Inc., Irvine,

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CA) has been approved for the treatment of GFL since 2002, also at a recommended dose of 20 U.[3]

Often perceived as a sign of aging, GFL, resulting from prolonged over activity of the corrugator and procerus muscles, are a cause of aesthetic concern to many people.[4,5] Of the various aesthetic options available to improve the appearance of GFL (e.g., skin resurfacing, filler injections, and surgical interventions), the intramuscular injection of BoNT/A has become a popular and well-established treatment of choice.[6]

To date, head-to-head comparison studies of BoNT/A preparations have shown similar efficacy and safety profiles for incobotulinumtoxinA and onabotulinumtoxinA in the management of neurological conditions.[7,8] Two randomized, double-blind, prospective, multicenter clinical trials in large populations have shown that incobotulinumtoxinA is noninferior to onabotulinumtoxinA for cervical dystonia (463 subjects)[7] and blepharospasm (300 subjects),[8] respectively. The subjects in these two studies had shown a response to at least 2 treatments with onabotulinumtoxinA before being randomized to receive either incobotulinumtoxinA or onabotulinumtoxinA in a 1:1 dose ratio. The median duration of treatment effect in both studies was 110 days for both incobotulinumtoxinA and onabotulinumtoxinA.[7,8]

Although the evidence base for incobotulinumtoxinA as a treatment for neurological indications is well established, there is currently a lack of well-designed, head-to-head comparison studies for GFL at the 20 U labeled dose in the United States. This may contribute to debate among US practitioners regarding the clinical efficacy of BoNT/A formulations when selecting an aesthetic treatment, despite the current evidence suggesting that the safety and efficacy profiles are similar.[9] Previous randomized, parallel-group trials comparing the efficacy of incobotulinumtoxinA and onabotulinumtoxinA for treating GFL have either used doses exceeding the FDA-recommended dose of 20 U[10] and/or have compared different doses of incobotulinumtoxinA and onabotulinumtoxinA.[11,12] In a large double-blind study of 381 subjects, which compared the same unit dose of incobotulinumtoxinA and onabotulinumtoxinA (24 U in each treatment group), responder rates (≥1-point improvement on the Facial Wrinkle Scale [FWS]) at 4 weeks after treatment were 96.4% and 95.7% for the incobotulinumtoxinA and onabotulinumtoxinA groups, respectively; at 12 weeks after treatment, the responder rates were 80.1% for incobotulinumtoxinA and 78.5% for onabotulinumtoxinA. Noninferiority of incobotulinumtoxinA to onabotulinumtoxinA was confirmed at both time points with a predefined noninferiority margin of 15%.[10]

This study is the first large, randomized, multicenter, double-blind, parallel-group trial to date comparing the FDA-labeled doses of incobotulinumtoxinA (20 U) and onabotulinumtoxinA (20 U) in the treatment of GFL.

Methods and Materials

Study Design

This was a prospective, multicenter, randomized, double-blind, parallel-group study (ClinicalTrials.gov identification number: NCT02096081). Subjects were randomized (1:1) to receive a single treatment with 20 U of either incobotulinumtoxinA or onabotulinumtoxinA at baseline, followed by a 4-month observation period with visits at 1, 2, 3, and 4 months after injection.

An independent biostatistician created the randomization schedule to obtain a balanced 1:1 randomization. As a result, blocks of appropriate size (variable from 2 to 6) were generated for this purpose to target enrollment of an approximately equal number of subjects in each treatment group per study site. The study was conducted in compliance with Good Clinical Practice and the ethical guidelines outlined in the Declaration of Helsinki. Before subject enrollment, an institutional review board at all participating sites reviewed and approved the study protocol. Written informed consent was obtained from all participants before study-related activities.

Subjects

The study was intended to include female subjects, aged 18 to 50 years, with moderate-to-severe GFL at maximum frown (severity score of 2 or 3 on the

4-point FWS, as assessed by the investigator's rating: 0 = "none," 1 = "mild," 2 = "moderate," and 3 = "severe").[13]

The main exclusion criteria were a FWS score of severe (3) at rest; any previous treatment with BoNT (any serotype) in the upper third of the face within the 6 months before injection; previous treatment with biodegradable or permanent fillers in the glabellar area; any surgery or scar in the glabellar area; a history of facial nerve palsy; any severe or uncontrolled systemic disease or medical condition; and known hypersensitivity to incobotulinumtoxinA or onabotulinumtoxinA or any of their excipients. Subjects who were pregnant, nursing, or planning to become pregnant during the study were also excluded.

