

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)

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Background: DaxibotulinumtoxinA for Injection (DAXI) is a novel botulinum toxin type A in clinical development. Phase 2 data have shown it offers a more prolonged duration of response than onabotulinumtoxinA.

Objective: To further evaluate the efficacy, duration of response, and safety of 40 U DAXI compared with placebo in the treatment of glabellar lines.

Methods: Two identical, multicenter, randomized, double-blind, placebo-controlled, phase 3 studies were performed (NCT03014622 and NCT03014635 on www.clinicaltrials.gov). Participants with moderate or severe glabellar lines were randomly assigned (2:1) to receive 40 U DAXI or placebo into the corrugator/procerus muscles. Glabellar line severity was assessed by investigators and participants for up to 36 weeks (≥ 24 weeks).

Results: Among 609 participants enrolled (405 DAXI, 204 placebo), 92% completed. DAXI was significantly more effective than placebo in reducing glabellar line severity and maintained none or mild glabellar line severity for a median of 24.0 weeks. It was also generally well tolerated—treatment-related adverse effects were most commonly headache (6.4% vs 2.0%) and injection site pain (3.7% vs 3.9%).

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Conflicts of interest: Dr Bertucci has been an investigator and consultant for Evolus, and a speaker, investigator, and consultant for Allergan, Galderma, Merz, and Revance Therapeutics, Inc. Dr Solish has been a consultant and/or speaker for Allergan, Revance Therapeutics, Inc, and Galderma. Dr Kaufman-Janette has been an advisory board participant for Revance Therapeutics, Inc, and declares ownership of a company with a patent for botulinum toxin in wound healing. Dr Yoelin has received research honoraria, consultant fees, and speaker fees from Allergan and has received research honoraria and consultant fees from Revance Therapeutics, Inc. Dr Shamban has received research honoraria, speaker fees, and/or consultant fees from Merz, Allergan, and Galderma.

Dr Schlessinger is an adviser to, and owns shares in, Revance Therapeutics, Inc. Authors Snyder, Gallagher, Liu, and Rubio are employees of, and hold stock/stock options in, Revance Therapeutics, Inc. Dr Shears is an employee of, and holds stock in, Write on Target Ltd.

Some of the data have previously been presented at the 20th Annual International Master Course on Aging Skin World Congress, Paris, France, February 1-3, 2018; at The Aesthetic Meeting 2018, New York, NY, April 26-May 1, 2018; and at the 77th Annual Meeting of the American Academy of Dermatology, Washington, DC, March 1-5, 2019.

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Limitations: The study population was predominantly female and white and received only a single treatment.

Conclusions: DAXI offers a prolonged duration of response for glabellar line reduction and is well tolerated. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2019.06.1313>.)

Key words: aesthetic; botulinum toxin; DAXI; daxibotulinumtoxinA; double-blind; duration; facial rejuvenation; glabellar lines; humans; injection; multicenter; neuromodulator; neuromuscular agent; peptide; phase 3; placebo; pooled; randomized; RT002; RTP004.

With time and repeated contraction, glabellar frown lines become more severe and may remain visible even in a resting face. Such lines are perceived as a sign of aging and affect the fidelity of nonverbal communication because they may be misinterpreted as signaling anger, anxiety, or irritation.¹

The treatment of glabellar lines with botulinum toxin type A (BoNTA) products is one of the most popular facial rejuvenation procedures in the United States (US) and BoNTA treatment of facial lines has been demonstrated to increase patients' self-esteem and quality of life.² Although proven effective and well tolerated, repeat treatments are typically needed approximately every 3 to 4 months to maintain effacement of glabellar lines. However, patients typically receive treatment only twice each year.³

Durable efficacy is very important to patients, and a product that increases the duration of clinical benefit beyond that attained with currently approved neuromodulators would be better at maintaining efficacy between injections, potentially enhancing patient satisfaction. And, for patients who currently receive treatment more than twice a year, it would offer greater convenience and save time, again potentially enhancing patient satisfaction.

DaxibotulinumtoxinA for Injection (DAXI, Revance Therapeutics, Inc, Newark, CA) is a novel BoNTA product that is in clinical development for aesthetic and therapeutic indications⁴⁻⁶ and has the potential to be the first neuromodulator with an extended duration of action to 6 months. DaxibotulinumtoxinA is a purified 150-kDa BoNTA (RTT150) that is devoid of accessory proteins and formulated with a proprietary stabilizing excipient peptide (RTP004) in a lyophilized powder. The peptide has a backbone of lysines that carry a

CAPSULE SUMMARY

- Phase 3 data confirm and expand on earlier phase 2 data that showed DaxibotulinumtoxinA for Injection offers a prolonged duration of improvement for reduction of glabellar line severity (median of 24 weeks).
- DaxibotulinumtoxinA for Injection provides sustained efficacy between treatments and may facilitate less frequent injections than currently approved botulinum toxin products.

positive charge, which results in the peptide binding electrostatically to the negatively charged core neurotoxin. The peptide allows the product to be formulated without human serum albumin and helps ensure that daxibotulinumtoxinA is stable at room temperature before reconstitution.

