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DaxibotulinumtoxinA for Injection for the Treatment of Glabellar Lines: Efficacy Results From SAKURA 3, a Large, Open-Label, Phase 3 Safety Study

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BACKGROUND DaxibotulinumtoxinA for Injection (DAXI) is botulinum toxin Type A formulated with a novel peptide excipient. Two pivotal, single-treatment, placebo-controlled trials demonstrated efficacy and safety for moderate or severe glabellar lines.

OBJECTIVE To further evaluate DAXI in a large, open-label, repeat-treatment study.

METHODS Subjects (n = 2,691) were enrolled from the preceding pivotal trials or de novo and received 40U DAXI. Those who received repeat treatments could be retreated when they returned to baseline on the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient FWS (PFWS) scales at/after 12 weeks and up to 36 weeks after treatment.

RESULTS High (>96%) response rates (none or mild severity) on the IGA-FWS scale were seen after each of the 3 treatments, with peak response between Weeks 2 to 4. At Week 24, ≥32% had a response of none or mild severity. Peak response rates of ≥92% were observed at Weeks 2 to 4 on the PFWS scale. The median duration for return to moderate or severe severity was 24 weeks. The safety profile was favorable and consistent with previous trials.

CONCLUSION DaxibotulinumtoxinA for Injection efficacy was highly consistent across treatment cycles. These results confirm the previously observed efficacy rates and duration of response.

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DaxibotulinumtoxinA for Injection (DAXI) is a 150-kDa botulinum toxin Type A (BoNTA) in clinical development for aesthetic and therapeutic conditions. DaxibotulinumtoxinA for Injection is formulated with a novel proprietary stabilizing peptide excipient (RTP004), which is highly positively charged and binds to the negatively charged core neurotoxin. This unique peptide allows DAXI to be formulated without human serum albumin (used in currently available BoNTA products) and ensures stability at room temperature before reconstitution.[1] Furthermore, DAXI is manufactured without the use of animal products.

The safety and efficacy of a single administration of DAXI 40U for the treatment of moderate or severe glabellar lines was studied in 2 identically designed, pivotal, multicenter, randomized, placebo-controlled, Phase 3 trials (SAKURA 1 and SAKURA 2).[2] The DAXI dose was determined based on a Phase 2, dose-ranging clinical trial in which the 40U dose provided the most favorable risk-benefit profile, demonstrating robust efficacy with no subjects experiencing eyelid ptosis.[3] Notably, the 40U dose of DAXI contains 0.18 ng of core neurotoxin,[2] similar to the onabotulinumtoxinA 20U dose.[4]

The high level of efficacy seen with DAXI in the Phase 2 glabellar lines study was confirmed with consistent results demonstrated in the SAKURA 1 and 2 trials involving a combined total of 609 subjects (405 subjects received a single treatment of DAXI 40U and 204 subjects received placebo).[2] The primary efficacy end point was achieved in both the SAKURA 1 and 2 trials, and the median duration of none or mild glabellar line severity was 24.0 weeks. In the Phase 2, dose-ranging and both Phase 3 SAKURA trials, the adverse event (AE) profile was similar to that seen with other neuromodulators, and no new safety signals were identified.

The SAKURA 3 open-label safety study contributes to the largest Phase 3 clinical development program for a neuromodulator in glabellar lines. SAKURA 3—an expansion of the pivotal Phase 3 studies—was designed to further characterize the safety profile of DAXI in a much larger patient population and with an expanded number of injectors. It is the first study to evaluate the safety and efficacy of DAXI with both single and repeat treatments in subjects with moderate or severe glabellar lines. The efficacy analysis was designed to understand the efficacy and durability of the response in a much larger population than the pivotal trials and with repeat treatments. The safety results are reported in the companion article,[5] and here, the authors report on the efficacy of DAXI with up to 3 repeat treatments.

Methods

Study Design

As described in the companion article on the safety outcomes from SAKURA 3,[5] this was a Phase 3, open-label, multicenter trial that evaluated single and repeat treatments of DAXI 40U, with post-treatment follow-up of up to 84 weeks (ClinicalTrials.gov identifier NCT03004248). Specific targets for the number of subjects exposed to single versus repeat treatments were outlined in the protocol; therefore, a subset of enrolled subjects received more than 1 treatment. The study was conducted in 65 centers in the United States and Canada from December 2016 to October 2018. The protocol was approved by the institutional review boards and/or independent ethics committees. All subjects provided written informed consent, and the study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki.