Treatment

Treatment was consistent with the current United States product label of incobotulinumtoxinA and onabotulinumtoxinA.[2,3] One 50 U vial of either incobotulinumtoxinA (BoNT/A 150 kDa) or onabotulinumtoxinA (BoNT/A 900 kDa) was provided for each subject. Both preparations were reconstituted with 1.25 mL preservative-free, sterile 0.9% sodium chloride. IncobotulinumtoxinA and onabotulinumtoxinA were reconstituted out of view of the treating physician and the subject by designated unblinded site personnel. Site personnel were monitored to ensure that exactly the same reconstitution volume was added to each vial. A total volume of 0.5 mL (20 U) of either incobotulinumtoxinA or onabotulinumtoxinA was administered in equal aliquots of 0.1 mL (4 U) to 5 injection points in the procerus muscle, each side of the medial (inner) part of the corrugator muscle, and each side of the middle part of the corrugator muscle (Figure 1). This standardized injection scheme was followed for all subjects regardless of anatomical variances in GFL.

Assessments and Outcomes

Both an independent masked panel of physicians and the treating physician who was also masked evaluated subject photographs in a blinded fashion at screening/baseline visits and at 1, 2, 3, and 4 months after injection. Raters were required to be qualified on the FWS through training and certification. The primary efficacy variable was the clinical response to treatment, defined as a ≥1-point improvement from baseline on the FWS at maximum frown, as rated by the independent masked panel of physicians at 1 month after injection (30 days ± 5 days). Secondary efficacy variables were the clinical response, as rated by the independent panel at 2, 3, and 4 months after injection (60, 90, and 120 days ± 7 days at each time point); the clinical response as rated by the treating physician at 1, 2, 3, and 4 months after injection; overall patient-reported treatment satisfaction at 1, 2, 3, and 4 months after injection, assessed using the categories: "extremely satisfied," "satisfied," "slightly satisfied," "slightly dissatisfied," "dissatisfied," and "extremely dissatisfied"; and patient-reported date of onset and peak effect.

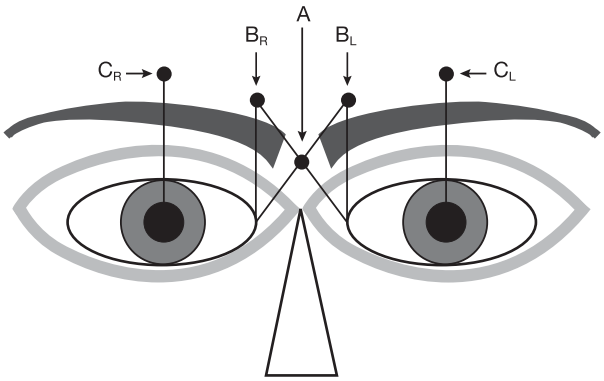

Figure 1. Injection scheme. One injection was given in the procerus muscle at the crossing of 2 lines that connect points B_R and B_L and the contralateral caruncle (point A). One injection on each side was given in the central part of the corrugator muscle, approximately 1 cm above the bony orbital rim on an imaginary line drawn vertically from the caruncle (points B_R and B_L). One injection on each side was given in the middle part of the corrugator muscle, at least 1.5 cm above the bony orbital rim on an imaginary line drawn vertically from the midpupillary line (points C_R and C_L).

Safety assessments included incidence of adverse events (AEs) recorded after the treatment through to the last study visit at 4 months and AEs of special interest (AESIs; defined according to a prespecified list of AEs that could potentially indicate toxin spread).

Statistical Analysis

Continuous variables were summarized by mean, standard deviation (SD), median, and percent frequencies. Statistical hypothesis testing for the

primary efficacy variable was carried out using a two-sided 95% Newcombe–Wilson confidence interval (CI) around the difference in clinical response rates at 1 month after injection between incobotulinumtoxinA and onabotulinumtoxinA. If the CI fell within the predefined limits of ±15%, then equivalence of incobotulinumtoxinA and onabotulinumtoxinA was concluded. This same type of statistical analysis was used for the secondary efficacy variables (difference in clinical response rates at 2, 3, and 4 months after injection, as rated by the independent panel, and difference in clinical response rates at 1, 2, 3, and 4 months after injection, as rated by the treating physician). However, for secondary efficacy variables, the two-sided 95% Newcombe–Wilson CI around the difference in response rates was considered exploratory, as the study was powered to make inferences on the primary efficacy hypothesis. Additionally, exploratory post hoc 95% CIs for within-group response rates were derived. Safety variables were analyzed descriptively for the safety evaluation set (all subjects who received study medication). All analyses were performed using SAS version 9.3 (Cary, NC).

