OPEN

Treatment of Upper Facial Lines With DaxibotulinumtoxinA for Injection: Results From an Open-Label Phase 2 Study

Jeffrey S. Dover, MD,* Shannon D. Humphrey, MD,† Z. Paul Lorenc, MD,‡§ Ava Shamban, MD,‖ Todd M. Gross, PhD,¶ Roman G. Rubio, MD,¶ and Domenico Vitarella, PhD¶

ABSTRACT BACKGROUND Simultaneous treatment of moderate-to-severe upper facial lines is reflective of real-world clinical practice.

OBJECTIVE To evaluate the efficacy and safety of daxibotulinumtoxinA-lanm for injection (DAXI) for simultaneous treatment of glabellar, forehead, and lateral canthal (LC) lines.

METHODS In this open-label, single-arm Phase 2 study, patients (48 enrolled, 94% completed, follow-up 24–36 weeks) received DAXI 40U (glabellar), 32U (forehead), and 48U (LC) lines. Key efficacy endpoints: percentages of patients achieving none/mild wrinkle severity (investigator-rated) for each upper facial line scale at Week 4.

RESULTS At Week 4, most patients achieved none/mild wrinkle severity (investigator-rated): glabellar (96%), forehead (96%), and LC (92%). Median times to loss of none/mild response (investigator- and patient-rated) among all patients were: 24.6 (glabellar), 20.9 (forehead), and 24.9 (LC) weeks; and 25.0, 24.0, and 28.1 weeks, respectively, among Week-4 responders. At Week 4, most patients reported improvements (Global Aesthetic Improvement Scale: 96%-98%) and high satisfaction rates (85%-98%). Five patients experienced treatment-related adverse events: injection-site erythema (3 patients/7 events), facial discomfort (2 patients/2 events), and headache (1 patient/1 event). No patients experienced eyebrow or eyelid ptosis.

CONCLUSION Simultaneous treatment of upper facial lines with DAXI was well tolerated and demonstrated high response rates, extended duration, and high patient satisfaction.

CLINICAL TRIAL REGISTRY https://clinicaltrials.gov/ct2/show/NCT04259086.

DaxibotulinumtoxinA-lanm for injection (DAXI; DAXXIFY, Revance Therapeutics, Inc., Nashville, TN) is a novel botulinum toxin Type A (BoNTA) formulation in development for various aesthetic and therapeutic indications. The DAXI formulation includes a 150-kD core neurotoxin and RTP004, a proprietary stabilizing peptide excipient. Currently available BoNTA products can include accessory proteins and are formulated with human serum albumin, both of which are not included in DAXI.[1]

The efficacy and safety of DAXI for treatment of glabellar lines (GL) has been established in 5 clinical trials evaluating over 3,000 patients, including the Phase 3 SAKURA clinical program, which included the placebo-controlled SAKURA 1 and 2 studies and a large open-label repeat-dose study, SAKURA 3.[2–6] These studies confirmed that DAXI 40U provides prolonged duration of clinical benefit (median ≥24 weeks) and is well tolerated over 3 cycles throughout an 84-week treatment period. In addition, separate Phase 2 studies were conducted in forehead lines (FHL; ClinicalTrials.gov Identifier: NCT03786770) and lateral canthal lines (LCL; ClinicalTrials.gov Identifier: NCT03911102) to establish an effective dose and injection pattern for DAXI in these upper facial areas.

Because simultaneous treatment of upper facial lines is more reflective of real-world clinical practice, the objective of this study was to evaluate the efficacy, duration of effect, and safety of DAXI for simultaneous treatment of GL, FHL, and LCL.