Subjects

Study participants were either rollover subjects who had completed the SAKURA 1 or 2 Phase 3 studies[2] or newly enrolled (de novo) subjects. Eligible subjects included those aged 18 years or older, in good health, with moderate or severe glabellar lines based on the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient FWS

(PFWS) scales.[2] Pregnant or nursing females were excluded from the study. During the study and evaluation period, all subjects were required to refrain from receiving facial fillers, laser treatments, use of any product that affects skin remodeling, or products that may cause an active dermal response in the treatment area. Key exclusion criteria included any neurologic condition that may place the subject at increased risk with exposure to BoNTA; muscle weakness or paralysis in the area receiving treatment or a history of facial nerve palsy; facial treatment with BoNTA within 24 weeks before screening, plans to receive BoNTA anywhere in the face through the duration of the trial, or treatment with ≥200U BoNTA anywhere else in the body within the past 3 months before screening or during the trial.

Treatments

The study was designed to enroll at least 2,100 subjects, of whom at least 400 were to receive up to 3 treatments. Once this target was reached, all subsequently enrolled subjects were eligible to receive only a single treatment. Subjects receiving multiple treatments could have been rollover subjects from SAKURA 1 or 2 or those newly enrolled in SAKURA 3. For rollover subjects, the blinding of the pivotal study random assignment to DAXI or placebo was maintained; therefore, all rollover subjects could receive only 2 additional treatments in the SAKURA 3 study: those who were treated with DAXI in the placebo-controlled trials received their second and third DAXI treatments in the SAKURA 3 study, whereas the placebo rollover subjects received their first and second DAXI treatments.

Each DAXI vial was reconstituted with unpreserved saline, and all subjects received DAXI 40U (0.5 mL) in total: one injection in the procerus muscle and injections into both the medial and lateral corrugator muscles, bilaterally.[5] Subjects who received repeat treatments could be retreated between Week 12 and Week 36 after their first and second treatments if their IGA-FWS and PFWS scores had returned to baseline and other eligibility criteria were met. Subjects were followed for up to 36 weeks after each treatment, except for their final treatment, where follow-up ended at Week 12 to characterize safety outcomes after the third treatment.

Outcome Measures

The primary objective of this study was to evaluate safety, as reported in the companion article.[5] Efficacy was also evaluated using investigator and subject assessments of glabellar line severity at maximum frown and at rest (after maximum frown).

The IGA-FWS and PFWS scales are separate, validated, photonumeric scales using a 4-point scale (0 = none to 3 = severe). Investigator Global Assessment–Frown Wrinkle Severity and PFWS assessments were made during each study visit at baseline; at Weeks 1, 2, and 4; and then at 4-week intervals up to Week 36 or until both IGA-FWS and PFWS scores at maximum frown returned to baseline. A similar schedule of study visits was followed after a second treatment. If a subject received a third treatment (SAKURA 3 treatment 2 for placebo rollover subjects), study visits were at Weeks 1, 2, 4, 8, and 12. Both investigators and subjects rated the change from baseline in glabellar lines using the 7-point Global Aesthetic Improvement Scale (GAIS).[2]

The following outcomes are reported for each treatment: proportion of subjects with the rating of none or mild on the IGA-FWS and PFWS scales (reported separately) at each study visit; proportion of subjects with a ≥2-point improvement from baseline on the IGA-FWS and PFWS scales at Week 4; proportion of subjects with a ≥1-point improvement from baseline on the IGA-FWS and PFWS scales at each visit over time; time to return to moderate or severe on the IGA-FWS and PFWS scales; time to return to (or worse than) baseline on the IGA-FWS and PFWS scales; and proportion of subjects with each rating option on the GAIS as assessed by investigators and subjects (reported separately). All results are reported for assessments made during maximum frown.

Statistical Methods

Descriptive statistics were provided for all efficacy variables at each timepoint and by the treatment

period. Summaries were performed using observed cases, with no imputation of missing data. For calculation of proportion responding, all treated subjects were included in the denominator even if subjects did not provide data at a given visit. For results of the second treatment, the denominator was adjusted to remove the placebo rollover subjects who were not followed beyond Week 12. The time to return to (or worse than) baseline and time to return to moderate (score of 2) or severe (score of 3), on both IGA-FWS and PFWS scales, were summarized with point estimates of median duration, 25th and 75th percentiles, and 2-sided, 95% confidence intervals (CIs), using log-log transformation. Kaplan–Meier survival curves were plotted.

