

Efficacy and Safety of IncobotulinumtoxinA in the Treatment of Upper Facial Lines: Results From a Randomized, Double-Blind, Placebo-Controlled, Phase III Study

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BACKGROUND Treating upper facial lines (UFL)—a combination of glabellar frown lines (GFL), horizontal forehead lines (HFL), and lateral periorbital lines (LPL)—is a common aesthetic practice.

OBJECTIVE To provide the first placebo-controlled evidence of the efficacy and safety of incobotulinumtoxinA for UFL.

METHODS Healthy subjects (≥ 18 years) with moderate-to-severe GFL, HFL, and LPL on the Merz Aesthetics Scales (MAS) at maximum contraction were randomized to incobotulinumtoxinA or placebo. For incobotulinumtoxinA, 54 to 64 U were administered (GFL, 20 U; HFL, 10–20 U; LPL, 24 U). Investigator-assessed MAS scores were evaluated for each area at maximum contraction on Day 30, both separately (responder = score of “none” [0] or “mild” [1]) and combined (UFL; sum score ≤ 3). Adverse events were recorded until 120 ± 7 days after treatment.

RESULTS Overall, 156 subjects were treated (incobotulinumtoxinA: 105; placebo: 51). On Day 30 at maximum contraction, a significant ($p \leq .0001$) effect of incobotulinumtoxinA versus placebo for GFL (84.5% vs 0.0%, respectively), HFL (70.9% vs 2.1%), LPL (64.1% vs 2.1%), and UFL combination (55.3% vs 0.0%) was demonstrated for investigator-assessed “none” or “mild” scores. Two cases of mild eyelid ptosis occurred with incobotulinumtoxinA.

CONCLUSION IncobotulinumtoxinA demonstrated significant efficacy in treating GFL, HFL, and LPL separately and combined, as well as a good safety profile.

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IncobotulinumtoxinA (Xeomin/Xeomeen/
Bocouture/XEOMIN Cosmetic; botulinum toxin
Type A free from complexing proteins [150 kDa]; NT

201) is indicated worldwide for the correction of
glabellar frown lines (GFL), in Europe for the
correction of lateral periorbital lines (LPL; crow’s

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feet), and has proven efficacy in these and other aesthetics indications, including the treatment of horizontal forehead lines (HFL).¹⁻⁷ Currently, common practice in facial aesthetics includes the combined treatment of different upper facial areas, such as GFL, HFL, and LPL, during the same treatment session.^{8,9} However, there is no placebo-controlled evidence for the efficacy of botulinum toxin Type A in the treatment of whole regions, such as the upper face. The aim of this study was to provide, for the first time, placebo-controlled evidence of the efficacy and safety of incobotulinumtoxinA for the treatment of moderate-to-severe upper facial lines (UFL), that is, the simultaneous treatment of GFL, HFL, and LPL.

Materials and Methods

This was a prospective, randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of incobotulinumtoxinA in subjects with moderate-to-severe UFL. The study was conducted in accordance with applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation—Good Clinical Practice. The protocol was approved by an independent ethics committee. Written informed consent was obtained from each subject before study enrolment.

This multinational study took place between July 2012 and October 2013 at 10 sites located across Germany, France, and the United Kingdom. At each site, a maximum of 2 medical doctors who were trained and experienced in aesthetic incobotulinumtoxinA therapy were responsible for administering treatment and performing subject assessments. Healthy male and female subjects were eligible for inclusion if they met the criteria outlined in Table 1.

A questionnaire, the Freiburg Life Quality Assessment 'Lebensqualität, Haut und Kosmetik' (FLQA-k) assessment tool, was completed by each subject at screening to evaluate eligibility for the study in terms of psychologic strain. The FLQA-k is a patient-reported outcome tool for the evaluation of self-perception of a subject's body and aesthetic appearance. The

questionnaire contains 44 items across several domains (body experience, body care, social contacts and avoidance, and self-confidence). A cutoff FLQA-k score of <0 was used in this study, which represents eligible subjects evaluated as having significant psychologic strain.

