

Prior Botulinum Toxin Treatment Does Not Impact Efficacy or Safety in Clinical Trials: Analysis of DaxibotulinumtoxinA for Injection in the SAKURA Program

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BACKGROUND Pivotal studies of approved botulinum toxin type A (BoNTA) formulations for treatment of glabellar lines have mostly included treatment-naïve participants, and the impact of prior BoNTA treatment on efficacy and safety is not well documented.

OBJECTIVE To evaluate whether prior BoNTA treatment affects efficacy, duration of response, and tolerability for treatment of glabellar lines.

METHODS Adults with moderate or severe glabellar lines treated with DaxibotulinumtoxinA for Injection (DAXI) or placebo from the randomized, double-blind SAKURA 1/2 trials and the open-label SAKURA 3 safety study were analyzed by prior BoNTA treatment status. Efficacy was evaluated using investigator and participant assessments.

RESULTS In this analysis, 609 participants (52.2% BoNTA-experienced) from the SAKURA 1/2 trials and 2,380 (38.0% BoNTA-experienced) from the SAKURA 3 study were evaluated. Proportion of participants with none or mild glabellar lines and duration of response were similar between the BoNTA-naïve and BoNTA-experienced cohorts in both the DAXI and placebo groups. The incidence of adverse events was also comparable regardless of prior BoNTA treatment status.

CONCLUSION Efficacy and tolerability were similar with DAXI and placebo regardless of prior BoNTA treatment. Assuming an appropriate washout is observed, future BoNTA trials should enroll both treatment-experienced and treatment-naïve participants to reflect clinical practice.

Controlled clinical trials evaluating botulinum toxin type A (BoNTA) for treatment of glabellar lines have enrolled populations that are mostly or entirely naïve to BoNTA treatment.^{1–5} There is potentially sound reasoning for this. It is possible that patients who have previously received BoNTA treatment may have

preconceived expectations of their treatment results, which may influence their self-evaluations. For example, in placebo-controlled trials, prior experience may bias participants' responses if they were randomized to placebo, potentially artificially lowering the placebo efficacy rate compared with those without prior experience. Furthermore, prior BoNTA treatment experience may make patients more aware of potential side effects and, therefore, less concerned or likely to report them, affecting the safety findings from the study. However, these rationales are purely speculative because there have been no large-scale analyses evaluating whether the efficacy and safety profiles of BoNTA for glabellar lines differ based on prior BoNTA treatment status or washout duration.

To address this gap and to provide evidence for the design of future clinical trials, we used data from the recently completed Phase 3 SAKURA clinical development program of DaxibotulinumtoxinA for Injection (DAXI, Revance Therapeutics, Inc., Newark, CA). This program is the largest undertaken for a BoNTA in treatment of glabellar lines, with 2,823 participants receiving a total of 4,444 treatments. The program incorporated 2 double-blind, placebo-controlled trials (SAKURA 1 [NCT03014622] and SAKURA 2 [NCT03014635]) in addition to a larger, open-label safety study (SAKURA 3 [NCT03004248]).^{6–9} Enrollment criteria in these studies were not restricted to participants naïve to BoNTA

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treatment, and approximately 50% and 40% of participants received prior BoNTA treatment in the SAKURA 1/2 trials⁶ and SAKURA 3 study,^{8,9} respectively. The large number of participants in the SAKURA clinical program allowed us to evaluate whether prior BoNTA experience affects the efficacy, duration of response, placebo response, and tolerability of DAXI for treatment of glabellar lines.

METHODS

Study Design

The study designs of the SAKURA 1/2 trials and the SAKURA 3 study have been previously described (See **Supplemental Digital Content 1**, Figure S1, <http://links.lww.com/DSS/A625>), which shows the SAKURA clinical program study design.⁶⁻⁹ Briefly, in the SAKURA 1/2 trials, adults with moderate or severe glabellar lines at maximum frown were randomized 2:1 to 40U DAXI ($n = 405$) or placebo ($n = 204$).^{6,7} Participants previously treated with BoNTAs were required to have a washout period of ≥ 6 months for treatments to the face and ≥ 3 months for doses >200 U anywhere in the body. After 24 weeks, participants were eligible to roll over into the SAKURA 3 study if both investigator and participant assessments of glabellar line severity at maximum frown returned to baseline. The SAKURA 3 study ($N = 2,691$) enrolled 2,214 de novo participants in addition to 477 who rolled over from the SAKURA 1/2 trials.⁸ In the current analysis, participants from the SAKURA 3 study only refer to those receiving their first dose of DAXI during this open-label portion ($n = 2,380$). Participants were defined as treatment-naïve if they never received BoNTA treatment for glabellar lines before the SAKURA trials and as treatment experienced if they previously received ≥ 1 BoNTA treatment for glabellar lines.