Sample Size

In order to make an assessment of equivalence at 1 month after injection, with a level of significance (α) of 5%, an equivalence margin of 15% for each side, an expected response rate of 90% for incobotulinumtoxinA and onabotulinumtoxinA at 1 month, and a 1:1 allocation ratio of both treatments, a total of 225 subjects was needed to achieve statistical power of 90%. To allow for subject dropouts and exclusions from the per-protocol set of about 10%, approximately 250 subjects were to be enrolled in the study.

Results

Participants

A total of 250 female subjects were recruited from 10 sites in the United States between February and April 2014 and were randomized to either incobotulinumtoxinA or onabotulinumtoxinA treatment groups (Figure 2). Subjects were evenly distributed for the primary and secondary efficacy analyses resulting in 116 and 119 subjects in the incobotulinumtoxinA

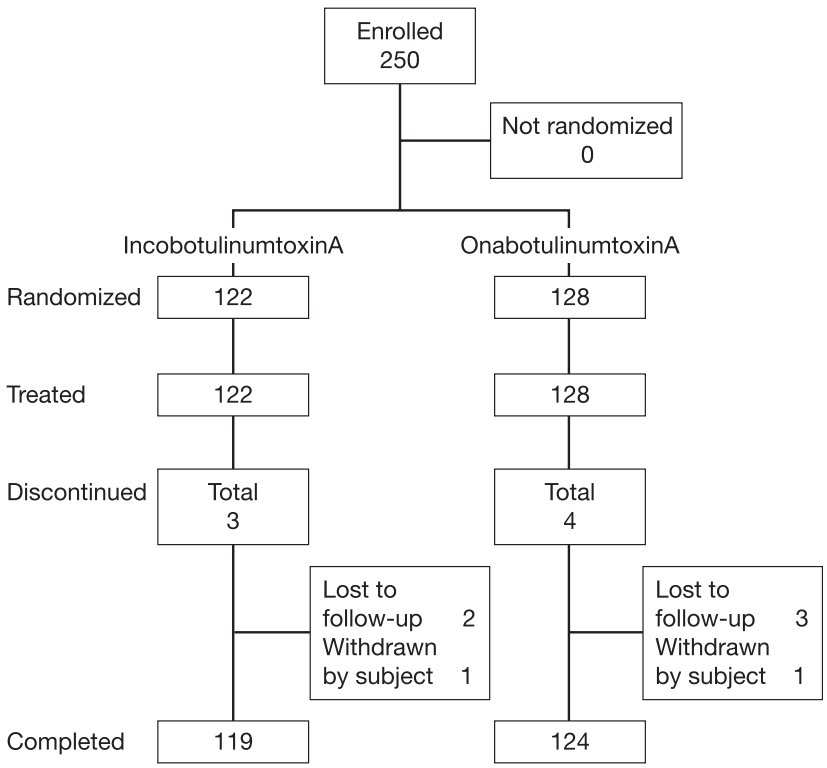

Figure 2. Disposition of study subjects. The per-protocol set included 116 subjects in the incobotulinumtoxinA group and 119 subjects in the onabotulinumtoxinA group.

and onabotulinumtoxinA groups, respectively. Demographic data were similar for both treatment groups and were reflective of the patient population commonly seeking treatment for GFL in clinical practice (Table 1).

Baseline GFL scores at maximum frown, as rated by the independent masked panel using subject photographs, were similar for both treatment groups, with mean (SD) scores of 2.5 (0.6) and 2.5 (0.7) for the incobotulinumtoxinA and onabotulinumtoxinA groups, respectively. These were similar to mean (SD) baseline GFL scores as rated by the treating physician (incobotulinumtoxinA, 2.5 [0.7]; onabotulinumtoxinA, 2.6 [0.7]).

Primary Efficacy Variable

Independent Masked Panel Rating at 1 Month After Injection

At 1 month after treatment, the percentages of subjects responding to treatment, defined as a ≥1-point improvement from baseline on the FWS at maximum frown, were 95.7% and 99.2%, for incobotulinumtoxinA and onabotulinumtoxinA groups, respectively (Figure 3). The two-sided 95% Newcombe–Wilson CI for the treatment difference Δ of −3.5% was −7.5 to 0.6, and fell within the prespecified equivalence margin of ±15%, thereby confirming the equivalence of incobotulinumtoxinA and onabotulinumtoxinA at 1 month after treatment.