Methods

Study Design

This multicenter, open-label, single-arm Phase 2 study was conducted at 8 sites (United States [US], Canada) between

*From the * SkinCare Physicians, Chestnut Hill, Massachusetts; † Department of Dermatology and Skin Science, University of British Columbia, Vancouver, British Columbia, Canada; ‡ Lorenc Aesthetic Plastic Surgery Center, New York, New York; § Department of Plastic Surgery, Lenox Hill Hospital, New York, New York; ‖ Ava MD, Santa Monica, California; ¶ Revance Therapeutics, Inc., Nashville, Tennessee*

J.S. Dover, S.D. Humphrey, P. Lorenc and A. Shamban have served as investigators and consultants for Revance Therapeutics, Inc. T.M. Gross, D. Vitarella and R.G. Rubio are employees or were employees of Revance Therapeutics at the time of the study. This analysis was supported by Revance Therapeutics, Inc. (Nashville, TN). Writing and editorial assistance was provided to the authors by Evidence Scientific Solutions (Philadelphia, PA) and was funded by Revance Therapeutics, Inc. Revance Therapeutics, Inc. was involved in the study design, collection, analysis, and interpretation of the data; writing of the report; and decision to submit the report for publication. The authors did not receive honoraria or payments for authorship.

The authors have indicated no significant interest with commercial supporters.

Address Correspondence and Reprint Requests to: Domenico Vitarella, PhD, Revance Therapeutics, Inc., 7555 Gateway Boulevard, Newark, CA 94560, or e-mail: dvitarella@revance.com

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatologicsurgery.org).

http://dx.doi.org/10.1097/DSS.0000000000003637

December 2019 and November 2020 (ClinicalTrials.gov identifier: NCT04259086). The study protocol was approved by the relevant institutional review board (Advarra, formerly Quorum Review IRB) and independent ethics committees and conformed to the ethical guidelines of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent, and agreed to the use and analysis of their data, before any study-related procedures.

Patients

Eligible patients were adults (≥18 years) with moderate or severe GL at maximum frown as assessed by the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient Frown Wrinkle Severity (PFWS) scales[2]; moderate or severe FHL at maximum eyebrow elevation as assessed by the Investigator Global Assessment–Forehead Wrinkle Severity (IGA-FHWS) and the Patient Forehead Wrinkle Severity (PFHWS) scales; and moderate or severe LCL at maximum smile effort as assessed by the Investigator Global Assessment–Lateral Canthal Wrinkle Severity (IGA-LCWS) and the Patient Lateral Canthal Wrinkle Severity (PLCWS) scales.

Patients were excluded for any of the following reasons: received facial BoNTA treatment in the 6 months before screening; used dermal fillers, barbed lifting sutures, or any product that could affect skin remodeling in the previous 12 months; used prescription oral retinoids in the previous 6 months; underwent nonablative laser or light treatments, microdermabrasion, or chemical peels in the previous 3 months; used a topical steroid, immunosuppressive agent, antiplatelet agent, or anticoagulant agent in the previous 30 days; used a nonsteroidal anti-inflammatory drug in the previous 7 days; used an agent that may interfere with neuromuscular transmission in the previous 14 days; or underwent any procedure that may affect the upper facial region in the previous 12 months.

Treatment and Procedures

On Day 1, patients received a single DAXI treatment as follows: DAXI 40U distributed via 5 standardized injections of 8U each in the glabellar region, DAXI 32U administered via 4 equal 8U injections in the frontalis, and DAXI 48U via 6 injections of 8U each (3 in each lateral canthal area) (Figure 1).

Baseline assessments of facial wrinkle line severity were conducted at the screening visit, no more than 14 days before Day 1. The severity of facial wrinkle lines was assessed by investigators and patients using 4-point scales from none (0) to severe (3) and included the validated IGA-FWS and PFWS scales[2] and the IGA-FHWS, PFHWS, IGA-LCWS, and PLCWS scales, which were scientifically validated and developed and in accordance with the US FDA guidance.

Patients were followed for at least 24 weeks and up to 36 weeks. Because of the coronavirus-19 (COVID-19) pandemic, some patients were followed remotely between Weeks 8 and 32; data were not collected for patients who could not attend a remote visit (Figure 1). Follow-up continued until patients' facial wrinkle severity scores returned to baseline, or worse, on investigator and patient assessments for all 3 treated areas. Any patient who returned to baseline wrinkle severity (or worse) before Week 36 for any upper facial line completed a final visit and were classified as an early completer. Standardized (before/after treatment) digital photographs at rest and at maximum frown, maximum eyebrow elevation, and maximum smile effort were captured throughout the study. Remote visits were conducted by telephone or video conference interview and included assessments of efficacy and safety and use of concomitant therapies and medications. If needed, patients were trained on how to take appropriate facial photographs.