Outcomes

Efficacy was evaluated using the validated photometric Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient Frown Wrinkle Severity (PFWS) scales, which grade glabellar line severity from 0 (none) to 3 (severe). Safety outcomes included the incidence of adverse events and treatment-related adverse events. Outcomes were evaluated at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 (and, potentially, Weeks 28, 32, and 36), or until both IGA-FWS and PFWS scale scores at maximum frown returned to baseline.

Statistical Methods

Statistical methods for the efficacy and safety populations of the SAKURA 1/2 trials and the SAKURA 3 study have been described previously.⁶⁻⁹ For the purposes of this analysis, efficacy was assessed separately for the SAKURA 1/2 trials and the SAKURA 3 study. This allowed for analysis of the placebo responder rates in the BoNTA treatment-experienced and treatment-naïve cohorts. The safety analysis combined all subjects receiving their first DAXI treatment (whether in the SAKURA 1/2 trials or SAKURA 3

study) to increase the sample size and permit meaningful between-group assessments. Descriptive statistics were provided for all efficacy variables at each time point and by treatment period. For calculation of the proportion of responders, all treated participants were included in the denominator even if participants did not provide data at a given visit. The time to return to baseline (or worse than baseline) on both IGA-FWS and PFWS assessments were summarized with point estimates of median duration and 2-sided, 95% confidence intervals, using log–log transformation.

The safety evaluable population included all subjects who received ≥ 1 dose of DAXI and had post-treatment safety data. Adverse events were recorded and classified using Medical Dictionary for Regulatory Activities version 20.1. Safety data were reported using descriptive statistics.

RESULTS

Participants

In this analysis, results from the 609 participants (DAXI, $n = 406$; placebo, $n = 203$) in the SAKURA 1/2 trials and the 2,380 participants receiving their first DAXI treatment in the SAKURA 3 study were evaluated. Overall, 318 participants (52.2%) included in this analysis from the SAKURA 1/2 trials were BoNTA treatment-experienced (214 [52.7%] with DAXI and 104 [51.2%] with placebo); and 291 (47.8%) were BoNTA treatment-naïve (192 [47.3%] and 99 [48.8%]). In the SAKURA 3 study, 905 (38.0%) participants were previously treated with BoNTA and 1,475 (62.0%) were treatment-naïve. Median time since prior BoNTA treatment was 17.0 months (range, 7–205 months) and 16.0 months (range, 6–121 months) in the DAXI and placebo groups, respectively, in the SAKURA 1/2 trials, and 18.7 months (range, 6–319.9) in the SAKURA 3 study.

Demographics and Baseline Characteristics

Baseline characteristics were similar between the BoNTA treatment-experienced and treatment-naïve cohorts in both the SAKURA 1/2 and SAKURA 3 studies, although a slightly higher proportion of participants in the BoNTA treatment-experienced cohorts were women (See **Supplemental Digital Content 2**, Table S1, <http://links.lww.com/DSS/A626>), which shows baseline demographics by prior BoNTA status. Most participants were white women with a mean age of approximately 50 years. Baseline glabellar line severity assessed by participants and investigators were generally comparable.

Efficacy

Overall, no differences in efficacy were seen between BoNTA treatment-experienced and treatment-naïve participants administered DAXI. The proportion of participants achieving none or mild glabellar lines as assessed by the PFWS scale was similar between the BoNTA treatment-experienced and treatment-naïve cohorts over 36 weeks in