Treatment

Subjects were randomized (2:1) to receive 1 injection of either incobotulinumtoxinA or placebo in the 3 treatment areas (GFL, HFL, and LPL) using the computerized randomization program RANCODE (Version 3.6; IDV Datenanalyse und Versuchsplanung, Gauting, Germany). Randomization in blocks of appropriate size and the blockwise distribution of the products to the investigational sites were to ensure an approximately equal ratio of treatment groups between sites. The randomization schedule was sealed and locked in the total quality management department of the study sponsor and was not accessible before database close. Placebo vials had the same appearance as the test product vials to ensure that the identity of the individual study materials remained unknown to the investigator, medical staff, and all subjects. All other individuals involved in the study also remained blinded, with the exception of one individual who was responsible for reporting adverse events (AEs) to the relevant authorities.

Each 100 U vial of incobotulinumtoxinA was reconstituted with 2.5 mL sterile physiological (0.9%) sodium chloride solution, resulting in a solution of 4 U per 0.1 mL. For each subject randomized to placebo, 1 vial of placebo was also reconstituted with 2.5 mL sterile physiological (0.9%) sodium chloride solution. The injection solution was filled in a 0.3, 0.5, or 1-mL syringe, according to the investigator's preference. Either 30-gauge or 32-gauge needles were used for injection. The total administered dose of incobotulinumtoxinA ranged from 54 to 64 U (1.35–1.6 mL, depending on the dose applied to the forehead area) split between the 3 aesthetic treatment areas: GFL (20 U, i.e., 0.5 mL in equal aliquots administered across 5 injection points), HFL (10–20 U, i.e., 0.25–0.5 mL across 5 horizontally oriented points), and LPL (12 U, i.e., 0.3 mL in equal aliquots administered across 3 points

TABLE 1. Study Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Male or female subjects aged 18 years or older	Previous administration of botulinum toxin of any type in the forehead, glabellar, and/or periorbital area within the last 6 months
Evaluated as having significant psychologic strain according to the FLQA-k assessment tool	Any previous facial cosmetic procedure (e.g., dermal filling, chemical peeling, photo rejuvenation) in the forehead, glabellar, and/or periorbital areas within the last 8 months
GFL, HFL, and symmetric LPL of moderate-to-severe intensity at maximum contraction, as assessed by the investigator using the 5-point MAS	Any previous insertion of permanent material in the forehead, glabellar, and/or periorbital area (regardless of the time between previous treatment and this study)
Stable medical condition	Any facial cosmetic procedure planned for within the study period
Use of a highly effective method of birth control (for women of childbearing potential)	Very severe lines (GFL, HFL, and/or LPL) at maximum contraction, as assessed by the investigator using the MAS
	Inability to substantially lessen UFL by physically spreading them apart
	Any previous surgery/existing scars in the treatment areas
	Marked facial asymmetry
	Pregnancy or lactation
	Known hypersensitivity to the study medication

on each side of the face [24 U, 0.6 mL in total]); for injection points and dosage, see Figure 1. Subjects in the control group received 1.35 to 1.6 mL placebo solution in the same facial areas and using the same injection technique as in the incobotulinumtoxinA group.

Study Assessment and Schedule

An overview of the assessment schedule is provided in Figure 2. At Visit 1 (screening visit, completed from 14 to 3 days before baseline), each subject underwent eligibility assessment for inclusion in the study. At baseline (Day 1, Visit 2), subjects were randomized and incobotulinumtoxinA or placebo was administered. Further assessments were performed at Day 8 ± 3 (Visit 3), Day

30 ± 7 (Visit 4), Day 60 ± 7 (Visit 5), Day 90 ± 7 (Visit 6), and finally at Day 120 ± 7 (Visit 7).