Secondary Efficacy Variables

Independent Masked Panel Rating at 2, 3, and 4 Months After Injection

The response rates as rated by the independent masked panel were similar for both treatment groups (Figure 3). Response rates for incobotulinumtoxinA and onabotulinumtoxinA were 89.7% and 95.0%, respectively, at Month 2 (Δ = −5.3; 95% CI −12.1 to 1.5); 80.2% and 80.7% at Month 3 (Δ = −0.5; 95% CI −10.6 to 9.6); and 62.1% and 67.2% at Month 4 (Δ = −5.2; 95% CI −17.4 to 7.1). Similarity between treatments was confirmed by the exploratory

TABLE 1. Baseline Demographics (Safety Evaluation Set)

	IncobotulinumtoxinA (*N* = 122)	*OnabotulinumtoxinA* (*N* = 128)	*Total* (*N* = 250)
Sex, n (%)			
Female	122 (100.0)	128 (100.0)	250 (100.0)
Age, years			
Mean (SD)	39.3 (7.4)	39.4 (7.8)	39.3 (7.6)
Median	41.0	41.0	41.0
Min, max	21, 54*	19, 50	19, 54*
Ethnic origin, n (%)			
Hispanic or Latino	23 (18.9)	35 (27.3)	58 (23.2)
Not Hispanic or Latino	99 (81.1)	93 (72.7)	192 (76.8)
Race, n (%)			
White	104 (85.2)	107 (83.6)	211 (84.4)
Black or African American	14 (11.5)	13 (10.2)	27 (10.8)
Asian	4 (3.3)	4 (3.1)	8 (3.2)
American Indian or Alaska Native	0 (0.0)	1 (0.8)	1 (0.4)
Other	0 (0.0)	3 (2.3)	3 (1.2)
Baseline FWS score at maximum frown, mean (SD)			
Rated by independent masked panel	2.5 (0.6)	2.5 (0.7)	—
Rated by treating physician	2.5 (0.7)	2.6 (0.7)	—

*In deviation from the protocol, 2 subjects >50 years of age were enrolled.
FWS, Facial Wrinkle Scale; SD, standard deviation.

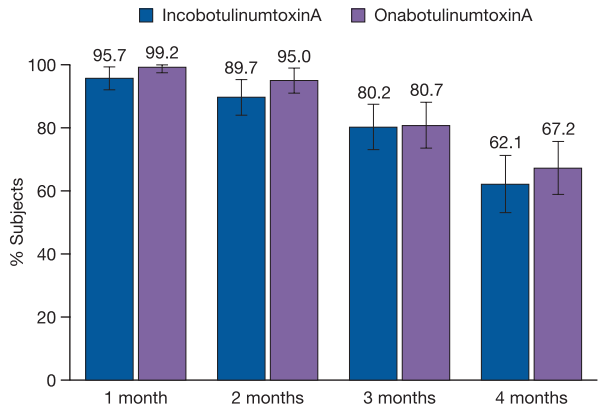

Figure 3. Clinical response rates by independent masked panel ratings (BOCF, per-protocol set). Clinical response was defined as a ≥1-point improvement from the baseline Facial Wrinkle Scale score. Error bars show post hoc exploratory, within-group 95% CIs. BOCF, baseline observation carried forward; CI, confidence interval.

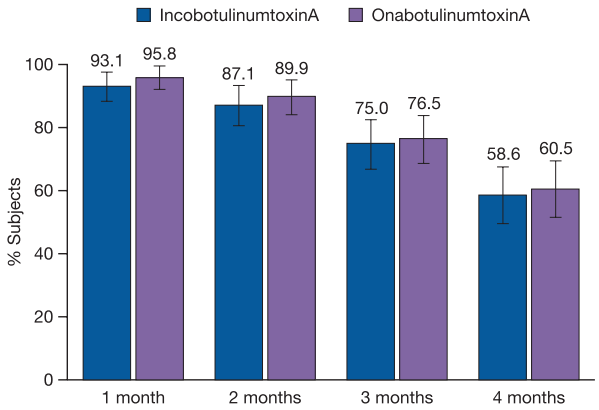

Figure 4. Clinical response rates by treating physician ratings (BOCF, per-protocol set). Clinical response was defined as a ≥1-point improvement from the baseline Facial Wrinkle Scale score. Error bars show post hoc exploratory, within-group 95% CIs. BOCF, baseline observation carried forward; CI, confidence interval.

two-sided 95% Newcombe–Wilson CI calculated around the differences in response rates at Months 2 and 3. At 4 months after treatment, the lower margin of 95% Newcombe–Wilson CI was below −15%; however, the study was not powered to demonstrate equivalence at this time point. Post hoc within-group 95% CIs were calculated for both treatment groups as an adjunctive analysis and overlapped at all posttreatment time points, as illustrated in Figure 3.