To remove possible selection effects in the results reported over successive treatment cycles, the analysis of key efficacy outcomes was repeated in the cohort of subjects who received all 3 treatments within this study.

Results

Subject Disposition and Baseline Characteristics

After screening 3,052 subjects, 2,691 subjects were enrolled in SAKURA 3. A total of 2,214 subjects were newly enrolled and 477 rolled over from SAKURA 1 and 2 (166 had received placebo and 311 received DAXI during the pivotal trials). Within SAKURA 3, 2,380 subjects received their first dose of DAXI, 882 received their second dose, and 568 received their third dose, for a total of 3,830 treatments.

Over the course of the study, 377 (14.0%) subjects discontinued prematurely for the following reasons: withdrew consent (196 [7.3%]), lost to follow-up (99 [3.7%]), protocol deviation (53 [2.0%]), investigator discretion (8 [0.3%]), AE (5 [0.2%]), victim of homicide (1 [<1%]), and other (15 [0.6%]).

Most subjects were white women, approximately 50 years of age (See **Supplemental Digital Content 1**, Table S1, http://links.lww.com/DSS/A397). Notably, approximately 20% were Latino, and 40% of enrolled subjects had previously received BoNTA in the glabella (median time since the last treatment was 18 months). Glabellar line severity at maximum frown was rated by investigators as moderate in 61% of subjects and severe in 39% of subjects.

Efficacy Outcomes

The proportion of subjects achieving a score of none (0) or mild (1) on the IGA-FWS scale at each visit is shown in Figure 1A for Treatment Cycles 1, 2, and 3. A high response rate (>90%) was seen as early as Week 1 in all 3 treatment cycles. The response rate peaked between Weeks 2 and 4 in all 3 treatment cycles (96.6%, 96.6%, and 97.7%, respectively). At Week 12, the response rate was >80% in all treatment cycles. At Week 24, the response rate was 34.0% and 38.5% for Treatment Cycles 1 and 2, respectively (Treatment Cycle 3 ended at Week 12).

The proportion of subjects achieving a score of none (0) or mild (1) on the PFWS scale for the 3 treatments is shown in Figure 1B. The peak response rate at Weeks 2 to 4 was 92.0%, 92.3%, and 93.1% for the 3 treatments, respectively. At Week 12, the responder rate was 68.4%, 69.7%, and 74.3%. At Week 24, the response rate was 26.5% and 27.0% for Treatments 1 and 2, respectively.

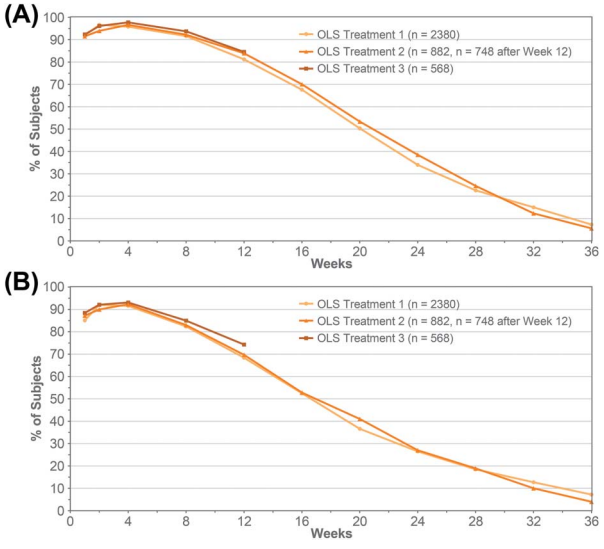

Figure 1. Proportion of subjects with none or mild severity based on the (A) IGA-FWS and (B) PFWS scales after Treatments 1, 2, and 3.

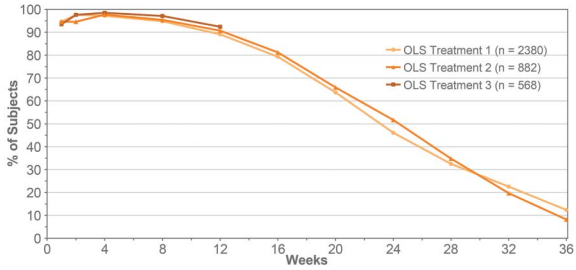

Figure 2. Proportion of subjects with a ≥1-point improvement on the IGA-FWS scale over 36 weeks after Treatments 1 and 2, and over 12 weeks after Treatment 3.