The results of a phase 2, randomized, dose-ranging, double-blind, multicenter study comparing DAXI with placebo and with 20 U onabotulinumtoxinA indicated that a 40-U dose of DAXI offered the most favorable risk-to-benefit profile and warranted evaluation in phase 3 studies.⁴ The 40-U dose of DAXI was also associated with significantly greater response rates—and, importantly, a significantly longer duration of response—than 20 U onabotulinumtoxinA.⁴

The potential clinical usefulness of DAXI has since been evaluated in 2 phase 3 studies (SAKURA 1 and SAKURA 2) and in a long-term safety study (SAKURA 3). Individual study results from SAKURA 1 and SAKURA 2 are published elsewhere,⁷ and pooled data are reported here.

METHODS

Study design

The objective of these multicenter, randomized, double-blind, parallel-group, prospective studies was to evaluate the efficacy, safety, and duration of clinical response of 40 U DAXI compared with placebo in the treatment of moderate to severe glabellar lines. Both studies used identical protocols (1620301 and 1620302) that conformed to the ethical principles of the Declaration of Helsinki and were approved by the relevant Institutional Review Boards in October and November 2016. All study participants provided written informed consent.

Abbreviations used:

BoNTA:	botulinum toxin type A
GAIS:	Global Aesthetic Improvement Scale
IGA-FWS:	Investigator Global Assessment —Frown Wrinkle Severity scale
PFWS:	Patient Frown Wrinkle Severity scale
US FDA:	United States Food and Drug Administration

Inclusion criteria

Participants were required to have moderate or severe glabellar lines during maximum frown on 2 wrinkle rating scales: the Investigator Global Assessment—Frown Wrinkle Severity scale (IGA-FWS) assessed by investigators and the Patient Frown Wrinkle Severity scale (PFWS) assessed by participants (Supplemental Table I, available at <http://dx.doi.org/10.17632/z8mxtfpzp2.1>).^{4,8} Additional inclusion and exclusion criteria are outlined in Supplemental Table II.

Randomization, masking, and treatment

Study participants were randomly assigned to receive 40 U DAXI or placebo in a 2:1 ratio within each study center using a block design with a block size of 3. Study treatments were provided in sequentially numbered clinical trial kits containing single-use 50-U vials, and were reconstituted with 0.6 mL sterile unpreserved saline by a blinded trained preparer. All vials looked identical to each other before and after reconstitution. An independent statistician produced a computer-generated randomization code (using SAS PROC PLAN [SAS Institute, Inc, Cary, NC]), which designated treatment assignment by clinical trial kit number. This was kept in a locked location, with treatment assignment known only to the statistician. The investigators, clinic staff, participants, and sponsor were masked to treatment. A physician trained in administering the products injected the dose in a standardized pattern split across 5 intramuscular injections—two 0.1-mL injections into each corrugator muscle and one 0.1-mL injection into the procerus muscle.

Outcome measures

Participants were evaluated for efficacy and safety for up to 36 weeks. After ≥ 24 weeks, if both investigator and participant assessments of glabellar line severity at maximum frown had returned to baseline, participants were eligible to exit the study and enter the long-term safety study. Evaluations were performed at baseline and weeks 1, 2, 4, 8, 12, 16, 20, and 24 (and potentially weeks 28, 32, and 36).

Investigators and participants were trained to rate glabellar line severity on the validated 4-point rating scales (IGA-FWS and PFWS, respectively; Supplemental Table I), and each study center was provided with a photonumeric guide.

The primary efficacy end point was the proportion of participants achieving at least a 2-point reduction in both IGA-FWS and PFWS scores at maximum frown at week 4 (a 2-point composite response). Other efficacy outcomes included the proportion of investigator or participant ratings at maximum frown showing glabellar line severity of none or mild, at least a 1-point improvement in glabellar line severity (an exploratory outcome), and an improvement on the Global Aesthetic Improvement Scale (an exploratory outcome; Supplemental Table I). In addition to participant reporting of PFWS scores at study visits, participants also reported PFWS scores in a daily diary for the first 14 days after treatment so that the onset of response, defined as the day the diary first reported at least a 1-point reduction from baseline in PFWS score, could be determined.

Duration of response was the time since treatment until none or mild glabellar line severity was lost according to both investigator and participant ratings. The time since treatment until glabellar line severity returned to baseline or worse on both investigator and participant ratings was also calculated. Participants used a 7-point scale to rate their satisfaction with treatment at week 4 (Supplemental Table I).

Any clinically significant symptoms arising after treatment were reported as adverse events, and participants were also queried in a general manner about adverse events that were potentially suggestive of the distant spread of toxin. Other safety assessments included physical examinations, clinical laboratory evaluations, electrocardiograms, and evaluations of vital signs, injection sites, cranial nerves II to VII, and facial muscle strength. In addition, testing for serum antibodies to daxibotulinumtoxinA was performed at screening and at weeks 2, 4, and 12.

