# IncobotulinumtoxinA in the Treatment of Upper Facial Lines: Results From Two Randomized, Double-Blind, Placebo-Controlled, Phase III Studies

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Aesthetic Surgery Journal
2025, Vol 45(3) 293–304
Editorial Decision date: October 17, 2024; online publish-ahead-of-print October 30, 2024.

https://doi.org/10.1093/asj/sjae222
www.aestheticsurgeryjournal.com

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## Abstract

**Background:** Two randomized, double-blind, placebo-controlled, Phase III studies of incobotulinumtoxinA for treating upper facial lines (UFLs; ie, a combination of glabellar frown lines [GFLs], horizontal forehead lines [HFLs], and lateral canthal lines [LCLs]) were conducted in the United States (ULTRA I: NCT04594213) and Germany (ULTRA II: NCT04622254).

**Objectives:** The aim of this study was to evaluate the safety and efficacy of simultaneous intramuscular injections for UFLs. Longer-term safety and efficacy were assessed in open-label extension periods.

**Methods:** Healthy participants (≥18 years) with moderate-to-severe GFLs, HFLs, and symmetric LCLs at maximum contraction on the 5-point Merz Aesthetics Scales were randomized 2:1:1 to receive up to 64 units of incobotulinumtoxinA in the main period for each trial. Treatment groups were: UFLs, GFLs, and HFLs (ULTRA I), LCLs (ULTRA II), and placebo. Primary efficacy endpoints were the proportions of GFL, HFL, and LCL responders, defined as a Merz Aesthetics Scale score for the respective area of 0 (no) or 1 (mild) and a ≥2-grade improvement from baseline to Day 30, as assessed by both investigator and participant.

**Results:** Overall, 362 and 368 participants received treatment in ULTRA I and ULTRA II, respectively. In both studies, incobotulinumtoxinA treatment was significantly more effective than placebo with respect to the primary endpoints ($P < .0001$) and key secondary endpoints ($P < .0001$). The open-label extension period results were consistent with those seen in the main period. No new safety findings were identified.

**Conclusions:** In ULTRA I and ULTRA II, the safety and efficacy of incobotulinumtoxinA for the simultaneous treatment of moderate-to-severe UFLs were demonstrated, with significant improvements across all primary and secondary endpoints vs placebo.

## Level of Evidence: 1 (Therapeutic)

The treatment of facial wrinkles with botulinum neurotoxin Type A (BoNT-A) is an effective and predictable aesthetic procedure. In the United States in 2022, BoNT-A treatment was the leading nonsurgical cosmetic procedure, accounting for 39% of the total top nonsurgical procedures, with 3.9 million administrations.[1] Aesthetic dermatologists and plastic surgeons commonly administer BoNT-A preparations to reduce the appearance of glabellar frown lines (GFLs), lateral canthal lines (LCLs), and horizontal forehead lines (HFLs) due to muscle overactivity.[2-10]

BoNT-A is synthesized by a wild-type strain of the anaerobic bacterium *Clostridium botulinum*.[10-12] BoNT-A forms a high-molecular-weight complex with hemagglutinins and other nontoxic nonhemagglutinin proteins.[10,12] BoNT-A selectively acts on peripheral cholinergic nerve endings by blocking release of the neurotransmitter acetylcholine and thereby inhibiting muscle contraction.[11,12]

IncobotulinumtoxinA, a freeze-dried formulation of BoNT-A, is highly purified without complexing proteins present.[7,13] Complexing proteins can induce neutralizing antibody formation leading to secondary treatment failure and are not required for effectiveness.[14] Treatment with incobotulinumtoxinA therefore lowers foreign protein

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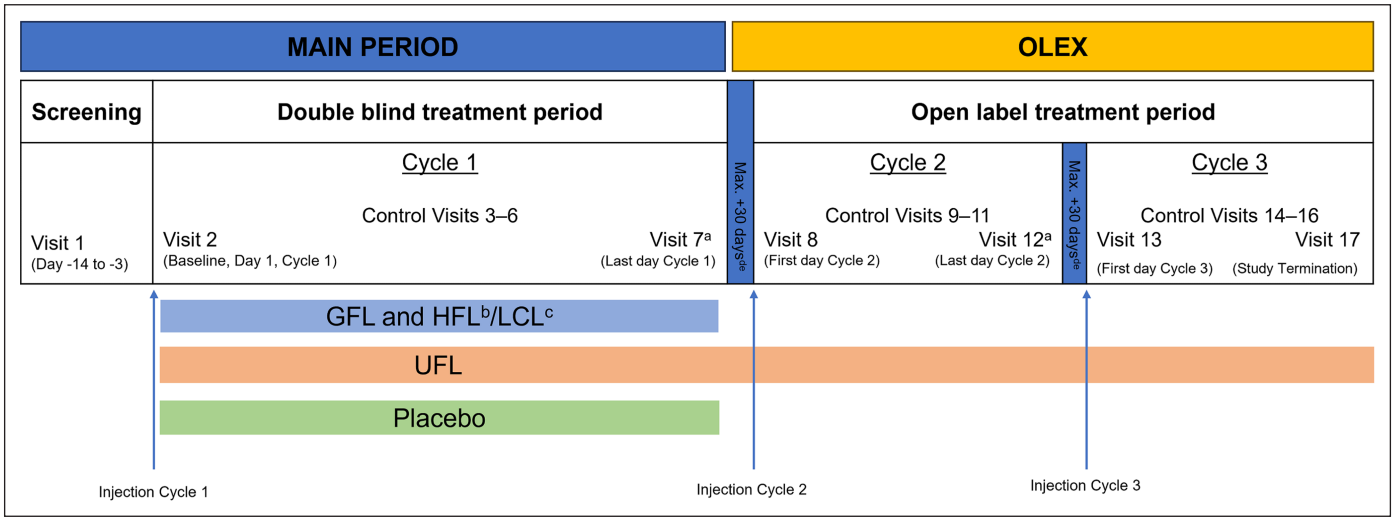


**Figure 1.** Study design for ULTRA I and ULTRA II. [a]Visit 7 (end-of-Cycle 1 visit) and Visit 8 (Cycle 2 baseline visit), as well as Visit 12 (end-of-Cycle 2 visit) and Visit 13 (Cycle 3 baseline visit) were performed on the same day if all eligibility criteria were met. [b]In ULTRA I, GFLs and HFLs were treated with incobotulinumtoxinA. [c]In ULTRA II, LCLs were treated with incobotulinumtoxinA. [d]If the eligibility criteria were not fulfilled, an eligibility reassessment for entry into the next cycle at an optional visit within 30 days if possible was required. [e]If a participant fulfilled the eligibility criteria at an additional eligibility visit, this visit was combined with the next injection visit. GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines; OLEX, open-label extension; UFLs, upper facial lines.

load delivered per unit of toxin.[14] As clients are seeking BoNT-A injections at an earlier age, and new indications are emerging, the purity of the toxin is of prime importance. Currently approved in more than 80 countries, including 30 European Union/European Economic Area countries, the United States, the United Kingdom, Canada, and Japan,[15-19] incobotulinumtoxinA is marketed under the brand names Xeomin, Bocouture (European Union/European Economic Area only), Xeomin Cosmetic (Canada only for aesthetic use) and Xeomeen (Belgium and Mexico only). IncobotulinumtoxinA is approved in the United States to treat or improve the symptoms of adult patients with chronic sialorrhea, upper-limb spasticity, cervical dystonia, and blepharospasm, and to achieve temporary improvement in the appearance of moderate-to-severe GFLs with corrugator and/or procerus muscle activity.[17] In the European Union it is approved for blepharospasm and cervical dystonia, spasticity, sialorrhea, GFLs, lateral periorbital lines, and upper facial lines (UFLs; ie, a combination of GFLs, HFLs, and LCLs).[16] Combined treatment for the upper facial region in the same session is desirable for many clients as it may result in a more harmonized aesthetic effect and maintenance of facial proportions.[20] These 2 Phase III studies were conducted in the United States and Germany to provide further safety and efficacy data for simultaneous intramuscular injections of incobotulinumtoxinA for treating UFLs, utilizing a horizontal injection technique in the HFL area. Open-label extension periods (OLEX) assessed longer-term safety and efficacy.