Endpoints

The key efficacy endpoints were the percentages of patients achieving none or mild wrinkle severity on each GL, FHL, and LCL scale (separately) at Week 4, by investigator assessment. Secondary efficacy endpoints were the percentages of patients achieving none or mild wrinkle severity on each GL, FHL, and LCL scale (separately) over time by investigator assessment and by patient assessment; the percentages of patients achieving a concurrent rating of none or mild wrinkle severity at Week 4 for all 3 treated facial areas concurrently (composite endpoint) by investigator assessment and by patient assessment; the median time to return to baseline or worse in GL, FHL, and LCL wrinkle severity by investigator and patient assessment combined; and the median time to loss of none or mild GL, FHL, and LCL wrinkle severity by investigator and patient assessment combined. Additional secondary efficacy endpoints were: improvement from baseline in visual appearance of GL, FHL, and LCL by investigator and patient assessments using the Global Aesthetic Improvement Scale (GAIS), a 7-point scale ranging from "very much worse" (−3) to "very much improved" (3)[2] and satisfaction with DAXI treatment of GL, FHL, and LCL as assessed by the patient via questionnaire on a 7-point scale from "very dissatisfied" to "very satisfied".[2] Safety was evaluated by the incidence, severity, and relationship to DAXI of treatment-emergent adverse events (TEAEs).

Statistical Analysis

Because this was an open-label study, all statistical analyses were descriptive and no formal hypothesis tests were performed. The percentages of patients with responses at a given time point were reported based on the proportion of treated patients (patients who exited the study were defined as nonresponders for all later visits) and, where indicated, on observed cases. Kaplan–Meier curves were plotted for time-to-event endpoints, and median durations with associated 95% confidence intervals were calculated. Missing data were imputed with the worst value from the previous time point and the next time point, up to the patient's last visit. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

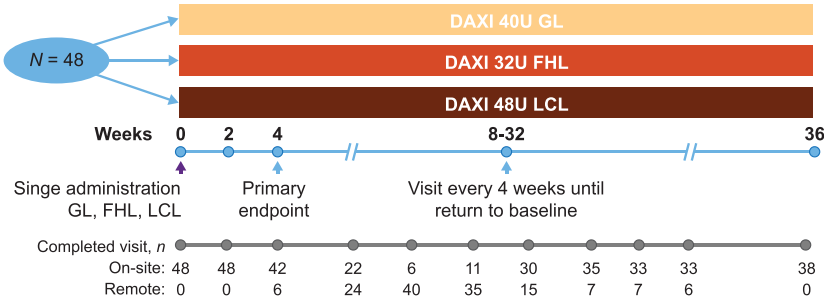

Figure 1. Study design, including number of patients who completed on-site and remote visits at each time point. DAXI, DaxibotulinumtoxinA for Injection; FHL, forehead lines; GL, glabellar lines; LCL, lateral canthal line.

Results

Patient Disposition and Baseline Characteristics

Of the 48 patients who enrolled, 45 (94%) completed the study (i.e., had a final visit) and 38 (79%) completed the full 36 weeks of follow-up. Three patients discontinued; 2 withdrew consent (1 relocated, 1 because of COVID-19) and 1 was lost to follow-up. Because of the COVID-19 pandemic, not all study visits could be conducted in person at the clinical sites. However, most patients (42/48, 88%) completed on-site study visits up to the key efficacy time point (Week 4) and from Week 20 until the end of the study at Week 36 (Figure 1). Most visits at Weeks 12 and 16 were conducted remotely (40 and 35 patients, respectively).

Most patients were women (83%), self reported "white" (92%), "not Hispanic/Latino" (73%), with a mean (SD) age of 48.9 (12.74) (see **Supplemental Digital Content,** Table S1, http://links.lww.com/DSS/B175). At baseline, more than two-thirds of patients had Fitzpatrick skin Type II or Type III and almost two-thirds of patients had been treated with a BoNTA previously; the mean time since BoNTA treatment was 28.9 months.