The proportion of subjects achieving a ≥1-point improvement by investigator assessment (IGA-FWS) for up to 36 weeks is shown in Figure 2. Results were similar for the subject's self-assessment (PFWS, data not shown). The peak response by investigator assessment was seen at Weeks 2 to 4 : 97.6%, 97.7%, and 98.5% for Treatments 1, 2, and 3, respectively. In Treatments 1 and 2, approximately 50% of subjects maintained a ≥1-point improvement on the IGA-FWS scale at Week 24, and approximately 20% of subjects maintained a ≥1-point improvement at Week 32. A total of 12.4% of treated subjects demonstrated a ≥1-point improvement on the IGA-FWS scale at Week 36 after Treatment 1 and 8.2% after Treatment 2.

The proportion of subjects with a ≥2-point improvement in glabellar line severity on both IGA-FWS and PFWS scales at Week 4 was 73.2%, 77.7%, and 79.6% in the 3 successive treatment cycles, respectively.

The median duration (95% CI) of maintaining a response of none or mild glabellar line severity after treatment with DAXI as assessed on both IGA-FWS and PFWS scales was 24.0 (23.9, 24.0) weeks after the first treatment and 24.1 (24.0, 24.7) weeks after the second treatment (Figure 3A). The 25th and 75th percentiles were 19.1/32.9 weeks for Treatment 1 and 19.6/31.9 weeks for Treatment 2. Consistency across Treatments 1 and 2 was also seen for the median duration (95% CI; 25th and 75th percentiles) of time to return to baseline glabellar line severity on both IGA-FWS and PFWS scales: 28.0 (28.0, 28.1; 23.6, 36.7) weeks for Treatment 1 and 28.1 (28.0, 28.4; 23.6, 35.9) weeks for Treatment 2 (Figure 3B). Of note, after Treatment 1, 413 of 2,380 treated subjects

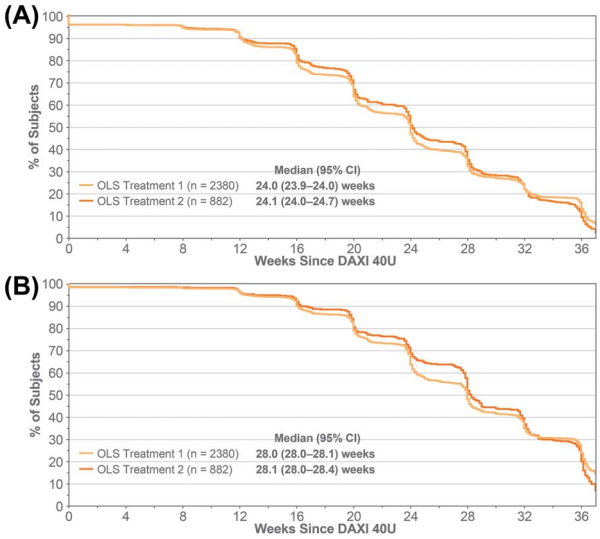

Figure 3. (A) Time to loss of none or mild severity and (B) Time to return to baseline severity on both IGA-FWS and PFWS scales after Treatments 1 and 2.

(17.4%) had not returned to baseline on both IGA-FWS and PFWS scales at Week 36 and, therefore, had not yet met the protocol-defined criteria for retreatment. After Treatment 2, 87 of 882 subjects (9.8%) were not at baseline at Week 36.

On the GAIS, in each of the 3 treatments, investigators assessed 98% of subjects with improvement (improved/much improved/very much improved) in their glabellar lines from baseline at the Week 4 evaluation. By Week 24, 48% and 52% of subjects were assessed as maintaining improvement in their glabellar lines from baseline after Treatments 1 and 2, respectively. At Week 36, investigators rated 13% and 10% of subjects as having improvement in their glabellar lines from baseline after Treatments 1 and 2, respectively (Figure 4A). Subject rating on the GAIS was slightly lower than the rating by investigators but followed a similar pattern (Figure 4B).