At each visit, concomitant therapies, vital signs, and wrinkle scores (subject assessed and investigator assessed) were evaluated on the validated 5-point Merz Aesthetics Scales (MAS), where 0 corresponds to “no lines,” 1 “mild lines,” 2 “moderate lines,” 3 “severe lines,” and 4 “very severe lines.”¹⁰ Biochemistry/hematology analysis and fasting glucose measurements were also performed at Visits 4 and 7. Further evaluations comprising a physical examination, body height/weight measurements, and a pregnancy test in women of childbearing potential were performed at Visit 7.

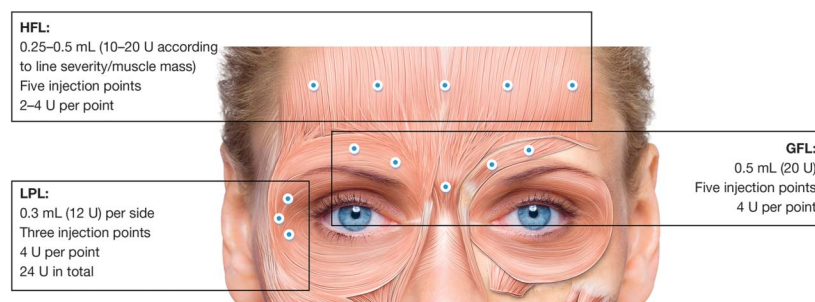


Figure 1. Division of the total administered dose of incobotulinumtoxinA (54–64 U) across the 3 aesthetic treatment areas. Figure reproduced with permission from Merz Pharmaceuticals GmbH.

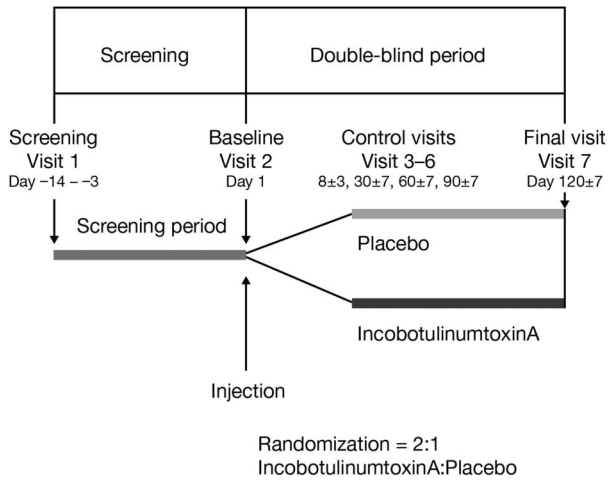


Figure 2. Study assessment schedule.

Efficacy Assessment

The primary efficacy variables comprised the rate of response as calculated by the proportion of investigator-assessed scores of “none” (0) or “mild” (1) on the 5-point MAS at maximum contraction on Day 30 for each individually treated area (GFL, HFL, and LPL) and also the investigator-assessed combined MAS sum score of ≤ 3 at maximum contraction on Day 30 for the 3 treated areas combined (GFL, HFL plus LPL). Investigator assessments were conducted by clinical evaluation in a blind manner.

Secondary efficacy variables comprised (1) an investigator-assessed response of “none” or “mild” on the MAS at maximum contraction on Days 8, 60, 90, and 120, individually for each treated area (GFL, HFL, and LPL) and simultaneously for GFL, HFL plus LPL (i.e., a sum score); (2) subject-assessed response of “none” or “mild” on the MAS at maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually; (3) investigator- and subject-assessed response of “none” or “mild” on the MAS at rest on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually; (4) investigator- and subject-assessed MAS response of at least 1-point improvement from baseline at rest and maximum contraction on Days 8, 30, 60, 90, and 120 for GFL, HFL, and LPL individually; (5) investigator- and subject-assessed responses on Day 30 for the overall appearance of the upper face according to the clinician’s and subject’s Global Impression of Change Scale (GICS); and (6) onset of

treatment effect after each injection for GFL, HFL, and LPL, individually.