Efficacy

Based on investigator assessment at Week 4, 96%, 96%, and 92% of patients achieved none or mild wrinkle severity for GL, FHL, and LCL, respectively (Figure 2). At Week 16, 71% of patients had none or mild GL, 58% had none or mild FHL, and 65% had none or mild LCL by investigator assessment (Figure 2). Based on patient self-assessment, 87.5%, 81%, and 77% of patients achieved none or mild GL, FHL, and LCL, respectively, at Week 4; 50% of patients achieved none or mild GL and LCL, and 45.8% achieved none or mild FHL at Week 16. Based on investigator and patient assessments at Week 4, more patients achieved none or mild wrinkle severity for GL and FHL compared with LCL; however, there were no major differences in response rates between the upper facial line groups for the duration of the study (Figure 2). The composite endpoint of the percentage of patients achieving none or mild wrinkle severity for all treated facial areas concurrently at Week 4 was 88% by investigator assessment and 71% by patient assessment.

For those patients achieving none or mild lines at Week 4, the median (95% CI) times to loss of none or mild GL, FHL, and LCL were 25.0 weeks (24.0, 28.0), 24.0 weeks (20.6, 26.3), and 28.1 weeks (24.0, 30.0), respectively, and the median times to return to baseline GL, FHL, and LCL wrinkle severity were 33.3 weeks (28.4, 36.7), 35.3 weeks (28.6, 36.7), and 35.3 weeks (28.4, 37.1), respectively. Representative photograph at baseline and after treatment are shown in Figure 3.

At Week 4, the visual appearance of most patients was rated as "improved", "much improved", or "very much improved" on the GAIS by investigators and patients (Figure 4). Global Aesthetic Improvement Scale ratings of "improved", "much improved", or "very much improved" GL, FHL, and LCL were reported for 98% of patients for each upper facial line group at Week 4 and for 75%, 77%, and 77% of patients, respectively, at Week 16 by investigator assessment. Global Aesthetic Improvement Scale ratings of "improved", "much improved", or "very much improved" GL, FHL, and LCL were reported by 98%, 98%, and 96% of patients, respectively, at Week 4 and by 75% of patients for each upper facial line group at Week 16.

At Week 2, nearly all patients were "satisfied" or "very satisfied" with DAXI treatment for their GL (96%), FHL (96%), and LCL (90%). At Week 4, 98%, 92%, and 85% of patients reported being "satisfied" or "very satisfied" with DAXI treatment for GL, FHL, and LCL, respectively. At Week 16, more than two-thirds of patients remained satisfied with their treatment (67% for GL, 69% for FHL, and 71% for LCL). By Week 28, more than half of the patients remained satisfied with their treatment (52% for GL, 50% for FHL, and 54% for LCL).

Safety

DaxibotulinumtoxinA for Injection was well tolerated when all 3 facial areas were injected simultaneously (Table 1). Ten patients (20.8%) experienced 26 TEAEs, with most being mild in severity. The most common TEAEs were injection site erythema (3 patients) and facial discomfort (2 patients). Five patients reported 10 treatment-related TEAEs; these included injection site erythema (3 patients/7 events), facial discomfort (2 patients/2 events), and headache (1 patient/1 event). No