# METHODS

## Study Design

Two prospective, randomized, double-blind, placebo-controlled, international, multicenter Phase III studies were conducted across 12 sites in the United States (ULTRA I; NCT04594213) and 12 sites in Germany (ULTRA II; NCT04622254). ULTRA I was conducted between September 2020 and May 2022 and ULTRA II was conducted between November 2020 and July 2022. The protocol was approved by IRBs and/or independent ethics committees: for the United States, Advarra, number Pro00044813; for Germany, the Ethics Committee of the Hamburg Medical Association, number PVN7390. All participants provided written informed consent, and the study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. Both studies (Figure 1) consisted of a similar study design: a double-blind, placebo-controlled main period (MP) with 1 incobotulinumtoxinA (Merz Pharmaceuticals GmbH, Frankfurt, Germany) injection cycle followed by an OLEX with 2 incobotulinumtoxinA injection cycles.

Participants were randomly assigned 2:1:1 by an interactive web response system into 3 different treatment groups. During the MP, participants in the UFL treatment group (Group U) received a total dose of 64 units (U) of incobotulinumtoxinA as simultaneous injections in all three facial areas; 20 U in the GFL area, 20 U in the HFL area, and 24 U in the LCL area. Participants in the placebo group (Group P) received placebo in all 3 facial areas; participants in the GFL and HFL treatment group (ULTRA I, Group G&H) received a total dose of 40 U, 20 U each in both the GFL and HFL areas and placebo in the LCL area; and participants in the LCL treatment group (ULTRA II, Group L) received a total dose 24 U in the LCL area (12 U each side) and placebo in the GFL and HFL areas. Randomization was stratified by investigational site in blocks of 8. During the MP, blinded personnel prepared the intervention. Sponsor staff and data management/biostatistics staff were blinded to the data.

The planned duration of the MP (Cycle 1) was 120 days plus screening (Days −3 to −14). All randomized participants were to be followed up for 120 days and eligibility for reinjection was confirmed before participants entered the respective OLEX for each study. The OLEX for each study comprised 2 additional treatment cycles, Cycle 2 and Cycle 3, with planned durations of 120 days each plus up to 30 days for eligibility reassessments per cycle.

## Study Participants

Eligible participants included male and female subjects, aged 18 years or older with HFLs, GFLs, and symmetric LCLs of moderate (score 2) to severe (score 3) intensity at maximum contraction as assessed by the investigator and participant according to the 5-point Merz Aesthetics Scales (MAS).[21,22] Exclusion criteria included previous BoNT treatment of any serotype in the face within the last 12 months

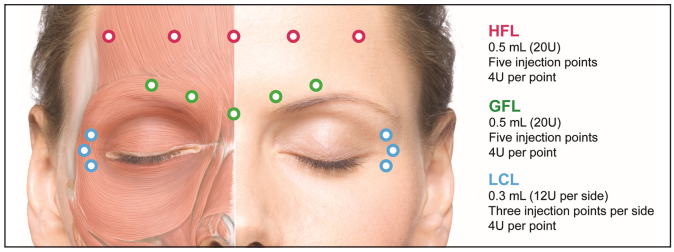


**Figure 2.** Injection scheme. GFL, glabellar frown lines; HFL, horizontal forehead lines; LCL, lateral canthal lines; U, units. Copyright of this image is held by Quintessence Publishing (Batavia, IL; www.quintessence-publishing.com) and has been reproduced with permission from the copyright holder.

before injection, any facial cosmetic procedure within the last 12 months before baseline injection (eg, dermal filling, chemical peeling, photorejuvenation, mesotherapy, photodynamic therapy), and use of topical or systemic retinoids within the last 6 months prior to injection. Complete inclusion/exclusion criteria are shown in Supplemental Table 1. Participants were recruited irrespective of gender, ethnic background, and pretreatment status.

## Study Treatment

IncobotulinumtoxinA was provided in quantities of 100 U in glass vials, lyophilized to be reconstituted with 2.5 mL unpreserved sterile physiological (0.9%) sodium chloride solution for injection. Placebo was provided in identical glass vials with excipients only (sucrose, human serum albumin). IncobotulinumtoxinA and placebo were manufactured by Merz Pharma GmbH, Dessau-Rosslau, Germany, and released by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. In the MP, each injection point was injected with either 0.1 mL of incobotulinumtoxinA or placebo. In the OLEX, each injection point was injected with 0.1 mL of incobotulinumtoxinA (Figure 2).

## Assessments

The severity of the GFLs, HFLs, and LCLs (left and right side separately) was determined according to the investigator's live assessment and the participant's self-assessment on the validated 5-point MAS for UFLs (0, "no lines"; 1, "mild lines"; 2, "moderate lines"; 3, "severe lines"; 4, "very severe lines"),[21,22] as indicated in the study visit schedules. While the 4-point Facial Wrinkle Scales range from none to severe,[23] the 5-point MAS has an advantage of including a very severe category,[20] supporting better participant selection. All investigators were trained and qualified on the MAS before evaluating study participants.

Using baseline photographs as a comparison, investigators and participants also individually assessed aesthetic improvement after treatment using the balanced 7-point Likert Global Aesthetic Improvement Scale (GAIS) (range −3 to +3, where −3 = very much worse to +3 = very much improved). The GAIS was assessed on all postinjection visits.

Assessments were to be completed independently at a place with adequate lighting and without disturbance at the beginning of the respective study visit. Participants also completed diaries to record the onset of treatment effect. Additionally, all occurrences of adverse events (AEs), related treatment-emergent AEs (TEAEs), TEAEs of special interest (TEAESIs) and treatment-emergent serious AEs (TESAEs) were recorded.

## Primary Endpoints

The 3 primary efficacy endpoints were the proportions of GFL-, HFL-, and LCL-responders at Day 30 of the MP. Response was defined as a MAS score for the respective area of 0 (no) or 1 (mild) and at least a 2-grade improvement from baseline to Day 30 of the MP at maximum contraction as assessed by both investigator and participant. Left and right LCLs were assessed separately.

## Key Secondary Endpoints

There were 7 key secondary efficacy endpoints: endpoints 1-3 were the proportion of participants with a score of 0 (no) or 1 (mild) on the MAS (as rated by the investigator) for GFLs, HFLs, and both the left and right LCLs at maximum contraction, respectively, at Day 30 of the MP; endpoints 4-6 were the proportion of participants with a score of 0 (no) or 1 (mild) on the MAS (as rated by the participant) for GFLs, HFLs, and both the left and right LCLs at maximum contraction, respectively, at Day 30 of the MP; endpoint 7 was the GAIS score as assessed by the participant at Day 30 of the MP.

## Further Secondary Endpoints

There were 4 further secondary efficacy endpoints: endpoints 1-3 were the proportion of participants with at least a 1-grade improvement from baseline to Day 30 of the MP on the MAS (as rated by the investigator) for GFLs, HFLs, and both the left and right LCLs at maximum contraction, respectively; endpoint 4 was the GAIS score as assessed by the investigator at Day 30 of the MP.

## Other Efficacy Endpoints

In the MP and OLEX (Cycle 2 and Cycle 3), the MAS was used to assess GFLs, HFLs, and both left and right LCLs. Assessments were made at each postinjection visit of the rating condition (maximum contraction/rest) and by each rater (investigator/participant). From these assessments, the proportions of participants with at least a 2-grade improvement from cycle baseline, and at least a 1-grade improvement from cycle baseline or a score of 0 (no) or 1 (mild) were derived. The GAIS score was also assessed by the investigator and participant at the same time points.

Onset of treatment effect was assessed as the time from injection until date at which the effect was first noted by the participant in the diary for each treated area. For the LCL region, the effect had to be present for the left and right side simultaneously.

## Safety Endpoints

No primary safety endpoint was defined. The secondary safety endpoint was the incidence of related TEAEs in the MP and OLEX. Other safety endpoints included incidences of TEAEs, TEAESIs, TESAEs, and TEAESIs.

## Statistical Analysis

Each study aimed to have 360 participants randomly allocated to the groups. The sample size was intended to ensure at least 300 participants completed the study to achieve statistical significance. The sample size provided sufficient power of >90% to assess efficacy under conservative assumptions for the responder rates in Group U and Group P.