Safety Assessment

Adverse events were to be reported from the time of providing each subject with the informed consent form until 120 ± 7 days after the administration of incobotulinumtoxinA or placebo. The following safety information was monitored: AE diagnosis or main symptom, date of onset, date of worsening, intensity, causal relationship, outcome, AEs leading to discontinuation of the study, and stop date. Adverse events of special interest that is indicating potential toxin spread were also monitored.

Statistical Analysis

For the primary analysis, a logistic regression model for all 3 treatment areas (GFL, HFL, and LPL) separately and the UFL combination was calculated to investigate the effect of treatment on response rates. Investigational site and baseline scores were included as factors alongside treatment group. As a confirmatory analysis, the 2-sided “Wald test” was used in a 4-step hierarchical test procedure (stepwise for each of the 3 indications and the UFL combination) based on the full analysis set (FAS) and also, for sensitivity purposes, the per-protocol set (subjects without major protocol deviations). The FAS comprised the subset of subjects from the safety evaluation set for whom primary efficacy data were available. Using this 4-step hierarchical test procedure, each test could be conducted with a significance level of 5% (2-sided), while assuring the overall significance level of 5% (2-sided).

Results

Baseline Demographics

In total, 240 subjects were screened and 156 randomized as detailed in Figure 3. There were 94 (89.5%) females and 11 (10.5%) males in the incobotulinumtoxinA group and 41 (80.4%) females and 10 (19.6%) males in the placebo group. The mean (\pm SD) age of subjects in the incobotulinumtoxinA and placebo groups was 47.4 ± 10.1 and 47.5 ± 8.4 years, respectively. Baseline MAS scores for each treatment area are presented in Table 2.

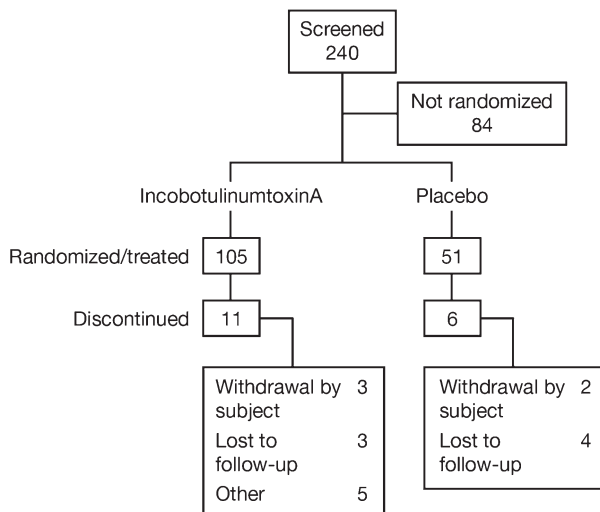


Figure 3. Patient flow diagram.

Efficacy Measurements—Primary

Investigator-assessed scores of “none” (0) or “mild” (1) on the MAS for GFL, HFL, and LPL at maximum contraction on Day 30 demonstrated a significant treatment effect of incobotulinumtoxinA, with a higher response rate among the incobotulinumtoxinA group compared with the placebo group ($p < .0001$, FAS—last observation carried forward; for observed cases, see Figure 4). Similarly, the response rate for the sum of investigator-assessed MAS scores ($MAS \leq 3$) for the 3 treated areas (GFL, HFL plus LPL) at maximum contraction on Day 30 was higher in the incobotulinumtoxinA group compared with the placebo group ($p = .0001$).