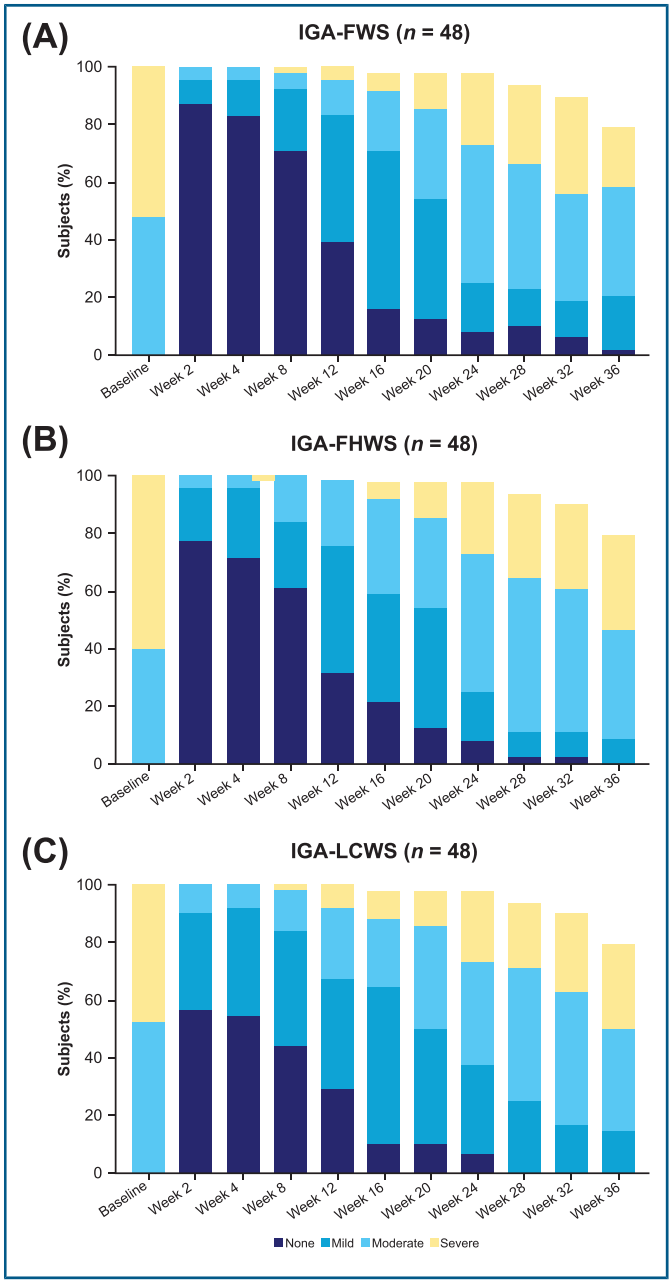

Figure 2. Percentage of patients with none, mild, moderate, or severe glabellar line, forehead line, or lateral canthal line wrinkle severity following DaxibotulinumtoxinA for Injection treatment by investigator assessment. IGA-FHWS, Investigator Global Assessment–Forehead Wrinkle Severity; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; IGA-LCWS, Investigator Global Assessment–Lateral Canthal Wrinkle Severity.

adverse events resulted in study discontinuation or death, and no cases of eyelid or eyebrow ptosis were reported. One serious adverse event (COVID-19 pneumonia) was reported, which was unrelated to treatment and resolved 8 days after onset.

Discussion

The presence of upper facial lines has a psychological effect on many patients and contributes to negative feelings and perceptions of age, attractiveness, and appearance.[7] This study demonstrated that DAXI is efficacious and well tolerated for simultaneous treatment of GL, FHL, and LCL. The key endpoints of investigator-assessed efficacy (none or mild severity for each of the 3 upper facial line types at Week 4) was achieved by nearly all patients. Patients were required to have moderate or severe upper facial lines to be candidates for treatment, and a rating of none or mild is consistent with the treatment goals for many patients who seek upper facial line treatment and for the physicians who treat them. The results of this study, which showed a long duration of effect for all 3 upper facial areas, support likely real-world clinical practice and patient experience, where patients may desire treatment of multiple facial areas in a single treatment session and long duration of activity.

In this study, 88% of patients achieved investigator-rated none or mild wrinkle severity concurrently in all 3 treatment areas. This finding is clinically relevant because simultaneous treatment of multiple upper facial lines has the potential to deliver better outcomes and patient satisfaction compared with treatment of a single area.[8] The efficacy of DAXI across all upper facial lines in this study is consistent with data from previous studies of DAXI for GL,[2,4,5] which have shown sustained efficacy duration of up to 24 weeks for time to loss of none or mild GL severity and 28 weeks for a return to baseline severity levels. In the current study, the median time to loss of none or mild upper facial line severity was 25.0 weeks for GL, 24.0 weeks for FHL, and 28.1 weeks for LCL in patients who had a none or mild response at Week 4. This extended duration of action with DAXI may be attributed to its formulation that contains the novel proprietary stabilizing peptide excipient (RTP004), which is highly positively charged at physiologic pH and forms a strong electrostatic bond with the negatively charged core neurotoxin.[1] This peptide also allows DAXI to be formulated without human serum albumin, which is used in currently available BoNTA products, and to be stable at room temperature before reconstitution.[1]