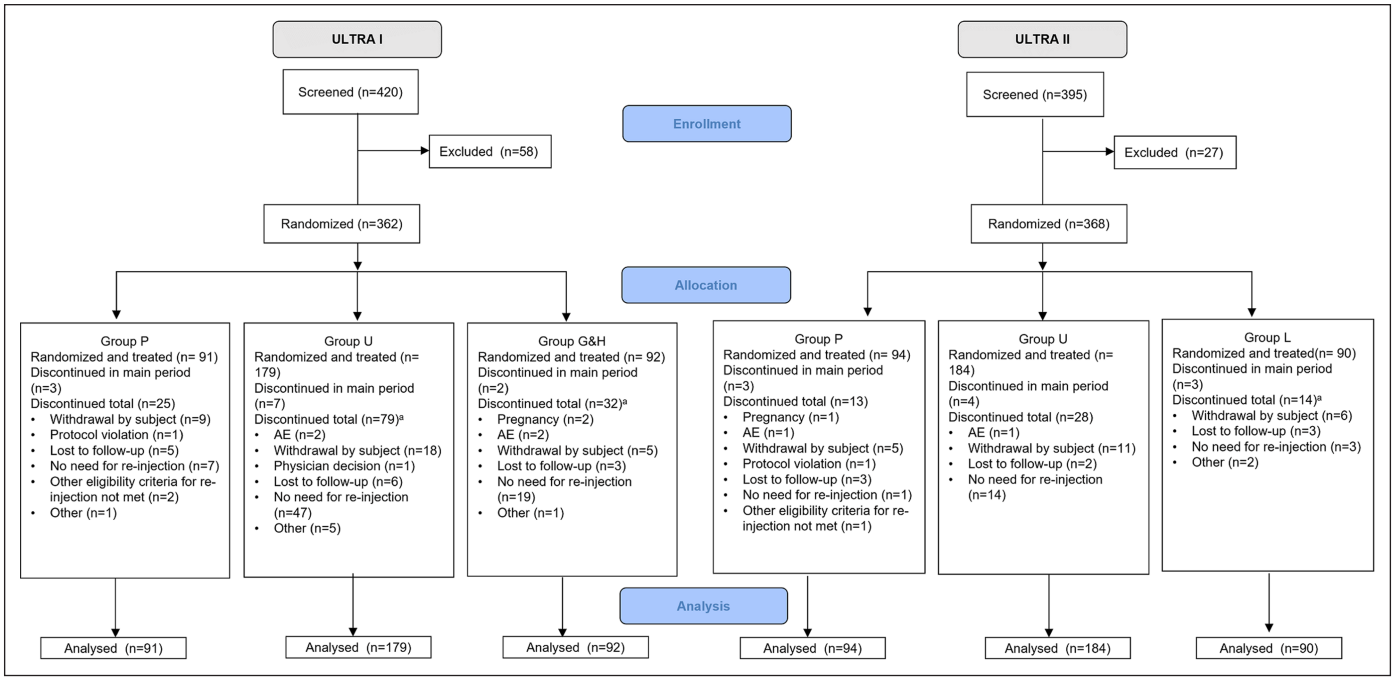


**Figure 3.** CONSORT diagram of participant allocation and analysis for ULTRA I and ULTRA II. [a]In ULTRA I, patients who discontinued during the study due to the COVID-19 pandemic were in Group U (n = 1) and Group G&H (n = 2). In ULTRA II, the only patient who discontinued due to the COVID-19 pandemic was in Group L (n = 1). AE, adverse event; COVID-19, coronavirus disease 2019; G&H, glabellar frown lines and horizontal forehead lines; L, lateral canthal lines; P, placebo; U, upper facial lines.

The MAS assessments at Day 30 were used to determine treatment efficacy. A composite strategy approach was applied for intercurrent events of BoNT treatment (except study medication) in the respective area and prohibited concomitant treatment indicating lack of efficacy. Treatment policy strategy was applied for intercurrent events of other prohibited treatments possibly confounding or moderating the treatment effect. Imputation of missing primary endpoint data followed a conservative approach.

Primary efficacy analysis was based on all randomized participants with HFLs, GFLs, and LCLs of moderate-to-severe intensity at maximum contraction, as assessed by both investigator and participant in Groups U and P (the target population of the main primary estimand). Group G&H (ULTRA I) and Group L (ULTRA II) were not included in the primary efficacy analysis. Responder rates across all anatomical sites in treatment Groups U and P were compared by 2-sided 95% Wilson CIs. Stratum-adjusted differences in responder rates and corresponding 95% CIs were calculated, together with the *P*-value from the Mantel-Haenszel test of the 2-sided null hypothesis. A hierarchical test procedure was applied to control the family-wise 2-sided Type I error level $\alpha = 0.05$. Several sensitivity and supplementary analyses were performed using the full analysis set (FAS), the per protocol set (PPS), and different strategies for handling missing data.

Key secondary efficacy endpoint analyses were also included in the hierarchical testing procedure. For the MAS-based endpoints, the same statistical method as described for the primary efficacy analysis was used. For the participant's GAIS endpoint, an analysis of covariance with factors treatment group and site and mean of baseline MAS for the 3 areas at maximum contraction assessed by the participant as a covariate was used to calculate the mean least squares (LS) difference and corresponding 95% CI and *t*-test *P*-value for the null hypothesis of no treatment difference. Several supplementary analyses were performed for the key secondary endpoints, using the FAS and the PPS.

Further secondary endpoints were not included in the statistical testing hierarchy and were analyzed using the FAS and the PPS, based on observed data. All 3 treatment groups were included; however, Group G&H (for ULTRA I) was not compared with placebo in the analysis for the LCL region, and Group L (for ULTRA II) was not compared with placebo in the analysis for the GFL and HFL regions because participants in these groups received placebo treatment in the respective areas.

Safety analyses were performed on the safety evaluation set, defined as all participants who were exposed to study medication at least once. All statistical analyses were performed with the SAS statistical software package, version 9.4 (SAS Institute, Cary, NC) by CRO Metronomia Clinical Research GmbH.

# RESULTS

## Demographics

From September 23, 2020 through May 9, 2022, a total of 362 participants in the United States underwent randomization in ULTRA I; and from November 12, 2020 through July 8, 2022, a total of 368 participants in Germany underwent randomization in ULTRA II. A total of 226 participants (62.4%) in ULTRA I and 313 participants (85.1%) in ULTRA II completed the entire trial, including the OLEX. In ULTRA I, 136 (37.6%) participants discontinued, and in ULTRA II, 55 (14.9%) participants discontinued. Approximately 20% to 30% of participants in both studies discontinued because participants did not require reinjection (ULTRA I: n = 73 [20.2%]; ULTRA II: n = 18 [32.7%]). Other reasons for discontinuation included withdrawal by participant (ULTRA I: n = 32 [8.8%]; ULTRA II: n = 22 [5.9%]), participant lost to follow-up (ULTRA I: n = 14 [3.8%]; ULTRA II: n = 8 [2.1%]), and AEs (ULTRA I: n = 4 [1.1%]; ULTRA II: n = 2 [0.5%]). Further information regarding participant disposition is shown in Figure 3.