Efficacy Measurements—Secondary

At each visit, the percentage of subjects with a response (score of “none” [0] or “mild” [1]) in all 3 areas at maximum contraction, based on the investigator’s rating, was significantly higher in the incobotulinumtoxinA contraction group than in the placebo group. The highest proportion of responders in the incobotulinumtoxinA group was seen at maximum contraction on Day 8 (GFL: 80.8%; HFL: 68.3%; LPL: 51.9%) and on Day 30 (GFL: 84.5%; HFL: 70.9%; LPL: 64.1%). Thereafter, the percentage of responders slowly decreased again to Day 120. For subject-assessed MAS scores of “none” or “mild” for GFL at maximum contraction, a significant treatment effect of incobotulinumtoxinA versus placebo was shown during all visits (Days 8, 30, 60, 90, and 120). Similar results to these were obtained for HFL and LPL, up to Day 120.

At each visit, the proportion of 1-point responders at maximum contraction based on the investigator’s MAS rating was significantly higher in the incobotulinumtoxinA group than in the placebo group for both GFL and HFL (Figure 5). Similar results were obtained for LPL, up to (but excluding) Day 120. The highest percentages of 1-point responders in the incobotulinumtoxinA group were seen on Day 8 and Day 30. At these visits, more than 90% of incobotulinumtoxinA subjects were 1-point responders across all areas. Thereafter, the proportion of responders slowly

TABLE 2. Baseline Severity of GFL, HFL, and LPL According to the MAS (Investigator’s Rating at Maximum Contraction)—FAS

Treatment Area	Baseline Severity (MAS Score)	IncobotulinumtoxinA Group (n = 105)		Placebo Group (n = 51)	
		n (%)	n (%)	n (%)	n (%)
GFL	Moderate (2)	32 (30.5)	13 (25.5)		
	Severe (3)	73 (69.5)	38 (74.5)		
HFL	Moderate (2)	18 (17.1)	13 (25.5)		
	Severe (3)	87 (82.9)	38 (74.5)		
LPL*	Moderate (2)	28 (26.7)	14 (27.5)		
	Severe (3)	76 (72.4)	37 (72.5)		

*One subject in the incobotulinumtoxinA group with very severe lines is not included here.

MAS scores: 0 = no lines; 1 = mild lines; 2 = moderate lines; 3 = severe lines; 4 = very severe lines.

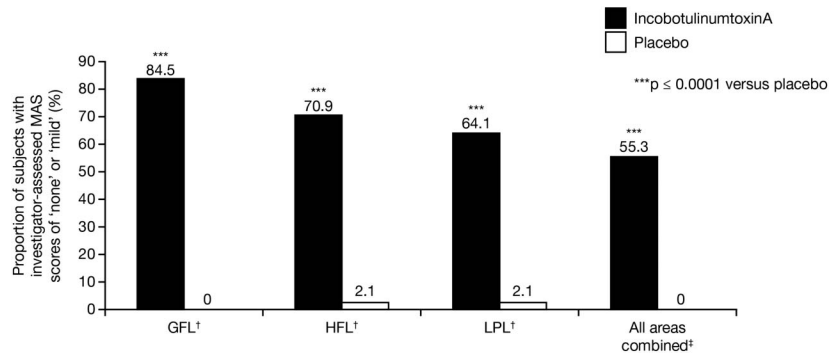


Figure 4. Response rates for investigator-assessed scores of “none” (0) or “mild” (1) on the 5-point MAS for GFL, HFL, and LPL and a sum score of 3 or lower in the UFL combination at maximum contraction on Day 30—observed cases, FAS. †Score of “none” (0) or “mild” (1); ‡sum score of 3 or lower.

decreased again. On Day 120 after incobotulinumtoxinA treatment, a treatment effect was still apparent with 1-point response rates of 30.1% (LPL; $p > .05$ vs placebo) and 41.7% (GFL and HFL; $p < .0001$ and $p = .0006$ vs placebo, respectively). Subject-assessed improvements of at least 1 point on the MAS for GFL, HFL, and LPL at maximum contraction also showed a significant treatment effect of incobotulinumtoxinA, with higher response rates for the incobotulinumtoxinA group compared with the placebo group at all visits.