Treating Physician Rating at 1, 2, 3, and 4 Months After Injection

Response rates assessed by the treating physician were similar for both treatment groups at all time points (Figure 4). Response rates were 93.1% and 95.8% for incobotulinumtoxinA and onabotulinumtoxinA, respectively at Month 1 (Δ = −2.7; 95% CI −8.5 to 3.2); 87.1% and 89.9% at Month 2 (Δ = −2.8; 95% CI −11.0 to 5.3); 75.0% and 76.5% at Month 3 (Δ = −1.5; 95% CI −12.4 to 9.5); and 58.6% and 60.5% at Month 4 (Δ = −1.9; 95% CI −14.4 to 10.7). The two-sided 95% Newcombe–Wilson CI calculated around the differences in response rates between incobotulinumtoxinA and onabotulinumtoxinA was within the prespecified equivalence bound of ±15% at 1 to 4 months (although the study was not sufficiently powered to demonstrate equivalence at the 4-month time point), supporting the similarity of both treatments across the entire duration of the study. Furthermore, the post hoc within-group 95% CIs for both treatment groups overlapped at all posttreatment time points.

Patient-Reported Outcomes

Patient satisfaction levels were consistently high and similar between treatment groups over the duration of the study, with >90% of subjects reporting to be extremely satisfied, satisfied, or slightly satisfied at all time points in both treatment groups (Figure 5). Time to onset of treatment effect was similar, with a median of 3.0 days for both groups and mean (SD) of 3.9 (2.4) and 3.5 (2.4) for the incobotulinumtoxinA and onabotulinumtoxinA groups, respectively. Additionally, no differences in peak effect were observed; 93.1% of subjects in the incobotulinumtoxinA group and

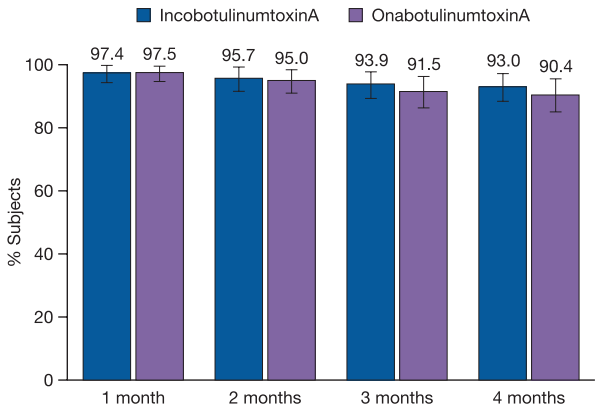

Figure 5. Proportion of subjects satisfied with treatment (proportion of subjects with a rating of "extremely satisfied," "satisfied," or "slightly satisfied"; error bars show post hoc exploratory, within-group 95% CIs). CI, confidence interval.

94.9% in the onabotulinumtoxinA group reported a peak effect within 4 weeks of treatment.

Figures 6–11 show typical subject photographs at screening, and at 1 month and 4 months after treatment with incobotulinumtoxinA or onabotulinumtoxinA.

Safety

A similar percentage of subjects in the incobotulinumtoxinA group (11.5%) and in the onabotulinumtoxinA group (14.1%) experienced at least 1 treatment-emergent adverse event (TEAE). Moreover, the percentage of subjects with TEAEs that were assessed by the treating physician to be treatment related (i.e., related to the study drug or the injection procedure) was similar between treatment groups (incobotulinumtoxinA, 6.6%; onabotulinumtoxinA, 6.3%; Table 2). Most TEAEs were mild or moderate in intensity. A total of 2 serious TEAEs were reported (1 subject in the incobotulinumtoxinA group experienced human ehrlichiosis and 1 subject in the onabotulinumtoxinA group experienced atypical pneumonia), and both were deemed unrelated to the study drug. There was no AESI in the incobotulinumtoxinA group and 2 AESI in the onabotulinumtoxinA group; both were considered nonserious events. In the onabotulinumtoxinA group, 1 subject experienced eyelid ptosis, which was considered related to the study drug and resolved within 19 days from onset without further complications. The other subject experienced blurred vision, which was also considered related to the study product and was resolving at the final 4-month visit (the subject was instructed to follow-up with her ophthalmologist). Overall, incobotulinumtoxinA and onabotulinumtoxinA were well tolerated and safe in the treatment of GFL.