Demographics and participant clinical characteristics at baseline were similar across the treatment groups in each trial and were considered representative of the typical population seeking BoNT-A treatment (Table 1). In ULTRA I, the mean participant age was 47.4 years (range, 22-76 years) and 85.1% (n = 308/362) of participants were female. In

**Table 1.** Participant Demographics in ULTRA I and ULTRA II, Full Analysis Set

| | ULTRA I | | | ULTRA II | | |
|---|---|---|---|---|---|---|
| | Group P[a] (N = 91) | Group U[a] (N = 179) | Group G&H[a] (N = 92) | Group P[a] (N = 94) | Group U[a] (N = 184) | Group L[a] (N = 90) |
| **Female sex** | 79 (86.8%) | 154 (86.0%) | 75 (81.5%) | 84 (89.4%) | 147 (79.9%) | 72 (80.0%) |
| **Age (years)** | | | | | | |
| Mean [SD] | 47.5 [13.0] | 47.2 [13.2] | 47.8 [13.5] | 44.8 [9.15] | 46.0 [9.92] | 45.9 [9.88] |
| Median (range) | 48.0 (23-74) | 49.0 (22-76) | 50.0 (22-73) | 45.0 (27-64) | 46.0 (19-70) | 44.5 (27-70) |
| **Age category** | | | | | | |
| 18-64 | 83 (91.2%) | 162 (90.5%) | 83 (90.2%) | 94 (100.0) | 177 (96.2%) | 85 (94.4%) |
| 65-84 | 8 (8.8%) | 17 (9.5%) | 9 (9.8%) | 0 (0.0) | 7 (3.8%) | 5 (5.6%) |
| **Ethnicity** | | | | | | |
| Hispanic or Latino | 28 (30.8%) | 49 (27.4%) | 29 (31.5%) | 1 (1.1%) | 2 (1.1%) | 2 (2.2%) |
| Not Hispanic or Latino | 63 (69.2%) | 130 (72.6%) | 63 (68.5%) | 93 (98.9%) | 182 (98.9%) | 88 (97.8%) |
| **Race** | | | | | | |
| White | 79 (86.8%) | 150 (83.8%) | 80 (87.0%) | 94 (100.0%) | 182 (98.9%) | 89 (98.9%) |
| Black or African American | 7 (7.7%) | 20 (11.2%) | 7 (7.6%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) |
| Asian | 2 (2.2%) | 7 (3.9%) | 3 (3.3%) | 0 (0.0%) | 0 (0.0%) | 1 (1.1%) |
| Other[b] | 3 (3.3%) | 2 (1.1) | 2 (2.2%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) |
| **Fitzpatrick skin type** | | | | | | |
| Type I | 3 (3.3%) | 3 (1.7%) | 1 (1.1%) | 1 (1.1%) | 3 (1.6%) | 2 (2.2%) |
| Type II | 22 (24.2%) | 37 (20.7) | 25 (27.2%) | 44 (46.8%) | 76 (41.3%) | 33 (36.7%) |
| Type III | 31 (34.1%) | 69 (38.5%) | 30 (32.6%) | 38 (40.4%) | 86 (46.7%) | 47 (52.2%) |
| Type IV | 23 (25.3%) | 49 (27.4%) | 23 (25.0%) | 11 (11.7%) | 17 (9.2%) | 8 (8.9%) |
| Type V | 9 (9.9%) | 15 (8.4%) | 10 (10.9%) | 0 (0.0%) | 2 (1.1%) | 0 (0.0%) |
| Type VI | 3 (3.3%) | 6 (3.4%) | 3 (3.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Height (cm)** | | | | | | |
| Mean [SD] | 166.54 [10.01] | 166.0 [9.03] | 165.68 [9.28] | 168.97 [7.84] | 169.51 [8.15] | 169.7 [8.97] |
| Median (range) | 165.1 (147.3-210.8) | 165.1 (142.2-198.1) | 164.0 (151.0-193.0) | 168.0 (150.0-190.0) | 169.0 (148.0-193.0) | 169.0 (150.0-195.0) |
| **Weight (kg)** | | | | | | |
| Mean [SD] | 68.99 [12.70] | 72.92 [15.30] | 71.90 [19.53] | 69.40 [13.29] | 70.83 [14.48] | 69.30 [12.61] |
| Median (range) | 65.8 (44.5-111.6) | 71.2 (45.8-119.7) | 66.7 (47.6-158.8) | 67.6 (43.0-110.0) | 68.5 (43.0-125.0) | 68.0 (45.0-101.2) |
| **BMI ($kg/m^2$)** | | | | | | |
| Mean [SD] | 24.9 [3.94] | 26.4 [5.11] | 26.1 [6.15] | 24.2 [3.73] | 24.5 [4.15] | 24.0 [3.59] |
| Median (IQR) | 24.0 (18-37) | 25.7 (18-46) | 24.4 (18-58) | 23.7 (17-36) | 23.9 (18-43) | 23.8 (18-40) |
| **Prior treatment with BoNT of any serotype for any indication** | | | | | | |
| Yes | 68 (74.7%) | 130 (72.6%) | 65 (70.7%) | 54 (57.4%) | 119 (64.7%) | 50 (55.6%) |
| No | 23 (25.3%) | 49 (27.4%) | 27 (29.3%) | 40 (42.6%) | 65 (35.3%) | 40 (44.4%) |

**Table 1.** Continued

| | ULTRA I | | | ULTRA II | | |
|---|---|---|---|---|---|---|
| | Group P[a] (N = 91) | Group U[a] (N = 179) | Group G&H[a] (N = 92) | Group P[a] (N = 94) | Group U[a] (N = 184) | Group L[a] (N = 90) |
| **Moderate (MAS score = 2) baseline severity, investigator assessed** | | | | | | |
| GFLs | 39.6% | 39.1% | 40.2% | 44.7% | 45.7% | 47.8% |
| HFLs | 33.0% | 30.7% | 26.1% | 27.7% | 29.3% | 28.9% |
| Right LCLs | 39.6% | 45.8% | 44.6% | 50.0% | 49.5% | 36.7% |
| Left LCLs | 39.6% | 45.8% | 44.6% | 50.0% | 49.5% | 36.7% |
| **Moderate (MAS score = 2) baseline severity, participant assessed** | | | | | | |
| GFLs | 35.2% | 36.3% | 40.2% | 46.8% | 39.1% | 38.9% |
| HFLs | 26.4% | 22.3% | 21.7% | 20.2% | 21.7% | 16.7% |
| Right LCLs | 35.2% | 35.8% | 32.6% | 39.4% | 39.1% | 30.0% |
| Left LCLs | 34.1% | 36.9% | 32.6% | 39.4% | 39.1% | 30.0% |
| **Severe (MAS score = 3) baseline severity, investigator assessed** | | | | | | |
| GFLs | 60.4% | 60.9% | 59.8% | 55.3% | 54.3% | 52.2% |
| HFLs | 67.0% | 69.3% | 73.9% | 72.3% | 70.7% | 71.1% |
| Right LCLs | 60.4% | 54.2% | 55.4% | 50.0% | 50.5% | 63.3% |
| Left LCLs | 60.4% | 54.2% | 55.4% | 50.0% | 50.5% | 63.3% |
| **Severe (MAS score = 3) baseline severity, participant assessed** | | | | | | |
| GFLs | 63.7%[c] | 62.6%[d] | 57.6%[e] | 53.2% | 60.3%[f] | 61.1% |
| HFLs | 72.5%[c] | 76.0%[d] | 77.2%[e] | 79.8% | 77.7%[f] | 83.3% |
| Right LCLs | 64.8% | 63.1%[d] | 66.3%[e] | 60.6% | 59.8%[f] | 70.0% |
| Left LCLs | 64.8%[c] | 62.0%[d] | 65.2%[e] | 60.6% | 60.3%[f] | 70.0% |

Values are n (%), mean [SD], median (range) or IQR (range). GFLs, glabellar frown lines; HFLs, horizontal forehead lines; IQR, interquartile range; LCLs, lateral canthal lines; SD, standard deviation. [a]Group P: placebo group, Group U: upper facial lines (a combination of GFLs, HFLs, and LCLs) treated with incobotulinumtoxinA; Group G&H: only GFLs and HFLs treated with incobotulinumtoxinA; Group L, only LCLs treated with incobotulinumtoxinA. [b]Other race includes American Indian, Alaska Native, Native Hawaiian or other Pacific Islander, and more than one race. [c]In ULTRA 1 Group P, 1.1% of participants rated their GFLs and HFLs and left LCLs as very severe. [d]In ULTRA 1 Group U, 1.1% of participants rated their GFLs and both left and right LCLs as very severe; and 1.7% rated their HFLs as very severe. [e]In ULTRA 1 Group G&H, 1.1% of participants rated their GFLs and HFLs and right LCLs as very severe, 2.2% rated their left LCLs as very severe, and 1.1% of participants rated their GFLs as mild. [f]In ULTRA 2 Group U, 0.5% of participants rated their GFLs and HFLs and left and right LCLs as very severe, and 0.5% rated their right LCLs as mild.