At rest, a significantly higher response (score of “none” [0] or “mild” [1]) was seen among subjects in the incobotulinumtoxinA group versus the placebo group, based on investigator’s ratings at all visits for GFL and HFL and for up to (but not including) 120 days in LPL. In the respective treatment areas, the response rate tended to decrease in the incobotulinumtoxinA group over time, whereas in the placebo group, it remained roughly the same over the course of the study. Subject-assessed scores of “none” or “mild” on the MAS for GFL, HFL, and LPL at rest also showed significantly higher response rates in the incobotulinumtoxinA group compared with the placebo group at all visits.

At each visit, the proportion of 1-point responders based on the investigator’s rating of GFL and HFL at rest was significantly higher in the incobotulinumtoxinA group than in the placebo group. A similar response was seen for LPL for up to 120 days. Up to Day 90, the majority of subjects showed a 1-point response in all 3 areas. For subject-assessed improvements of at least 1

point on the MAS for GFL, HFL, and LPL at rest, significantly greater responses were seen in the incobotulinumtoxinA group compared with the placebo group on Days 8, 30, 60, 90, and 120 ($p < .0001$ for all comparisons).

Investigator-assessed and subject-assessed ratings for “much improved” (an increase of 2 points) or “very much improved” (an increase of 3 points) on the GICS were significantly more common in the incobotulinumtoxinA group compared with the placebo group ($p < .0001$; Table 3).

By the time of the first post-treatment visit (Day 8), onset of treatment effect in the GFL, HFL, and LPL facial areas was seen in the majority of subjects in the incobotulinumtoxinA group (GFL: 85.7% of subjects; HFL: 90.5% of subjects; left LPL: 73.3% of subjects; right LPL: 72.4% of subjects). The proportion of subjects for whom no date of onset was reported was higher in the LPL area (>16% of subjects) than in the GFL and HFL areas (<7%). In the placebo group, at least 80% of subjects did not report a date of onset of treatment effect in any of the treatment areas.

Safety

In total, 61.9% of subjects in the incobotulinumtoxinA group and 54.9% of subjects in the placebo group experienced a treatment-emergent AE. Treatment-emergent AEs in the incobotulinumtoxinA group occurred most frequently in the system organ class “infections and infestations” (34.3%); the most common AEs ($\geq 3\%$ of subjects in either treatment