Discussion

The potencies of BoNT/A formulations are measured in proprietary units that are specific to each of the formulations, with no international standard measure. However, preclinical data derived from lethal dose, 50% studies in mice suggest that the unit potency of incobotulinumtoxinA is similar to that of onabotulinumtoxinA.[14] Clinical studies have demonstrated

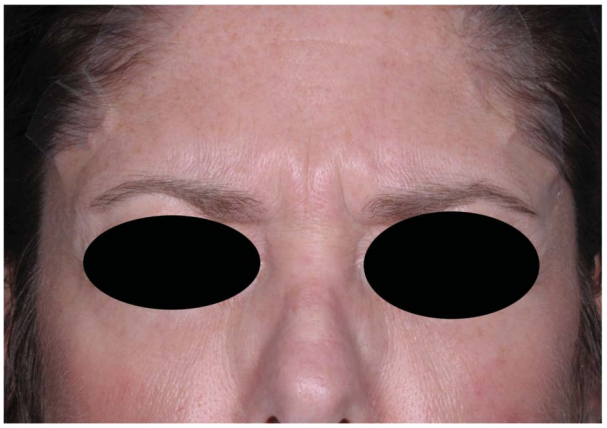

Figure 6. Subject A, maximum frown at baseline. Baseline—Facial Wrinkle Scale score 3.

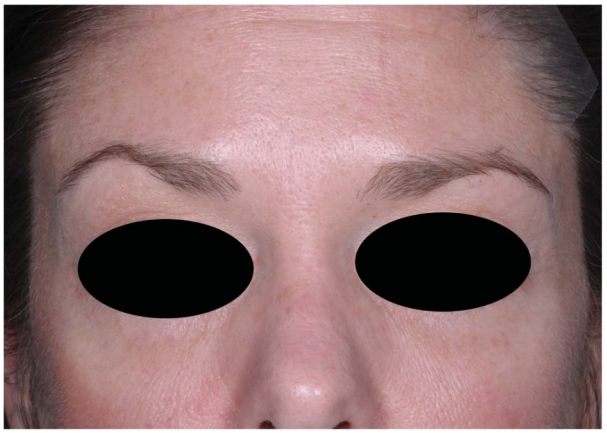

Figure 7. Subject A, maximum frown 1 month after treatment with incobotulinumtoxinA. One month after treatment—Facial Wrinkle Scale score 0.

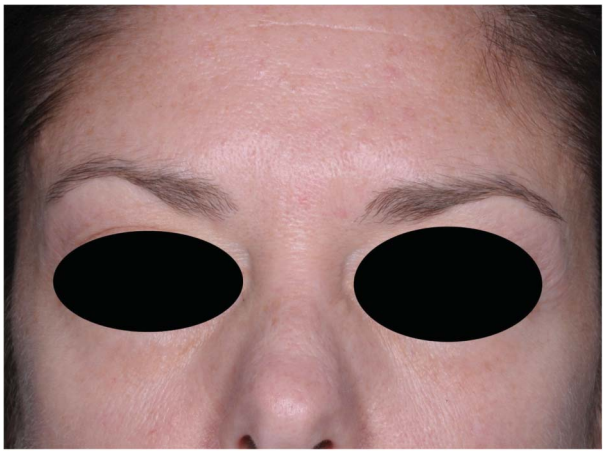

Figure 8. Subject A, maximum frown 4 months after treatment with incobotulinumtoxinA. Four months after treatment—Facial Wrinkle Scale score 0.

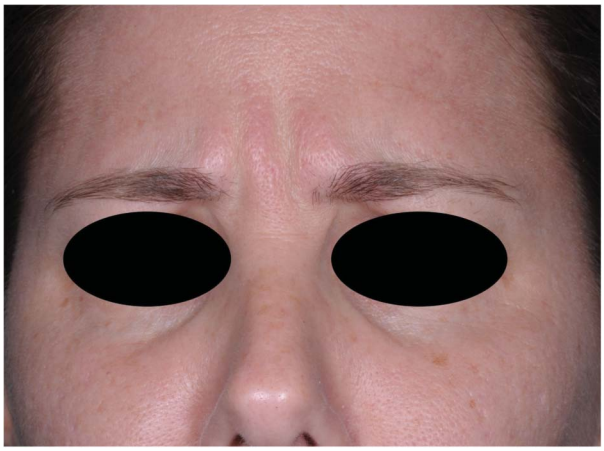

Figure 9. Subject B, maximum frown at baseline. Baseline—Facial Wrinkle Scale score 3.

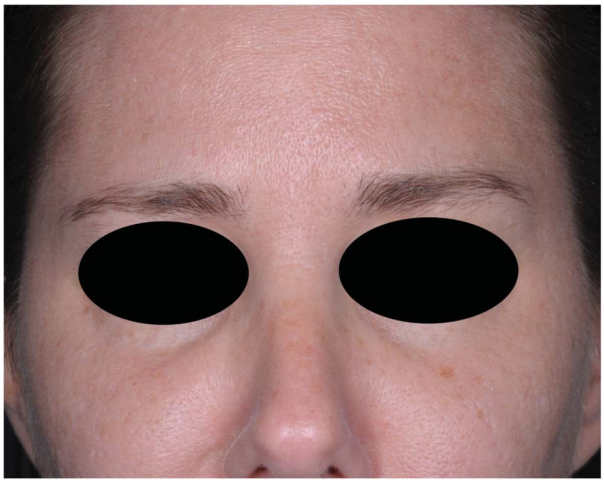

Figure 10. Subject B, maximum frown 1 month after treatment with onabotulinumtoxinA. One month after treatment—Facial Wrinkle Scale score 0.