ULTRA II, the mean age was 45.7 years (range, 19-70 years) and 82.3% (n = 303/368) of participants were female. Baseline severity of GFLs, HFLs, and LCLs at maximum contraction were comparable across treatment groups in both ULTRA I and ULTRA II, as rated by both investigator and participant (Table 1). Participant ratings tended to be more severe than investigator ratings. The mean total observation period was 316.7 days (range, 35-477 days) for participants in ULTRA I and 347.7 days (range, 1-442 days) in ULTRA II.

## Primary Efficacy Analysis

In both studies, incobotulinumtoxinA treatment was significantly more effective than placebo in achieving the primary efficacy outcome. In ULTRA I, there was a statistically significant difference in the proportion of responders at Day 30 between Group U and Group P for all 3 primary efficacy endpoints (Table 2). The stratum-adjusted risk difference was 51.9% (95% CI, 44.5-59.3; $P < .0001$) for GFLs, 66.6% (95% CI, 59.6-73.5; $P < .0001$) for HFLs, and 51.2% (95% CI, 43.8-58.6; $P < .0001$) for LCLs.

Similarly, in ULTRA II, a statistically significant difference in the proportion of responders at Day 30 between Group U and Group P was observed for all 3 primary efficacy endpoints (Table 2). The stratum-adjusted risk difference was 49.4% (95% CI, 42.1-56.7; $P < .0001$) for GFLs, 57.6% (95% CI, 50.4-64.8; $P < .0001$) for HFLs, and 32.1% (95% CI, 25.3-38.9; $P < .0001$) for LCLs.

**Table 2.** Primary Efficacy Endpoint Analysis, Including Sensitivity and Supplementary

| Area of treatment | ULTRA I | | | | | | | ULTRA II | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group P[a] | | Group U[a] | | Stratum-adjusted risk difference[b] | | *P*-value | Group P[a] | | Group U[a] | | Stratum-adjusted risk difference[b] | | *P*-value |
| | n/N | % | n/N | % | % | 95% CI | | n/N | % | n/N | % | % | 95% CI | |
| GFLs | 0/90 | 0 | 92/176 | 52.3 | 51.9 | 44.5-59.3 | *P* < .0001 | 0/94 | 0 | 90/182 | 49.5 | 49.4 | 42.1-56.7 | *P* < .0001 |
| HFLs | 0/90 | 0 | 117/176 | 66.5 | 66.6 | 59.6-73.5 | *P* < .0001 | 0/94 | 0 | 105/182 | 57.7 | 57.6 | 50.4-64.8 | *P* < .0001 |
| LCLs | 0/90 | 0 | 91/176 | 51.7 | 51.2 | 43.8-58.6 | *P* < .0001 | 0/94 | 0 | 59/182 | 32.4 | 32.1 | 25.3-38.9 | *P* < .0001 |

The table includes the proportion of participants with score of 0 (no) or 1 (mild) and at least a 2-grade improvement from baseline to Day 30 of MP in GFLs, HFLs, and LCLs as assessed by both investigator and participant on the MAS (target population of the main primary estimand). GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines; MAS, Merz Aesthetics Scale; MP; main period; n/N, number of responders/number of subjects in respective analysis set. [a]Group P: placebo group, Group U: upper facial lines (a combination of GFLs, HFLs, and LCLs) treated. [b]Mantel-Haenszel stratum weights and the Sato variance estimator used to calculate the stratum-adjusted risk difference with associated 95% CI and the *P*-value for the Mantel Haenszel test of the null hypothesis that the common risk difference (Group U-Group P) is zero. Study site served as stratum variable.

**Table 3.** Summary of Key Secondary Endpoints

| Rater and area of treatment | ULTRA I | | | | | | | ULTRA II | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group P[a] (N = 91) | | Group U[a] (N = 176) | | Stratum-adjusted risk difference[b] | | | Group P[a] (N = 94) | | Group U[a] (N = 182) | | Stratum adjusted risk difference[b] | | |
| | n (%) | 95% CI[c] | n (%) | 95% CI[c] | % | 95% CI[c] | *P*-value | n (%) | 95% CI[c] | n (%) | 95% CI[c] | % | 95% CI[c] | *P*-value |
| MAS | | | | | | | | | | | | | | |
| Investigator-assessed GFLs | 0 | 0.0-4.1 | 156 (88.6%) | 83.1-92.5 | 88.4 | 83.7-93.2 | *P* < .0001 | 0 | 0.0-3.9 | 158 (86.8%) | 81.1-91.0 | 87.1 | 82.3-91.9 | *P* < .0001 |
| Investigator-assessed HFLs | 0 | 0.0-4.1 | 162 (92.0%) | 87.1-95.2 | 92.0 | 88.0, 96.0 | *P* < .0001 | 1 (1.1%) | 0.2-5.8 | 157 (86.3%) | 80.5-90.5 | 85.3 | 79.9-90.6 | *P* < .0001 |
| Investigator-assessed LCLs | 3 (3.3%) | 1.1-9.3 | 143 (81.3%) | 74.8-86.3 | 77.9 | 70.9-84.9 | *P* < .0001 | 2 (2.1%) | 0.6-7.4 | 138 (75.8%) | 69.1-81.5 | 73.4 | 66.5-80.3 | *P* < .0001 |
| Participant-assessed GFLs | 2 (2.2%) | 0.6-7.7 | 133 (75.6%) | 68.7-81.3 | 73.3 | 66.3-80.3 | *P* < .0001 | 1 (1.1%) | 0.2-5.8 | 134 (73.6%) | 66.8-79.5 | 72.8 | 66.1-79.5 | *P* < .0001 |
| Participant-assessed HFLs | 1 (1.1%) | 0.2-6.0 | 136 (77.3%) | 70.5-82.8 | 76.3 | 69.8-82.8 | *P* < .0001 | 2 (2.1%) | 0.6-7.4 | 144 (79.1%) | 72.6-84.4 | 77.0 | 70.3-83.7 | *P* < .0001 |
| Participant-assessed LCLs | 3 (3.3%) | 1.1-9.3 | 116 (65.9%) | 58.6-72.5 | 62.3 | 54.4-70.2 | *P* < .0001 | 3 (3.2%) | 1.1-9.0 | 119 (65.4%) | 58.2-71.9 | 61.9 | 54.2-69.7 | *P* < .0001 |
| GAIS | | | | | | | | | | | | | | |
| Participant-assessed GAIS | Group P[a] | | Group U[a] | | LS-mean difference vs Group P | | | Group P[a] | | Group U[a] | | LS-mean difference vs Group P | | |
| | LS-mean | 95% CI | LS-mean | 95% CI | LS-mean | 95% CI | *P*-value[d] | LS-mean | 95% CI | LS-mean | 95% CI | LS-mean | 95% CI | *P*-value[d] |
| | 0.08 | −0.06 to 0.23 | 2.24 | 2.14-2.35 | 2.16 | 1.98-2.34 | *P* < .0001 | 0.02 | −0.11 to 0.15– | 2.00 | 1.90-2.09 | 1.98 | 1.81-2.14 | *P* < .0001 |

The table includes (1-6) GFLs, HFLs, LCLs scoring 0 (no) or 1 (mild) at maximum contraction at Day 30 as assessed by investigator and participant on MAS and (7) covariance analysis of participant-assessed GAIS at Day 30 (target population of main key secondary estimand). GAIS, Global Aesthetic Improvement Scale; GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines; LS, least squares; MAS, Merz Aesthetics Scale; n, number of participants. [a]Group P: placebo group, Group U: upper facial lines (a combination of GFLs, HFLs, and LCLs) treated with incobotulinumtoxinA. [b]Mantel-Haenszel stratum weights and the Sato variance estimator used to calculate the stratum-adjusted risk difference with associated 95% CI and the *P*-value for the Mantel-Haenszel test of the null hypothesis that the common risk difference (Group U-Group P) is zero. Study site served as stratum variable. [c]Wilson CI. [d]*t*-test of the null hypothesis that the LS-mean treatment difference (LS-mean Group U – LS-mean group P) is zero.

The sensitivity and supplementary analyses performed using the FAS and the PPS and different strategies for handling missing data for both trials showed comparable results.