Of the upper facial lines, dynamic FHL are often considered the most difficult to treat because of interindividual variability in forehead anatomy, the risk of negatively affecting eyebrow position, and the need to appropriately titrate doses to balance duration of efficacy with the desired aesthetic outcome.[9,10] In addition to the current study, DAXI was evaluated for FHL treatment (after GL treatment) in a 36-week, open-label dose escalation study (Solish and colleagues, Maui Derm for Dermatologists Poster Presentation, 2020). At Week 4, 86%, 87%, 94%, and 100% of subjects achieved none or mild FHL severity (investigator assessment) with the 12U, 18U, 24U, and 30U doses, respectively, and the median time to loss of none or mild response by investigator and patient assessments for Week 4 responders was 20 weeks for the 18U, 24U, and 30U doses. DAXI doses of 18U and 24U balanced the duration of effect while preserving some movement, as demonstrated by a greater proportion of patients who maintained mild lines after treatment (Revance Therapeutics, unpublished data). At the highest

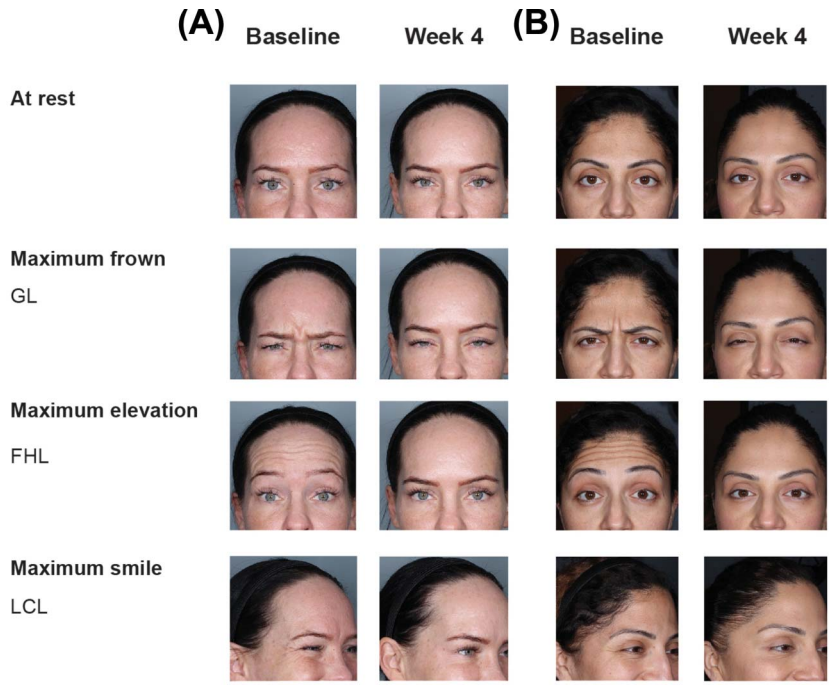

Figure 3. Representative photographs at baseline and after treatment with DaxibotulinumtoxinA for Injection 40U for GLs, 32U for FHLs, and 48U for LCLs. Representative images are shown for (A) a 36-year-old woman and (B) a 42-year-old woman. GLs, glabellar lines; FHLs, forehead lines; LCLs, lateral canthal lines.

dose, which may be appropriate for patients who desire no forehead movement, 87% of subjects achieved a score of none on the FHL rating scale at Week 4 by investigator assessment. Taken together, these results suggest that practitioners may select from a range of doses that can provide a desired aesthetic outcome, independent of duration of effect.

Consistent with the improvements in facial line severity, improvements in the visual appearance (GAIS) of all 3 upper facial lines were reported by most patients (98%) at Week 4 of DAXI treatment and high levels of patient satisfaction (≥90%) were reported as early as Week 2, suggesting a rapid onset of action. In parallel with the duration of treatment effect, the improvements in visual appearance were maintained by ≥75% of patients at Week 16 and ≥50% of patients remaining satisfied with their treatment at Week 28.