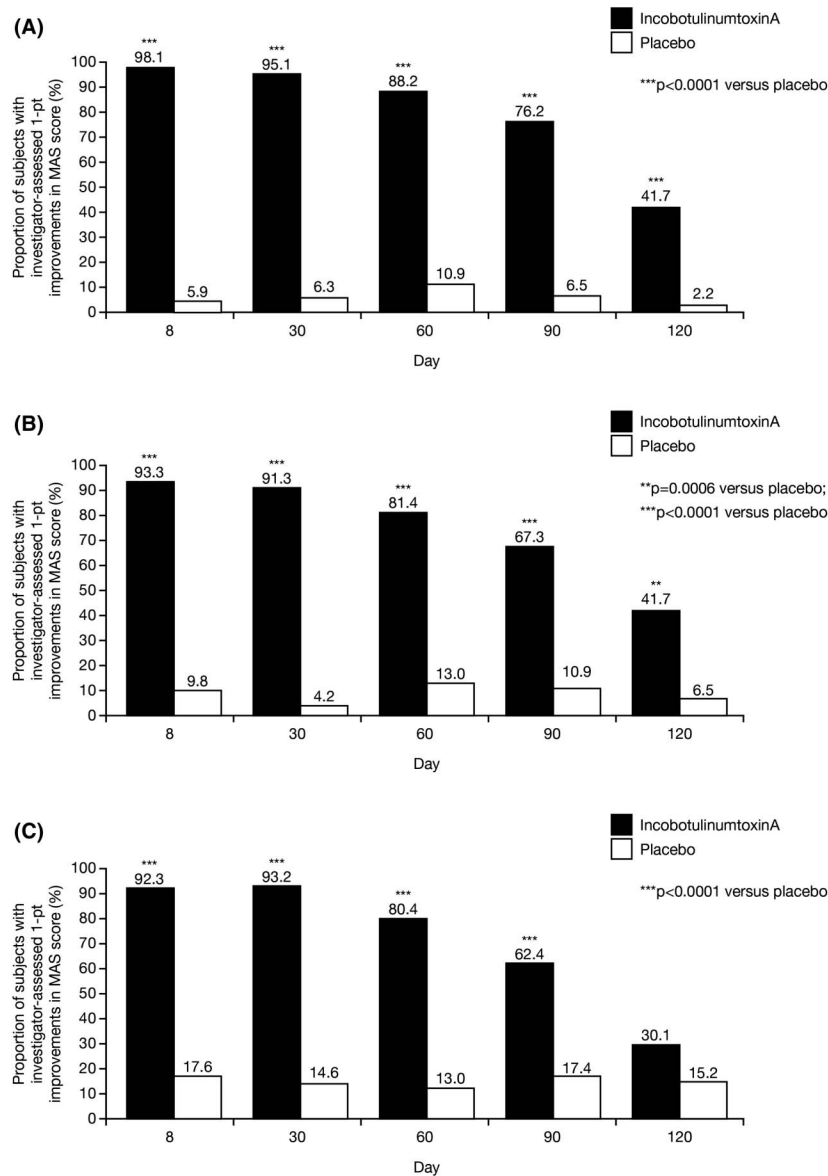


Figure 5. Response rates for investigator-assessed 1-point improvement in MAS score for (A) GFL, (B) HFL, and (C) LPL at maximum contraction at all visits—observed cases, FAS.

group) were headache (incobotulinumtoxinA, 22.9%; placebo, 2.0%), nasopharyngitis (19.0% and 19.6%), injection-site hematoma (3.8% and 5.9%), influenza (3.8% and 2.0%), upper respiratory tract infection (1.9% and 3.9%), and back pain (1.0% and 3.9%). Treatment-emergent AEs of special interest were documented for 3 subjects in the incobotulinumtoxinA group: 2 cases of eyelid ptosis, with one case being unilateral and the other being bilateral ($n = 2$; 1.9%), and 2 cases of dry eyes ($n = 2$; 1.9%). Both incidences of eyelid ptosis were considered to be mild.

Discussion

The aim of this study was to assess the efficacy and safety of incobotulinumtoxinA in subjects with moderate-to-severe UFL, using an evidence-based study design equivalent to Level I according to the Sackett¹¹ classification. The results provide the first double-blind placebo-controlled evidence that incobotulinumtoxinA produces significantly higher response rates versus placebo in both investigator- and subject-assessed MAS scores. The positive effects of treatment were maintained for up to 120 days, and the treatment was well tolerated.

TABLE 3. Proportion of Subjects With a “Much Improved” (Increase of 2 Points) or “Very Much Improved” (Increase of 3 Points) Score on the GICS at Day 30—Observed Cases, FAS

	<i>IncobotulinumtoxinA Group (n = 105)</i> Proportion (%)	<i>Placebo Group (n = 51)</i> Proportion (%)	<i>p (Logistic Regression Model)</i>
Investigator’s rating	86.4	2.1	<.0001
Subject’s rating	77.7	2.1	<.0001

Logistic regression model (including investigational site and treatment group as factors) for the treatment area combination (GFL, HFL plus LPL).
 Rating according to the GICS: -3 = very much worse; -2 = much worse; -1 = minimally worse; 0 = no change; 1 = minimally improved; 2 = much improved; 3 = very much improved.