## Key Secondary Efficacy Analysis

In ULTRA I, a statistically significant difference in the proportion of responders between Group U and Group P was observed for all MAS-based key secondary efficacy endpoints as assessed (separately) by the investigator and by the participant (Table 3). Endpoints based on investigator assessments showed stratum-adjusted risk differences of 88.4% (95% CI, 83.7-93.2; *P* < .0001) for GFLs, 92.0% (95% CI, 88.0-96.0; *P* < .0001) for HFLs, and 77.9% (95% CI, 70.9-84.9; *P* < .0001) for LCLs. Endpoints based on participant ratings showed stratum-adjusted risk differences of 73.3% (95% CI, 66.3-80.3; *P* < .0001) for GFLs, 76.3% (95% CI, 69.8-82.8; *P* < .0001) for HFLs, and 62.3% (95% CI, 54.4-70.2; *P* < .0001) for LCLs,

For participant-assessed GAIS at maximum contraction at Day 30, there was a statistically significant improvement in the GAIS score in those treated with incobotulinumtoxinA vs placebo and the estimated LS-mean difference for Group U compared with Group P was 2.16 (95% CI, 1.98-2.34; *P* < .0001).

Similarly, in ULTRA II, statistically significant differences in the endpoints between Group U and Group P were observed for all key secondary efficacy endpoints as assessed (separately) by the investigator and participant (Table 3). The investigator assessments showed stratum-adjusted risk differences of 87.1% (95% CI, 82.3-91.9; *P* < .0001) for GFLs, 85.3% (95% CI, 79.9-90.6; *P* < .0001) for HFLs, and 73.4% (95% CI, 66.5-80.3; *P* < .0001) for LCLs. The participant assessments showed stratum-adjusted risk differences of 72.8% (95% CI, 66.1-79.5; *P* < .0001)


**Figure 4.** Representative participant photographs at maximum contraction: baseline (left) and Day 30 of the main period (right). (A) Baseline GFLs. (B) Day 30 GFLs. (C) Baseline HFLs. (D) Day 30 HFLs. (E) Baseline LCLs. (F) Day 30 LCLs. GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines.

for GFLs, 77.0% (95% CI, 70.3-83.7; $P < .0001$) for HFLs, and 61.9% (95% CI, 54.2-69.7; $P < .0001$) for LCLs.

For participant-assessed GAIS at maximum contraction at Day 30, there was an estimated LS-mean difference of 1.98 (95% CI, 1.81-2.14; $P < .0001$) for Group U compared with Group P, indicating a statistically significantly improved GAIS score in those treated with incobotulinumtoxinA vs placebo.

The supplementary analyses performed using the FAS and the PPS for both trials showed comparable results.

Representative photographs of participants used for GAIS assessments at baseline and Day 30 of the MP are shown in Figure 4. Representative at-rest photographs are provided in Supplemental Figure 1.

## Further Secondary Endpoints

In ULTRA I, the statistical analyses indicated differences in Group U, Group G&H, and for the combined total incobotulinumtoxinA group in comparison to Group P for GFLs and HFLs. For LCLs, differences were seen in Group U in comparison to Group P. No comparisons were made for Group G&H for the LCL region because this region was treated with placebo in this group (Table 4).

In ULTRA II, the statistical analyses indicated differences in Group U, Group L, and for the combined total incobotulinumtoxinA group in comparison to Group P for LCLs. For GFLs and HFLs, the analyses indicated differences in Group U in comparison to Group P. No comparisons were made for Group L with the GFLs and HFLs because these regions were treated with placebo (Table 4).

In both trials, analysis of GAIS as assessed by investigator also indicated an improvement in incobotulinumtoxinA treatment groups compared with placebo.

The results presented for further secondary endpoints are those for the FAS; however, the PPS results were comparable.

## Other Efficacy Endpoints

In the OLEX for both trials, results across Cycles 2 and 3 were consistent with those seen for Group U in the MP. Rates of participants meeting each of the defined other secondary endpoints at maximum contraction were high, with peak efficacy observed early in both cycles (ie, Day 8 and Day 30) and then decreased towards the end of each cycle.

In ULTRA I, the estimated median time to onset of treatment effect in both Group U and Group G&H during the MP was 4 days for GFLs and 3 days for HFLs. Additionally, the median time to onset of treatment effect for LCLs was 4 days in Group U.

In ULTRA II, the estimated median time to onset of treatment effect in Group U during the MP was 4 days for GFLs and HFLs, and 5 days for LCLs. For Group L, the median time to onset of treatment effect was 7 days.

For Group P in both trials, the median time to onset of treatment effect was not estimable due to the overall low rate of participants noting a treatment effect.

Median time to onset of treatment effect in the OLEX of both trials was similar to that of Group U during the MP.

## Safety Analysis

In the MP of ULTRA I, for participants treated with incobotulinumtoxinA, the incidence of any AE was 21.0% and the incidence of TEAEs was 6.3%, compared with 15.4% and 2.2% treated with placebo, respectively (Table 5). The overall incidences of TESAEs and of TEAEs leading to discontinuation were low (0.4% and 1.1%, respectively) and none were related to treatment. In Group P participants, the incidence of TESAEs was 1.1% and no participants in Group P had a TEAE that led to discontinuation. No TEAESIs were observed. Injection site bruising was the most common AE (3.0% in total incobotulinumtoxinA group vs 2.2% in the placebo group) behind COVID-19 (3.7% in total incobotulinumtoxinA group vs 3.3% in the placebo group).

In the OLEX, the incidence of any AEs was 26.4% and the incidence of TEAEs was 6.3% (Supplemental Table 2).

In the MP of ULTRA II, for participants treated with incobotulinumtoxinA, the incidence for any AE was 45.6%, and the incidence of TEAEs was 16.4%, compared with 44.7% and 12.8% in Group P, respectively (Table 5). The incidences of TESAEs, TEAEs leading to discontinuation, and TEAESIs were low (1.1%, 0.4%, and 0.4%, respectively). In Group P participants, the incidence of TESAEs was 4.3% and no participants in Group P had a TEAE that led to discontinuation. Additionally, there were no TEASIs in Group P. None of the TESAEs, TEAEs leading to discontinuation, or TEAESIs were related to treatment. The most commonly documented TEAE in all groups was injection site hematoma (8.8% in total incobotulinumtoxinA group vs 8.5% in the placebo group).

**Table 4.** Summary of Further Secondary Endpoints

| Rater and area of treatment | | ULTRA I | | | | ULTRA II | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Group P[a] (N = 91) | Group U[a] (N = 179) | Group G&H[a] (N = 92) | Total Inco (N = 271) | Group P[a] (N = 94) | Group U[a] (N = 184) | Group L[a] (N = 90) | Total Inco (N = 274) |
| MAS | | | | | | | | | |
| Investigator-assessed GFLs | Crude response rates | 1 (1.1%) | 167 (96.5%) | 89 (96.7%) | 256 (96.6%) | 5 (5.5%) | 175 (96.7%) | 4 (4.5%) | NE[d] |
| | Stratum-adjusted risk differences compared with Group P[b] (95% CI) | — | 95.3% (91.6-99.0) | 95.4% (90.0-99.8) | 95.3% (92.1-98.6) | — | 91.1% (85.7-96.6) | NE[d] | NE[d] |
| Investigator-assessed HFLs | Crude response rates | 2 (2.2%) | 166 (96.0%) | 89 (96.7%) | 255 (96.2%) | 3 (3.3%) | 174 (96.1%) | 3 (3.4%) | NE[e] |
| | Stratum-adjusted risk differences compared with Group P[b] (95% CI) | — | 93.7% (89.3-98.1) | 94.4% (89.5-99.4) | 94.0% (90.0-97.9) | — | 92.9% (88.1-97.6) | NE[e] | NE[e] |
| Investigator-assessed LCLs | Crude response rates | 7 (7.9%) | 154 (89.0%) | 27 (29.3%) | NE[c] | 8 (8.8%) | 166 (91.7%) | 60 (68.2%) | 226 (84.0%) |
| | Stratum-adjusted risk differences compared with Group P[b] (95% CI) | — | 81.7 (74.6-88.8) | NE[c] | NE[c] | — | 83.0% (76.0-90.1) | 59.7% (48.7-70.7) | 75.3% (68.1-82.5) |
| GAIS[f] | | | | | | | | | |
| Investigator-assessed GAIS | LS-mean differences compared with Group P (95% CI) | — | 2.38 (2.22, 2.54) | 1.94 (1.75, 2.12) | — | — | 2.20 (2.06, 2.34) | 0.65 (0.49, 0.82 | — |