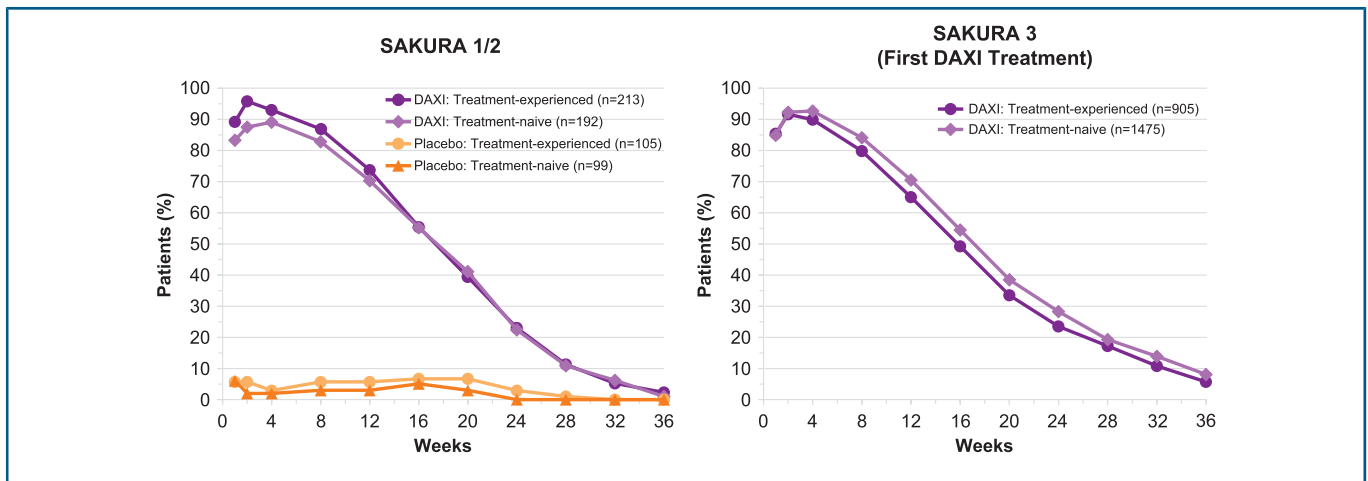


Figure 1. Proportion of participants with none or mild glabellar line severity at maximum frown by prior botulinum toxin type A status based on the Patient Frown Wrinkle Severity scale. DAXI, DaxibotulinumtoxinA for Injection.

both the SAKURA 1/2 and SAKURA 3 studies (Figure 1). The response rate in participants receiving DAXI at Week 4 in BoNTA treatment-experienced and treatment-naive participants was 93.0% and 89.1% in the SAKURA 1/2 trials, and 89.9% and 92.7% in the SAKURA 3 study, respectively. A similar pattern was observed with the IGA-FWS scale assessment (Figure 2). In the SAKURA 1/2 trials, the response rate to DAXI at Week 4 in BoNTA treatment-experienced and treatment-naive participants was 98.6% and 96.4%; in the SAKURA 3 study, rates were 95.5% and 95.9%, respectively.

Duration of response with DAXI was also similar between the BoNTA treatment-experienced and treatment-naive cohorts of the SAKURA 1/2 and SAKURA 3 studies (Table 1). Median time to return to moderate or severe glabellar lines on both the IGA-FWS and PFWS scales at maximum frown was 24.0 weeks and 23.7 weeks in the BoNTA treatment-experienced and treatment-naive cohorts, respectively, in the SAKURA 1/2 trials, and 24.0 weeks in both cohorts in the SAKURA 3 study.

In the placebo group of the SAKURA 1/2 trials, the proportion of participants reporting none or mild glabellar lines as assessed by the PFWS and IGA-FWS scales was very low, as expected, and comparable over 36 weeks between participants with and without prior BoNTA treatment (Figures 1 and 2). At Week 4, the PFWS response rate with placebo was 2.9% in those with BoNTA treatment experience and 2.0% in those who were treatment naive; the respective rates as assessed by the IGA-FWS scale were 4.8% and 4.0%.

Safety

The incidence of adverse events and treatment-related adverse events were generally similar in the DAXI and placebo groups regardless of prior BoNTA treatment in the pooled SAKURA 1/2 and SAKURA 3 safety population (See **Supplemental Digital Content 3**, Table S2, <http://links.lww.com/DSS/A627>), which shows adverse events by prior BoNTA status. An exception was injection site pain in the placebo group, which occurred in more BoNTA treatment-