Treatment of age-related lines and wrinkles across multiple facial areas, such as the whole upper face, results in a more complete aesthetic effect and aids harmonization of facial proportions without any notable safety concerns.¹² No previous study has provided placebo-controlled data on the use of incobotulinumtoxinA in the treatment of the UFL combination; however, 2 large placebo-controlled trials of incobotulinumtoxinA for a single indication (GFL) have been published.^{13,14} In both studies, investigators and subjects rated GFL as significantly improved with incobotulinumtoxinA versus placebo at 30 days after treatment, which is in line with the results of this study. A pooled post hoc analysis of these 2 GFL studies showed that the high response rate was maintained for up to 120 days.¹⁵ In addition, a previous study that investigated fixed doses of onabotulinumtoxinA (32, 64, and 96 U) for treatment of the whole upper face demonstrated efficacy with all 3 doses and a clear dose–response relationship. The authors of this study suggested that the 64 U dose offered a good balance between efficacy and safety in female subjects.¹⁶ Previous data has demonstrated that 24 U incobotulinumtoxinA gives good tolerability, high rates of satisfaction, and was equally as effective as onabotulinumtoxinA for the treatment of GFL.³ For the treatment of the lateral periorbital area, 12 U incobotulinumtoxinA per side has been shown to be well tolerated with comparable efficacy and duration of treatment effect to onabotulinumtoxinA.^{2,17} A retrospective study of daily aesthetic practice demonstrated good physician satisfaction with incobotulinumtoxinA for the treatment of UFL.⁹ Furthermore, a recent retrospective analysis of real-life evidence from across Europe shows that incobotulinumtoxinA is commonly used for LPL and HFL in combination with GFL and is

well tolerated.¹⁸ This study shows a high level of similarity between subject- and investigator-assessed response rates and indicates a high level of overall improvement (as assessed by subject and investigator) in the holistic appearance of UFL after treatment compared with the baseline. This is in agreement with a retrospective study of incobotulinumtoxinA for UFL, which demonstrated a high degree of subject satisfaction.⁹ In addition, an assessment of patient-reported outcomes from a study of onabotulinumtoxinA in UFL showed that the desired aesthetic effect was achieved.¹⁶ The benefits of treating UFL with incobotulinumtoxinA have been demonstrated recently in a 16-week prospective study.¹² It was shown that incobotulinumtoxinA had a significant impact on the subjects’ quality of life and satisfaction with their appearance. Patients were significantly more satisfied with their appearance after treatment, and the majority felt “younger” and “more attractive.”

Previous studies have also demonstrated good efficacy of incobotulinumtoxinA for the correction of LPL.^{2,17} Interestingly, when compared with the findings reported here, the cited investigation by Prager and colleagues shows an even higher proportion of responders at 4 months using the same dose, but an alternative definition of responder.

In this study, the response rate indicated an early onset of treatment effect in most subjects, as shown by a response at the first scheduled post-treatment visit on Day 8 ± 3. Indeed, previous evidence shows that the onset of effect of incobotulinumtoxinA in GFL occurs within the first 3 days.¹⁹ In the treatment of HFL with incobotulinumtoxinA, the dose needs to be individualized according to the subject’s age and muscle

volume to achieve the optimal aesthetic effect, as practiced in this study. It is particularly noteworthy that the treatment efficacy recorded during this investigation was maintained for up to 120 days in the majority of subjects without the need to increase the administered dose from existing recommendations.²⁰

A potential limitation of this study was that a considerable proportion of subjects that were considered otherwise eligible by the investigators were excluded owing to failing the FLQA-k score requirement. The FLQA-k was used in this study at the request of the German federal body Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) to exclude potential subjects who did not present with adequate psychologic strain as a result of their aesthetic appearance. However, these data suggest that FLQA-k should not be used in any further analyses of this type, as it appears in this case to have excluded a significant proportion of subjects who were otherwise considered suitable subjects who might benefit from botulinum toxin treatment.

Conclusion

This study provides the first placebo-controlled double-blind evidence for a significant improvement in combined UFL (GFL, 20 U; HFL, 10–20 U; LPL, 24 U), as assessed by investigators and subjects after treatment with incobotulinumtoxinA. The effects were maintained for up to 120 days, and the treatment was well tolerated.

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