The table includes (1-3) GFLs, HFLs, and LCLs with at least a 1-grade improvement from baseline to Day 30 of the MP at maximum contraction at Day 30 as assessed by investigator on the MAS, and (4) the covariance analysis of investigator-assessed GAIS at Day 30 (FAS [OC]). FAS, full analysis set; GAIS, Global Aesthetic Improvement Scale; GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines; inco, incobotulinumtoxinA; MAS, Merz Aesthetics Scale; MP, main period; n/N, number of participants; NE, not evaluated; OC, observed cases. [a]Group P: placebo group; Group U: upper facial lines (a combination of GFL, HFLs, and LCLs) treated with incobotulinumtoxinA; Group G&H: only GFLs and HFLs treated with incobotulinumtoxinA; Group L, only LCLs treated with incobotulinumtoxinA. [b]Mantel-Haenszel stratum weights and the Sato variance estimator used to calculate the stratum-adjusted risk difference with associated 95% CI and the *P*-value for the Mantel Haenszel test of the null hypothesis that the common risk difference (test group—Group P) is zero. Study site served as stratum variable. [c]No comparisons were made for Group G&H (or total incobotulinumtoxinA) with Group P for this endpoint because participants in Group G&H received placebo treatment in the LCLs. [d]No comparisons were made for Group L or Total incobotulinumtoxinA with Group P for this endpoint because participants in Group L received placebo treatment in the GFLs. [e]No comparisons were made for Group L or Total incobotulinumtoxinA with Group P for this endpoint because participants in Group L received placebo treatment in the HFLs. [f]GAIS analysis numbers for ULTRA I Group U (N = 172), and for ULTRA II Group U (N = 181), Group L (N = 88).

In the OLEX, the incidence of any AE was 62.7% and the incidence of TEAEs was 17.9% (Supplemental Table 2). Injection site hematoma incidence increased slightly in the OLEX, with an incidence of 12.1% in total.

## DISCUSSION

BoNT-A treatment for aesthetic improvement is popular amongst men and women who want to maintain a youthful and healthy appearance without having surgery and is currently the most widely used nonsurgical procedure worldwide.[24]

In these 2 Phase III trials, the efficacy and safety of incobotulinumtoxinA vs placebo for improving moderate-to-severe UFLs was demonstrated. UFLs were targeted through simultaneous treatment in the GFL, HFL, and LCL areas, and the treatment effect with incobotulinumtoxinA was evident after 4 to 5 days in all treatment groups. Additionally, many participants discontinued as they did not meet the reinjection eligibility criteria. Therefore, those participants did not require reinjection and treatment effect was observed for up to 150 days.

The overwhelmingly positive primary endpoint results across both trials clearly showed statistically significant treatment effects of incobotulinumtoxinA compared with placebo, with the primary efficacy endpoints met in all 3 facial areas, confirming the efficacy of simultaneous UFL treatment. Results of the sensitivity, subgroup, and supplementary analyses were generally consistent with the results of the primary analysis. These results were further supported by significant treatment effects of incobotulinumtoxinA vs placebo in all 7 key secondary endpoints, as assessed by both participants and investigators, in addition to participant-assessed GAIS score. Participant ratings, both at baseline and at the specific endpoint assessments, tended to be more severe than investigator ratings. This resulted in slightly lower participant-based ratings of treatment effects compared with investigator ratings—a difference that has been seen in other studies and demonstrates the tendency of participants to have a more critical self-appraisal of facial aging.[25] Despite this, overwhelmingly positive treatment responses were clearly demonstrated by both the investigator and participant assessments. Overall results were also comparable between Group U in the MP and the OLEX period and showed no reduction in efficacy due to

**Table 5.** Safety Summary for Main Period, Safety Evaluable Set

| | ULTRA I | | | | ULTRA II | | | |
|---|---|---|---|---|---|---|---|---|
| | Group P[a] (N = 91) | Group U[a] (N = 179) | Group G&H[a] (N = 92) | Total Inco (N = 271) | Group P[a] (N = 94) | Group U[a] (N = 184) | Group L[a] (N = 90) | Total Inco (N = 274) |
| n (%) of participants with: | | | | | | | | |
| **Any AEs** | 14 (15.4%) | 37 (20.7%) | 20 (21.7%) | 57 (21.0%) | 42 (44.7) | 90 (48.9) | 35 (38.9) | 125 (45.6%) |
| **TEAEs** | 2 (2.2%) | 11 (6.1%) | 6 (6.5%) | 17 (6.3%) | 12 (12.8) | 35 (19.0) | 10 (11.1) | 45 (16.4%) |
| **Any serious AEs** | 1 (1.1%) | 0 (0.0%) | 1 (1.1%) | 1 (0.4%) | 4 (4.3) | 1 (0.5) | 2 (2.2) | 3 (1.1%) |
| **Any serious TEAEs** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Any AEs leading to discontinuation** | 0 (0.0%) | 0 (0.0%) | 3 (3.3%) | 3 (1.1%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 1 (0.4%) |
| **Any TEAEs leading to discontinuation** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Any fatal TEAEs** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Any TEAEs related to COVID-19** | 3 (3.3%) | 8 (4.5%) | 2 (2.2%) | 10 (3.7%) | 5 (5.3%) | 3 (1.6%) | 0 (0.0%) | 3 (1.1%) |
| n (%) of participants with TEAEs (incidence ≥ 2% in any treatment group) | | | | | | | | |
| **General disorders and administration site conditions**[b] | 4 (4.4%) | 6 (3.4%) | 5 (5.4%) | 11 (4.1%) | 11 (11.7%) | 23 (12.5%) | 12 (13.3%) | 35 (12.8%) |
| Injection site bruising | 2 (2.2%) | 4 (2.2%) | 4 (4.3%) | 8 (3.0%) | NR | NR | NR | NR |
| Injection site hematoma | NR | NR | NR | NR | 8 (8.5%) | 15 (8.2%) | 9 (10.0%) | 24 (8.8%) |
| **Nervous system disorders** | 3 (3.3%) | 4 (2.2%) | 1 (1.1%) | 5 (1.8%) | 8 (9.6%) | 21 (11.4%) | 9 (10.0%) | 30 (10.9%) |
| Headache | 2 (2.2%) | 4 (2.2%) | 1 (1.1%) | 5 (1.8%) | 8 (8.5%) | 19 (10.3%) | 7 (7.8%) | 26 (9.5%) |
| **Infections and infestations** | 3 (3.3%) | 13 (7.3%) | 6 (6.5%) | 19 (7.0%) | 15 (16.0) | 30 (16.3%) | 7 (7.8%) | 37 (13.5%) |
| Nasopharyngitis | NR | NR | NR | NR | 4 (4.3%) | 3 (1.6%) | 3 (3.3%) | 6 (2.2%) |
| COVID-19 | 3 (3.3%) | 8 (4.5%) | 2 (2.2%) | 10 (3.7%) | 4 (4.3%) | 2 (1.1%) | 0 (0.0%) | 2 (0.7%) |
| **Skin and subcutaneous tissue disorders** | 0 (0.0%) | 5 (2.8%) | 0 (0.0%) | 5 (1.8%) | 3 (3.2%) | 6 (3.3%) | 1 (1.1%) | 7 (2.6%) |
| Brow ptosis | 0 (0.0%) | 3 (1.7%) | 0 (0.0%) | 3 (1.1%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 1 (0.4%) |
| Eyelid ptosis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

AE, adverse-event; inco, incobotulinumtoxinA; NR, not reported; OLEX, open-label extension period; TEAE, treatment-emergent adverse event. [a]Group P: placebo group, Group U: upper facial lines (a combination of glabellar frown lines, horizontal forehead lines, and lateral canthal lines) treated with incobotulinumtoxinA; Group G&H: only glabellar frown lines and horizontal forehead lines treated with incobotulinumtoxinA; Group L, only lateral canthal lines treated with incobotulinumtoxinA. [b]Includes: injection site bruising, discomfort, injection site pruritis, edema, and injection site hematoma.

repeated treatment cycles. The response rates for various endpoints in the present trials are similar to those reported in a previous European placebo-controlled, Phase III study and its OLEX, which also evaluated incobotulinumtoxinA for UFL treatment.[20,25]

Across the study periods (MP and OLEX) 136 participants in ULTRA I and 55 participants in ULTRA II discontinued. However, the discontinuation reason for many of these participants was that they did not require reinjection (ULTRA I: n = 73; ULTRA II: n = 18), which, whilst it qualifies as a reason for discontinuation, actually indicates successful treatment, especially longer-lasting treatment effects. Importantly, although "withdrawal by participant" was a common reason for discontinuation, with 32 (8.8%) participants withdrawing in ULTRA I, and 22 (6.0%) participants withdrawing in ULTRA II, no participants in either trial withdrew because of a lack of treatment effect.