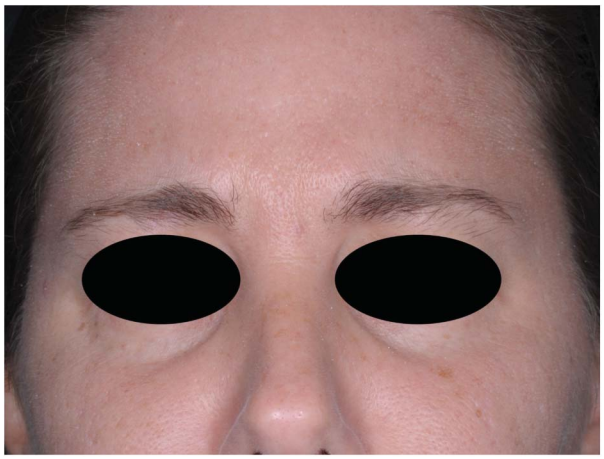

Figure 11. Subject B, maximum frown 4 months after treatment with onabotulinumtoxinA. Four months after treatment—Facial Wrinkle Scale score 0.

the superiority of incobotulinumtoxinA over placebo for the treatment of GFL, as shown in a pooled analysis of two large-scale, randomized, placebo-controlled studies.[13] However, the value of direct comparison studies using identical dose regimens and treatment endpoints cannot be understated. Interindividual differences in baseline severity can impact greatly on treatment outcomes, and this must be considered when comparing responder rates using data derived from different trials.[13]

The objective of this study was to demonstrate the equivalence of incobotulinumtoxinA and onabotulinumtoxinA 1 month after treatment of moderate-to-severe GFL using the FDA-recommended dose of 20 U. The clinical equivalence of incobotulinumtoxinA and onabotulinumtoxinA was demonstrated for the primary endpoint at 1 month after treatment, based on the ratings of the independent masked panel. This result was confirmed by the ratings from the treating physician at 1 month after treatment. This study was powered to demonstrate equivalence at 1 month based on expected responder rates; however, due to the robust response rates observed at 2 and 3 months, equivalence was also established at these time points. As a result of lower responder rates observed in both treatment groups at Month 4, the sample size may not have been adequate to detect equivalence and definitive conclusions could not be established. The clinical efficacy results were similar at 2, 3, and 4 months between the treatment groups and were reflected by patient satisfaction ratings, with more than 90% of patients being satisfied with the treatment throughout the duration of the study. The similarity of ratings for incobotulinumtoxinA and onabotulinumtoxinA indicates that patients were equally satisfied.

The clinical equivalence observed in this study is consistent with findings from previous randomized, large-scale head-to-head comparisons of incobotulinumtoxinA and onabotulinumtoxinA for neurological indications such as blepharospasm and cervical dystonia.[7,8] In the area of aesthetics, an earlier study using a higher dose than 20 U has previously demonstrated the noninferiority of incobotulinumtoxinA to onabotulinumtoxinA.[10] However, well-designed comparative studies that clearly

TABLE 2. Summary of AEs (Safety Evaluation Set)*

Subjects with ≥1 AE, n (%)	*IncobotulinumtoxinA (N = 122)*		*OnabotulinumtoxinA (N = 128)*	
	14 (11.5)		*18 (14.1)*	
	Related	*Unrelated*	*Related*	*Unrelated*
Subjects with ≥1 AE	8 (6.6)	6 (4.9)	8 (6.3)	10 (7.8)
Headache	5 (4.1)	2 (1.6)	4 (3.1)	1 (0.8)
Facial asymmetry	2 (1.6)	0	3 (2.3)	0
Acne	0	1 (0.8)	0	0
Atypical pneumonia	0	0	0	1 (0.8)
Brow ptosis	1 (0.8)	0	0	0
Ear infection	0	1 (0.8)	0	0
Eczema	0	0	0	1 (0.8)
Eyelid edema	1 (0.8)	0	0	0
Eyelid ptosis	0	0	1 (0.8)	0
Foot fracture	0	0	0	1 (0.8)
Human ehrlichiosis	0	1 (0.8)	0	0
Injection-site bruising	0	0	1 (0.8)	0
Laceration	0	1 (0.8)	0	0
Musculoskeletal pain	0	0	0	1 (0.8)
Nasopharyngitis	0	0	0	1 (0.8)
Paresthesia (brow)	1 (0.8)	0	0	0
Pneumonia	0	0	0	1 (0.8)
Rheumatoid arthritis	0	1 (0.8)	0	0
Rib fracture	0	1 (0.8)	0	0
Scratch	0	0	0	1 (0.8)
Sinusitis	0	1 (0.8)	0	1 (0.8)
Skin abrasion	0	0	0	1 (0.8)
Thrombosis	0	1 (0.8)	0	0
Vision blurred	0	0	1 (0.8)	0