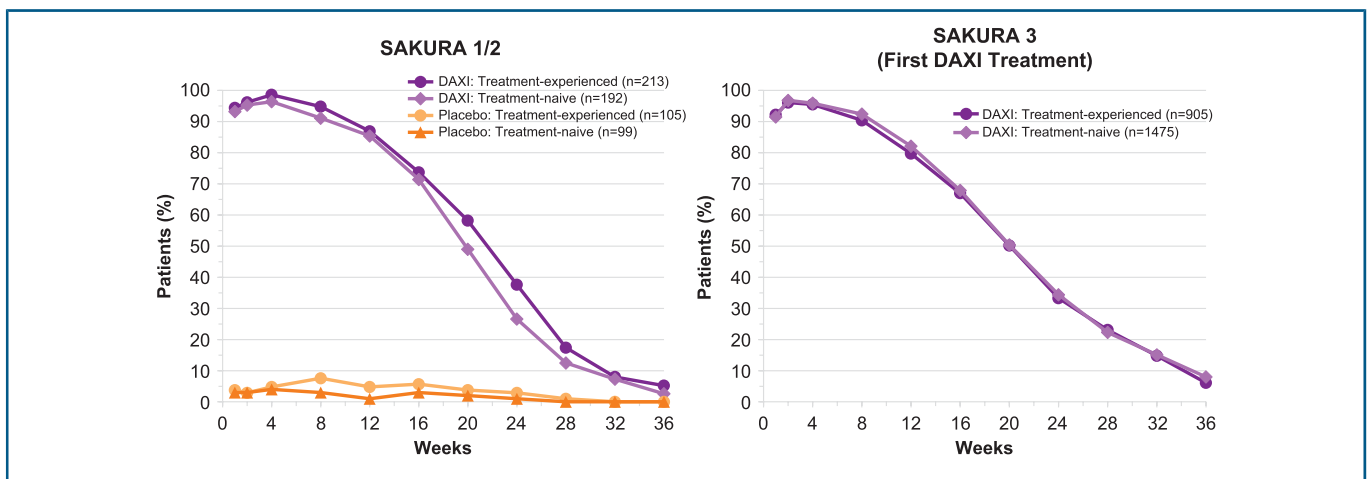


Figure 2. Proportion of participants with none or mild glabellar line severity at maximum frown by prior botulinum toxin type A status based on the Investigator Global Assessment-Frown Wrinkle Severity scale. DAXI, DaxibotulinumtoxinA for Injection.

TABLE 1. Duration of Response With DAXI in the SAKURA 1/2 Trials and SAKURA 3 Study

Weeks (95% CI)	SAKURA 1/2		SAKURA 3 (First DAXI Treatment)	
	BoNTA Treatment-Experienced (<i>n</i> = 213)	BoNTA Treatment-Naive (<i>n</i> = 192)	BoNTA Treatment-Experienced (<i>n</i> = 905)	BoNTA Treatment-Naive (<i>n</i> = 1,475)
Median time to return to moderate or severe on both IGA-FWS and PFWS scales at maximum frown	24.0 (23.7–24.3)	23.7 (20.3–24.0)	24.0 (23.7–24.0)	24.0 (23.9–24.1)
Median time to return to baseline on both IGA-FWS and PFWS scales at maximum frown	27.9 (26.0–28.1)	24.4 (24.1–27.9)	28.0 (27.0–28.0)	28.0 (28.0–28.1)

BoNTA, botulinum toxin type A; DAXI, DaxibotulinumtoxinA for Injection; IGA-FWS, Investigator Global Assessment–Frown Wrinkle Severity; PFWS, Patient Frown Wrinkle Severity.

experienced versus treatment-naive participants (7.7% vs 0%). In both the BoNTA treatment-experienced and treatment-naive cohorts, headache occurred in a higher percentage of DAXI-treated participants (6.0%–6.1%; treatment related, 4.6%) versus placebo-treated participants (1.9%–3.0%; treatment related, 1.9%–2.0%).

Discussion

In this analysis of 2,823 participants from the Phase 3 SAKURA clinical program, we demonstrated that the efficacy, durability of response, and tolerability of DAXI for treatment of glabellar lines are similar regardless of whether participants were experienced or naive to BoNTA treatment. In addition, we evaluated the effect of prior BoNTA treatment among participants treated with placebo in the SAKURA 1/2 trial, confirming that the data observed were not just because of expected results of treatment in participants experienced with BoNTA. Together, these data suggest that prior BoNTA treatment status did not influence the results of the SAKURA 1/2 trials or SAKURA 3 study in either the active- or placebo-treated groups. Furthermore, the results provide confidence in enrolling both BoNTA-experienced and BoNTA-naive participants in future clinical trials of BoNTAs. This would make the trials less restrictive and improve enrollment rates, and encompass a population that better represents clinical practice.