Several studies have shown that BoNTAs are safe and effective for treatment of at least 2 moderate-to-severe upper facial lines simultaneously.[11–15] Consistent with these studies, there were no differences in the frequency and types of adverse events when all 3 facial lines were treated simultaneously with DAXI compared with individually. Importantly, no cases of eyelid ptosis were reported in this

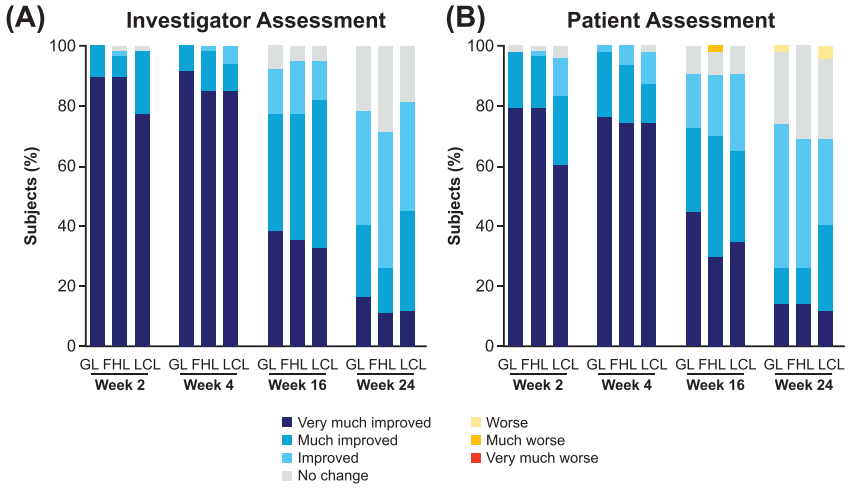

Figure 4. Global aesthetic improvement of facial lines (Global Aesthetic Improvement Scale) following treatment with DaxibotulinumtoxinA for Injection by (A) investigator assessment and (B) patient assessment. Observed cases only. FHL, forehead line; GL, glabellar line; LCL, lateral canthal line.

TABLE 1. Summary of Adverse Events	
Event	**All Patients, *n* (%) (*N* = 48)**
Death	0
Serious adverse event	1 (2.1)
Any TEAE	10 (20.8)
Any TEAE leading to study discontinuation	0
Treatment-related TEAEs	5 (10.4)
Injection site erythema	3 (6.3)
Facial discomfort	2 (4.2)
Headache	1 (2.1)

TEAE, treatment-emergent adverse event.

study or in the dose-escalating Phase 2 trials in patients who received DAXI 40U (GL),[16] 30U (FHL; Solish and colleagues, Maui Derm for Dermatologists Poster Presentation, 2020), or 48U (LCL; Keaney and colleagues American Society for Dermatologic Surgery Annual Meeting Poster Presentation, 2020). Furthermore, in the large, open-label, Phase 3 safety study of repeated-doses of DAXI 40U for glabellar treatment, eyelid ptosis was only reported in 0.9% of treatments (1.3% of 2,691 patients).[4] It is important to note that the definition of a unit of DAXI is based on proprietary testing of biological activity and a proprietary reference standard. Therefore, it is not possible to compare or convert doses of DAXI to those of any other botulinum toxin formulation.

Two limitations of this study are that it was open label and did not include a comparator group. Of note, the findings were similar to other placebo-controlled studies of DAXI for treatment of GL,[2–5] which suggests that the effects of reporting bias and the lack of a comparator group were likely to be minimal. Furthermore, because of the COVID-19 pandemic, it was necessary to conduct remote assessments, which may have contributed to the lower number of total visits from Week 20 onward, and the corresponding results for these time points. However, most patients (42/48) were assessed at clinic visits until at least the key efficacy endpoint (Week 4), and investigators received detailed training on how to conduct visits remotely.

Conclusions

The outcomes of the current study extend the findings from previous DAXI studies and provide evidence that the high degree of efficacy, safety, and extended duration of effects observed for DAXI in GL can be achieved in FHL and LCL when treated simultaneously.