The finding of consistent efficacy with a trend toward increased response after subsequent treatments was also observed among the 340 subjects who received 3 treatments within the current study. Responder rates for subjects with none or mild glabellar lines (IGA-FWS) were consistently high (>96%) across treatments at Week 4 and increased after the initial treatment at Weeks 12 and 24. For example, at Week 12, 80.3% (Treatment 1), 85.3% (Treatment 2), and

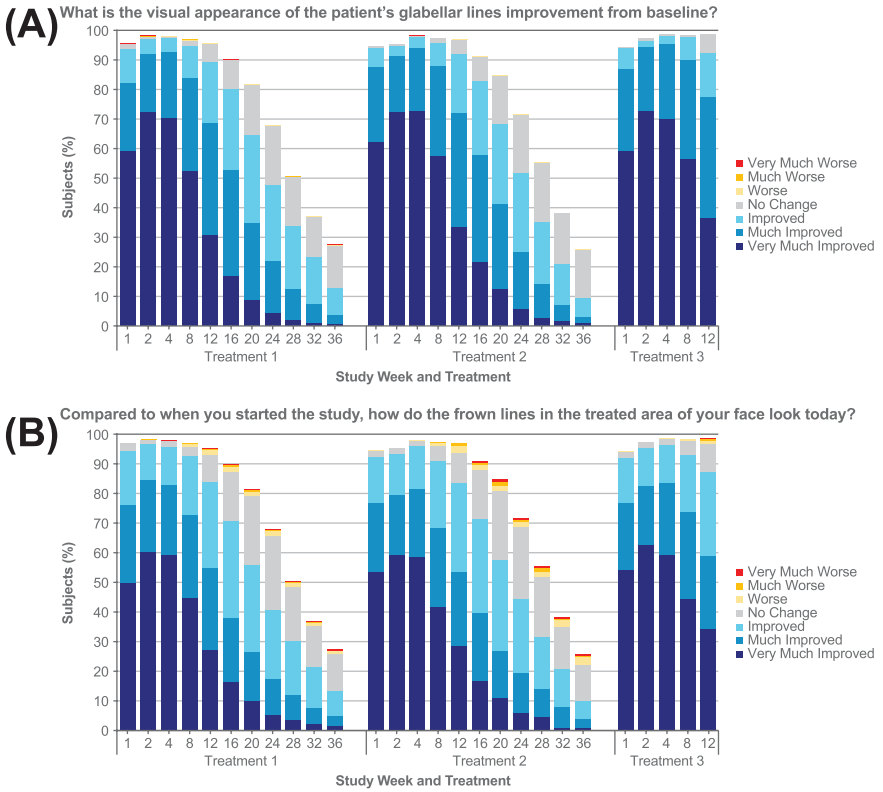

Figure 4. (A) Investigator and (B) subject ratings on the Global Aesthetic Improvement Scale across study visits after Treatments 1, 2, and 3.

85.0% (Treatment 3) of subjects had none or mild. glabellar lines Similar patterns were observed for other efficacy end points.

Figure 5. (A) Example of a 23-year-old female subject with a 2-point improvement on IGA-FWS and PFWS scales at Week 4. The 2-point improvement was sustained through Week 16 and a 1-point improvement through Week 24. (B). Example of a 44-year-old female subject with a 2-point improvement on IGA-FWS and PFWS scales at Week 4. She had a 1-point improvement on both IGA-FWS and PFWS scales at Week 16 and at Week 24; she maintained a 1-point improvement on the IGA-FWS scale and returned to baseline on the PFWS. IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; PFWS, Patient FWS.

Photographic documentation representative of the reduction in glabellar line severity obtained with DAXI is illustrated in Figures 5A,B.

Safety

The safety outcomes from this trial based on the safety population are detailed in the companion article in this issue.[5] In brief, 1,043 (38.8%) subjects reported an AE, of which 29 subjects (1.1%) had a serious AE (all assessed as unrelated to treatment). One death occurred (homicide), and the 5 AEs leading to study discontinuation were basal cell carcinoma, bile duct cancer, "brow spocking," fractured humerus, and optic neuritis; only the unnatural lateral brow elevation was considered to be related to treatment.

Treatment-related AEs occurred in 480 (17.8%) subjects; the most frequent AEs occurring in ≥1% of subjects were headache (4.6%), injection site pain (3.6%), injection site erythema (3.0%), injection site edema (2.8%), and eyelid ptosis (1.3%). No subjects

developed neutralizing antibodies to DAXI at any timepoint during the study.