In the current studies, up to 64 U of incobotulinumtoxinA was well tolerated when administered to all 3 facial regions, with no new safety findings; this is consistent with previous studies of incobotulinumtoxinA and other BoNT-A formulations, including onabotulinumtoxinA, daxibotulinumtoxinA, and abobotulinumtoxinA.[3-5,20,26-29]

Frequent TEAEs seen with BoNT-A formulations include eyebrow or eyelid ptosis, headache, blepharoptosis, injection site events, and unilateral eyelid ptosis.[3,26,27] In both studies, there were no serious TEAEs in either the MP or the OLEX, and relatively low numbers of treatment-related brow and eyelid ptosis were recorded. In the ULTRA I MP, brow ptosis, a known side effect for the single indication GFL, was reported in only 3 participants in Group U and there were no cases of eyelid ptosis. No cases of brow or eyelid ptosis were recorded in the OLEX. In the ULTRA II MP, brow ptosis was reported in 1 participant, and there were no cases of eyelid ptosis. In the OLEX, there were 5 cases of brow ptosis and 3 cases of eyelid ptosis. The low rates of brow and eyelid ptosis could be attributed to the horizontal injection pattern in the HFLs as shown in Figure 2, which has shown previous success in a European study of incobotulinumtoxinA for UFLs.[20] Overall, safety was comparable between the MP and

OLEX, indicating that up to 3 cycles of simultaneous treatment in 3 UFL indications did not raise any additional safety concerns.

Although both trials demonstrated overwhelmingly positive efficacy results and safety profile, marginal differences were observed in outcomes between Germany and the United States. For example, the number of any TEAEs was higher in the ULTRA II trial in all cohorts vs ULTRA I (Group U: 48.9% vs 20.7%; Group L: 38.9% vs Group G&H: 21.7%; Group P: 44.7% vs 15.4%). Similarly, rates of TEAEs were higher in the ULTRA II trial in all cohorts, including the placebo group, with the most frequently reported related TEAEs being headaches, injection site hematoma, and injection site bruising. However, no serious TEAEs were observed in any group, in either the MP or the OLEX, across both trials. A potential reason for the increased frequency of AE reporting could be due to cultural/national differences.

The results of these 2 Phase III clinical trials add valuable information regarding the efficacy and safety of incobotulinumtoxinA for the simultaneous treatment of UFLs in a large sample of adult participants from the United States and Germany. In addition, the results from the OLEX of both studies provide long-term efficacy and safety data for multiple treatment cycles of incobotulinumtoxinA over a period of approximately 1 year.

Regarding the study limitations, as with many other trials with BoNT-As,[26] more than 80% of participants in both trials were women. Although this is representative of the typical population seeking aesthetic procedures, there is currently an increasing interest being seen among men, and future trials could be required to confirm any sex-specific differences in treatment. A pooled analysis of male participants from 3 Phase III studies of incobotulinumtoxinA indicated that males demonstrated lower response rates on wrinkle severity scales and that variations in treatment response can be attributed to male anatomic differences.[30] Further investigation into the need for customized treatment for males could be warranted. Although the statistically significant positive outcomes observed on the participant-assessed GAIS suggest participants were satisfied with their treatment, this measure is unlikely to be as sensitive as a specific participant satisfaction endpoint (using an instrument such as the validated Facial Lines Treatment Satisfaction Questionnaire).[31] Finally, although the participants who continued through the OLEX were followed for approximately 1 year as per FDA guidance for BoNT-A treatment,[32] as clients are seeking treatment at an earlier age, future studies assessing even longer-term effects of both one-off and repeated treatments would be informative.

## CONCLUSIONS

The Phase III ULTRA I and ULTRA II studies successfully demonstrated the safety and efficacy of incobotulinumtoxinA for the improvement of moderate-to-severe UFLs (whilst simultaneously treating the GFL, HFL, and LCL regions), with improvements compared with placebo seen across all primary and secondary efficacy endpoints. In both studies, incobotulinumtoxinA was well tolerated across up to 3 cycles of treatment and no new safety findings were identified.

## Supplemental Material

This article contains supplemental material located online at https://doi.org/10.1093/asj/sjae222.

## Acknowledgments

The authors would like to thank the following investigators from both trials and their respective institutions for participation in this study and all the study participants.

ULTRA I: Cheryl M. Burgess, MD (Washington, DC); Joel L. Cohen, MD (Greenwood Village, CO); William P. Coleman, III, MD (Metairie, LA); Sabrina Fabi, MD (San Diego, CA); Steven Fagien, MD (Boca Raton, FL); Michael H. Gold, MD (Nashville, TN); Michael A. Kane, MD (New York, NY); Z. Paul Lorenc, MD (New York, NY); Mark Steven Nestor, MD, PhD (Aventura, FL); Neil Sadick, MD (New York, NY); and Steve Yoelin, MD (Newport Beach, CA).

ULTRA II: Matthias Imhof (Bad Soden, Germany); Thomas M. Proebstle (Mannheim, Germany); Martina Hund (Berlin, Germany); Johannes Niesmann (Bochum, Germany); Welf Prager (Hamburg, Germany); Tanja Fischer (Potsdam, Germany); Thomas Dirschka (Wuppertal, Germany); Tatjana Pavicic (Munich, Germany); Gerd Gauglitz (Munich, Germany); Eva Kristina Bee (Drensteinfurt, Germany); Rodrigo da Mota (Düsseldorf, Germany).

The authors would also like to acknowledge the study teams at Merz, Susanna Roll, Martin Gonzalez, Rada Dakovic, and Petra Weissenberger for their contributions. Medical writing support was provided by Bryony McNamara and Adam Taylor of Alchemy Medical Writing Ltd. (Stirling, Scotland) and funded by Merz in accordance with Good Publication Practice guidelines.

## Disclosures

Dr Joseph is a consultant, investigator, and advisory board member for Merz North America, Inc. (Raleigh, NC), Jetema Co. (Seoul, South Korea), Allergan (Irvine, CA), Galderma (Lausanne, Switzerland), Evolus (Newport Beach, CA), and Revance Therapeutics, Inc. (Nashville, TN). Dr Joseph participated in the research and data collection and was the lead investigator for the ULTRA I study. Dr Sudimac is an employee of Merz Aesthetics GmbH (Frankfurt, Germany) and participated in the data interpretation, writing of the manuscript, and journal selection. Dr Mesmann is a consultant for Merz Aesthetics GmbH and participated in data interpretation and analysis. Dr Kerscher is a consultant, investigator, and advisory board member for Merz North America, Inc. and Merz Aesthetics GmbH, Allergan/Abbvie (North Chicago, IL), Ipsen Innovation (Les Ulis, France), Kythera Biopharmaceuticals, Inc. (Calabasas, CA), Q-Med (Uppsala, Sweden)/Galderma, L'Oréal (Clichy, France), and Neauvia (Geneva, Switzerland). Dr Kerscher participated in the research and data collection and was the lead investigator for the ULTRA II study. All authors reviewed and approved the manuscript.

## Funding

This work was funded by Merz Aesthetics GmbH (Frankfurt, Germany).

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