References

1. Malmirchegini R, Too P, Oliyai C, Joshi A. Revance's novel peptide excipient, RTP004, and its role in stabilizing daxibotulinumtoxinA (DAXI) against aggregation. *Toxicon* 2018;156:S72–S73.
2. Carruthers JD, Fagien S, Joseph JH, Humphrey SD, et al. DaxibotulinumtoxinA for Injection for the treatment of glabellar lines: results from each of two multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (SAKURA 1 and SAKURA 2). *Plast Reconstr Surg* 2020;145:45–58.
3. Bertucci V, Solish N, Kaufman-Janette J, Yoelin S, et al. DaxibotulinumtoxinA for Injection has a prolonged duration of response in the treatment of glabellar lines: pooled data from two multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (SAKURA 1 and SAKURA 2). *J Am Acad Dermatol* 2020;82:838–45.
4. Green JB, Mariwalla K, Coleman K, Ablon G, et al. A large, open-label, phase 3 safety study of DaxibotulinumtoxinA for Injection in glabellar lines: a focus on safety from the SAKURA 3 study. *Dermatol Surg* 2021;47:42–6.
5. Fabi SG, Cohen JL, Green LJ, Dhawan S, et al. DaxibotulinumtoxinA for Injection for the treatment of glabellar lines: efficacy results from SAKURA 3, a large, open-label, phase 3 safety study. *Dermatol Surg* 2021;47:48–54.
6. Solish N, Carruthers J, Kaufman J, Rubio RG, et al. Overview of DaxibotulinumtoxinA for Injection: a novel formulation of botulinum toxin type A. *Drugs* 2021;81:2091–101.
7. Dayan S, Yoelin SG, De Boulle K, Garcia JK. The psychological impacts of upper facial lines: a qualitative, patient-centered study. *Aesthet Surg J Open Forum* 2019;1:ojz015.
8. Sundaram H, Signorini M, Liew S, Trindade de Almeida AR, et al. Global Aesthetics Consensus: botulinum toxin type A—evidence-based review, emerging concepts, and consensus recommendations for aesthetic use, including updates on complications. *Plast Reconstr Surg* 2016;137:518e–29e.
9. Anido J, Arenas D, Arruabarrena C, Domínguez-Gil A, et al. Tailored botulinum toxin type A injections in aesthetic medicine: consensus panel recommendations for treating the forehead based on individual facial anatomy and muscle tone. *Clin Cosmet Investig Dermatol* 2017;10:413–21.
10. Kaminer MS, Cox SE, Fagien S, Kaufman J, et al. CME: Re-examining the optimal use of neuromodulators and the changing landscape: a consensus panel update. *J Drugs Dermatol* 2020;19:35–15.
11. De Boulle K, Werschler WP, Gold MH, Bruce S, et al. Phase 3 study of onabotulinumtoxinA distributed between frontalis, glabellar complex, and lateral canthal areas for treatment of upper facial lines. *Dermatol Surg* 2018;44:1437–48.
12. Hexsel D, Cartier H, Hedén P, Delmar H, et al. Efficacy, safety, and subject satisfaction after abobotulinumtoxinA treatment of upper facial lines. *Dermatol Surg* 2018;44:1555–64.
13. Moers-Carpi M, Carruthers J, Fagien S, Lupo M, et al. Efficacy and safety of onabotulinumtoxinA for treating crow's feet lines alone or in combination with glabellar lines: a multicenter, randomized, controlled trial. *Dermatol Surg* 2015;41:102–12.
14. Streker M, Luebberding S, Krueger N, Harrington L, et al. Patient-reported outcomes after incobotulinumtoxinA treatment for upper facial wrinkles. *Dermatol Surg* 2015;41(Suppl 1):S29–S38.
15. Carruthers J, Rivkin A, Donofrio L, Bertucci V, et al. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of repeated onabotulinumtoxinA treatments in subjects with crow's feet lines and glabellar lines. *Dermatol Surg* 2015;41:702–11.
16. Carruthers J, Solish N, Humphrey S, Rosen N, et al. Injectable daxibotulinumtoxinA for the treatment of glabellar lines: a phase 2, randomized, dose-ranging, double-blind, multicenter comparison with onabotulinumtoxinA and placebo. *Dermatol Surg* 2017;43:1321–31.