Discussion

The open-label SAKURA 3 study results confirm the safety and efficacy observed in the placebo-controlled pivotal SAKURA 1 and 2 trials of DAXI 40U for the treatment of moderate or severe glabellar lines,[2] in a substantially larger sample of subjects and broader selection of clinical sites. The efficacy results were remarkably consistent between SAKURA 1 and 2 and all 3 treatments in SAKURA 3. The findings of this study confirm the consistent and reliable high response rates and long duration of efficacy observed with DAXI 40U in both the Phase 2 and the pivotal trials.[2,3] It took a median of 24 weeks for the severity of glabellar lines to return to moderate or severe, with a median time to return to baseline severity of 28 weeks, and 25% of subjects had not returned to moderate or severe at Week 32. With the average patient having a duration of response lasting approximately 6 months, it would be feasible to expect to maintain none or mild glabellar line severity for an entire year with only 2 DAXI treatments.

DaxibotulinumtoxinA for Injection seems to offer a longer duration of response than other marketed BoNTA options for the correction of glabellar lines. DaxibotulinumtoxinA for Injection 40U demonstrated a significantly longer duration of response than onabotulinumtoxinA 20U in subjects with moderate or severe glabellar lines in a Phase 2 study.[3] Comparative trials of DAXI with other neuromodulators are not available; however, pivotal trials of currently available agents have reported a duration of 3 to 4 months.[6,7]

In the placebo-controlled pivotal trials of DAXI, subjects recorded daily ratings for the first 2 weeks, and the median onset of a 1-point improvement was 3 days.[2] In SAKURA 3, while daily ratings were not recorded, similar to SAKURA 1 and 2, >90% of subjects achieved a response of none or mild on the IGA-FWS scale at 1 week. Taken together, the rapid onset and long duration of response provide an improved profile of a neuromodulator for use in the treatment of glabellar lines. It should be noted that when making comparisons, units of biological activity are not interchangeable across BoNTA products because of substantial differences in formulations, potency testing differences, and lack of an international reference standard defining the activity of a unit.[8]

An aim of SAKURA 3 was to evaluate DAXI for the use in glabellar lines in settings that mirror clinical practice. As DAXI is investigational, this was accomplished by increasing the number of subjects exposed to DAXI by 5-fold and doubling the number of injectors. Subjects enrolled could be either naive or have received previous facial aesthetic treatment with BoNTA (at least 6 months was required between the previous treatment and DAXI treatment in SAKURA 3), mirroring clinical situations in which the patient is new to BoNTA treatment or is switching from another neuromodulator. Furthermore, the efficacy end points used in this study are applicable to clinical practice. Achievement of none or mild glabellar line severity is the desired response to maintain, and a return to moderate or severe lines often signals the need for retreatment.

Despite the possibilities for variability in results under this more realistic setting, the efficacy of DAXI 40U was highly consistent across treatment cycles and similar to the results of the pivotal Phase 3 trials.[2] Responder rates using the more restrictive definition from the pivotal trials (≥2-point improvement on both IGA-FWS and PFWS scales) were similar across treatment cycles in SAKURA 3 (73.2%–79.6%) and with that of SAKURA 1 (73.6%) and SAKURA 2 (74.0%). These are higher than the 2-point composite response rates from registration trials of other BoNTAs using a similar responder definition.[9–11] The proportion of subjects achieving none or mild severity on the IGA-FWS scale at Week 4 in SAKURA 3 across treatments (97%–98%) was essentially the same as in SAKURA 1 and 2 (97.5% for both), which are also notably higher than those reported in the label of currently marketed BoNTAs.[9,11–13]

Limitations of this study include the open-label design allowing for the potential of bias in efficacy reporting. However, the very close alignment of the efficacy profile and the median duration of clinical benefit with

the pivotal Phase 3 trials strongly support the validity of the results. This study would have benefited from inclusion of patient satisfaction data, as inclusion of patient satisfaction questionnaires across treatments may have captured patient satisfaction with the prolonged duration of response and the need for fewer injections per year to maintain the correction of their glabellar lines. However, the GAIS provides insight into the subjects' evaluation of their improvement from baseline and allows for an evaluation of the magnitude of improvement at each study visit. As common in many clinical trials, the trial population was relatively homogenous, primarily white women, which limits applicability of the results to other patient types. However, according to the 2018 statistics from the American Society of Plastic Surgeons, the aesthetic population seeking treatment with BoNTAs is primarily white (78%) and only 6% are men.[14]

The SAKURA 3 study is part of the largest Phase 3 clinical development program for a neuromodulator in the treatment of glabellar lines. The efficacy of DAXI was highly consistent across successive treatment cycles and multiple end points evaluating response rates and duration of effect. The results of this large study confirm the high and extended response rates, as well as the median 24-week duration of clinical benefit with DAXI seen in the pivotal Phase 3 trials.

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