*The total number of AEs may exceed the number of subjects with ≥1 AE as some subjects experienced >1 AE.
AE, adverse event.

demonstrate equivalence within the parameters of the FDA-recommended dose of 20 U are currently lacking. Other existing studies in GFL reduction, while indicative of equivalence between incobotulinumtoxinA and onabotulinumtoxinA, have used a design that precluded direct comparison of active treatments.[11,12]

The lack of informative comparative trials using BoNT/A preparations for aesthetic indications may have contributed to debate among practitioners regarding the relative effectiveness of available treatments and the appropriate dose.[9] This study confirms previous literature conclusions that provide no statistically significant evidence to suggest that incobotulinumtoxinA or onabotulinumtoxinA is more potent or has a longer duration of action compared to the other. In addition, both products were safe and well tolerated without any serious treatment-related AEs.

In conclusion, these findings confirm the clinical equivalence of incobotulinumtoxinA and onabotulinumtoxinA for the treatment of moderate-to-severe GFL at the FDA-labeled dose of 20 U for each product within the prespecified margin of equivalence of ±15% at the primary endpoint. The safety and efficacy profiles of both treatments were similar up to 4 months after treatment. Patient-reported outcomes were also similar and satisfaction rates were consistently high across all time points.

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References

1. Frevert J. Pharmaceutical, biological, and clinical properties of botulinum neurotoxin type A products. Drugs R D 2015;15:1–9.
2. Merz Pharmaceuticals, LLC. Xeomin US prescribing information. Available from: http://www.xeomin.com/consumers/pdf/xeomin-full-prescribing-information.pdf. Accessed June 4, 2015.
3. Allergan, Inc. Botox US prescribing information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5232lbl.pdf. Accessed June 4, 2015.
4. Carruthers A, Kiene K, Carruthers J. Botulinum A exotoxin use in clinical dermatology. J Am Acad Dermatol 1996;34:788–97.
5. Carruthers A, Carruthers J. Clinical indications and injection technique for the cosmetic use of botulinum A exotoxin. Dermatol Surg 1998;24:1189–94.
6. Beer KR, Boyd C, Patel RK, Bowen B, et al. Rapid onset of response and patient-reported outcomes after onabotulinumtoxinA treatment of moderate-to-severe glabellar lines. J Drugs Dermatol 2011;10:39–44.
7. Benecke R, Jost WH, Kanovsky P, Ruzicka E, et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology 2005;64:1949–51.
8. Roggenkämper P, Jost WH, Bihari K, Comes G, et al. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm 2006;113:303–12.
9. Poulain B, Trevidic P, Clave M, Aharoni C, et al. Clinical equivalence of conventional OnabotulinumtoxinA (900 KDa) and IncobotulinumtoxinA (neurotoxin free from complexing proteins—150 KDa): 2012 multidisciplinary French consensus in aesthetics. J Drugs Dermatol 2013;12:1434–46.
10. Sattler G, Callander MJ, Grablowitz D, Walker T, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg 2010;36(Suppl 4):2146–54.
11. Moers-Carpi M, Dirschka T, Feller-Heppt G, Hilton S, et al. A randomised, double-blind comparison of 20 units of onabotulinumtoxinA with 30 units of incobotulinumtoxinA for glabellar lines. J Cosmet Laser Ther 2012;14:296–303.
12. Prager W, Rappl T. Phase IV study comparing incobotulinumtoxinA and onabotulinumtoxinA using a 1:1.5 dose-conversion ratio for the treatment of glabellar frown lines. J Cosmet Dermatol 2012;11:267–71.
13. Jones D, Carruthers J, Narins RS, Coleman WP III, et al. Efficacy of incobotulinumtoxinA for treatment of glabellar frown lines: a post hoc pooled analysis of 2 randomized, placebo-controlled, phase 3 trials. Dermatol Surg 2014;40:776–85.
14. Dressler D, Mander G, Fink K. Measuring the potency labelling of onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin) in an LD50 assay. J Neural Transm 2012;119:13–5.

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