This analysis confirmed that response rates were consistent between the BoNTA treatment-experienced and treatment-naive cohorts in the DAXI group; however, it was surprising that response rates were also similar between the experienced and naive cohorts in the placebo group. It could be hypothesized that participants who previously received BoNTA treatment would recognize the lack of response to placebo, whereas participants naive to BoNTA treatment may rate their response better because they have no expectation. The observation that placebo-treated participants generally rated themselves similarly regardless of prior BoNTA treatment status further supports the

inclusion of participants with previous experience in future clinical trials of BoNTAs.

This analysis also demonstrated that the durability of the response with DAXI was not affected by prior BoNTA treatment. The median time to return to moderate or severe glabellar lines was nearly identical between the BoNTA-experienced and BoNTA-naive cohorts in both the SAKURA 1/2 trials and SAKURA 3 study. A similar effect was observed in the SAKURA 3 study for median time to return to baseline glabellar line severity; however, the duration of response was slightly longer in those who were BoNTA treatment-experienced versus treatment-naive in the SAKURA 1/2 trials, although as the confidence intervals overlapped, these were not statistically different. It should be noted that although participants included in this analysis were required to have ≥ 6 -month washout period between their last BoNTA treatment and study drug, a length of time that should be sufficient to fully wash out current FDA-approved formulations, a longer washout period may be necessary in future BoNTA clinical trials because of the longer duration of response with DAXI compared with BoNTAs currently approved for glabellar lines (median, 24.0 vs 12.1–17.9 weeks^{2,6,8,10,11}).

We evaluated adverse events in a pooled population of participants treated with DAXI from the SAKURA 1/2 trials and SAKURA 3 study. Participants were combined to increase the sample size to give confidence in the results observed. We observed no substantial difference in the type and frequency of either adverse events or treatment-related adverse events between the BoNTA treatment-experienced and treatment-naive cohorts in the DAXI group. Headache occurred in a similar proportion of DAXI-treated participants in both the BoNTA treatment-experienced and treatment-naive cohorts, and the rate (~6%) is consistent with those reported for BoNTAs approved for glabellar lines (5%–12%).^{12–14} In the analysis of the placebo-treated participants, it was observed that injection site pain was recorded in a higher percentage of treatment-experienced participants. As this was not observed in the significantly

larger analysis of adverse events in DAXI-treated participants, and the placebo formulation is identical to that of the active treatment minus the BoNTA, this may be accounted for by variability because of the smaller sample size in the placebo population.

Although participants with previous BoNTA treatment have been included in pivotal trials for various BoNTAs currently approved for treatment of glabellar lines,^{1,5,15,16} few studies have conducted a subgroup analysis to evaluate the effect of prior BoNTA treatment on the efficacy of BoNTAs. Two studies with abobotulinumtoxinA found that outcomes were similar in BoNTA treatment-experienced and treatment-naive participants; however, the data were limited to a single statement on the similarity between the groups.^{4,17} A more in-depth analysis with incobotulinumtoxinA found that prior BoNTA treatment did not affect patient- or investigator-assessed outcomes; however, the study was limited by a small population ($n = 45$).¹⁸ Therefore, because the impact of prior BoNTA treatment has not been comprehensively analyzed in a large-scale population, our analysis provides needed information to both clinicians and researchers. Particularly for clinicians, it provides support that the efficacy and safety profiles of DAXI should be similar in participants who are new to BoNTA treatment in their practice and those switching from other BoNTA products.

There were a few limitations of this analysis. First, this was a retrospective, posthoc analysis, and the study was not powered to evaluate differences in efficacy and safety between the BoNTA treatment-experienced and treatment-naive cohorts. However, because the participants enrolled in the SAKURA 1/2 trials and SAKURA 3 study were similar, we were able to combine the data to enhance the analysis. A second limitation was that the population was mostly women and white, making it challenging to identify if there are sex- or race-specific differences in the efficacy and/or safety. Finally, the number of participants in the placebo group was relatively small compared with the DAXI group; however, including the placebo group in the analysis serves as a control in evaluating if participants' expectations of treatment could influence the results.

This robust analysis of a large Phase 3 clinical program demonstrated that participants treated with DAXI for glabellar lines have similar efficacy, duration of response, and tolerability regardless of prior BoNTA treatment status. This indicates that once approved and used in clinical practice, patients should respond similarly to DAXI regardless of whether they were previously treated with BoNTA. Furthermore, future clinical trials of BoNTAs in glabellar lines need not restrict recruitment based on prior BoNTA treatment history, as long as the appropriate washout period is observed.

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