Statistical analyses

Data from a previous dose-ranging study⁴ were used to estimate that a sample of 300 participants (200 DAXI, 100 placebo) would have $>99\%$ power to detect a difference between groups in the primary efficacy outcome on a 2-sided χ^2 test at an α level of 0.05 (assuming response rates of $\geq 50\%$ vs 1%). It was also estimated to provide sufficient power to detect a difference between groups for the proportion of participants with a ≥ 1 -point improvement in

glabellar line severity from baseline (eg, 90% power for a response rate of 8.7% vs 1% using a 1-sided χ^2 test).

A statistical analysis plan was provided before database lock and unblinding of the randomization code, and statistical analyses were performed after all participants had exited the study and all data had been entered in the database and verified. Efficacy analyses used the intent-to-treat population according to treatment assignment. Missing IGA-FWS and PFWS data were imputed at the participant level as worst outcome for DAXI and best outcome for placebo. Because assessment visits were mandatory only up to week 24, imputations and statistical comparisons were not performed beyond this time. Safety analyses included all participants who had at least 1 post-treatment safety assessment, according to the treatment actually received.

The proportions of participants with a 2-point composite response at week 4, with none or mild glabellar line severity, or with at least a 1-point improvement in glabellar line severity, were compared between groups using the Cochran-Mantel-Haenszel test stratified by study center using a 2-sided test with a type 1 error rate of 0.05. Between-group differences and confidence intervals were calculated using the Mantel-Haenszel estimate of the common risk difference. Point estimates of the median duration (ie, time to event) and 2-sided 95% confidence intervals were estimated using the Kaplan-Meier survival curves. All statistical programming was performed using SAS 9.4 or higher software.

RESULTS

The studies were conducted at 30 experienced clinical trial centers (24 in the US and 6 in Canada). The first participant's informed consent was signed on November 22, 2016 (first treatment on December 5, 2016), and the last participant's last visit occurred on November 14, 2017. The studies were first submitted to www.clinicaltrials.gov (NCT03014622 and NCT03014635) on December 22, 2016.

Participants

Investigators enrolled 609 participants (405 DAXI, 204 placebo) across both trials, of whom 92% completed (Supplemental Fig 1, <http://dx.doi.org/10.17632/z8mxtfpzp2.1>). Discontinuations were attributable predominantly to withdrawal of consent and loss to follow-up, with none being due to adverse events (Supplemental Fig 1). Demographic characteristics were similar in both groups (Supplemental Table III).

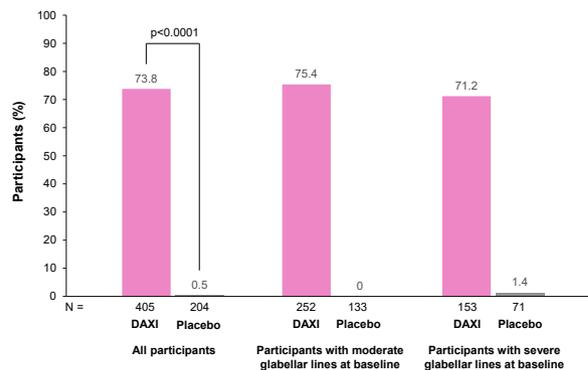


Fig 1. The proportion of participants achieving the primary efficacy end point—a 2-point composite response defined as at least a 2-point improvement from baseline in both investigator and participant ratings of glabellar line severity at maximum frown at week 4—was significantly greater after treatment with 40 U DaxibotulinumtoxinA for Injection (DAXI) than placebo. Investigators used the Investigator Global Assessment—Frown Wrinkle Severity scale and participants used the Patient Frown Wrinkle Severity scale. Investigator and participant ratings were performed independently of each other and without referring to baseline photographs.

Efficacy

The primary end point of a 2-point composite response at week 4 was achieved in 73.8% of participants in the DAXI group versus 0.5% in the placebo group ($P < .0001$), for a difference of 73.5% (95% confidence interval, 69.2%–77.9%; Fig 1). The proportion of responders to DAXI was similar regardless of whether baseline glabellar line severity had been moderate (75.4%) or severe (71.2%) (Fig 1).

The percentage of participants achieving the other efficacy outcomes with investigator or participant ratings was also consistently higher with DAXI than placebo (Fig 2, Supplemental Figs 2-3). According to investigator ratings at weeks 4, 20, and 24, respectively, glabellar line severity of none or mild was achieved in 97.5%, 53.8%, and 32.3% of DAXI-treated participants versus 4.4%, 2.9%, and 2.0% of placebo-treated participants ($P < .0001$ for weeks 1-24; Fig 2). For the same time points, at least a 1-point improvement on IGA-FWS was achieved in 99.0%, 69.3%, and 42.4% of DAXI-treated participants versus 7.1%, 4.3%, and 1.6% of placebo-treated participants ($P < .0001$ for weeks 1-24; Supplemental Fig 2). Similarly, at least a 1-point improvement on the GAIS scale was achieved in 98.0%, 69.8%, and 43.7% of DAXI-treated participants versus 3.1%, 3.7%, and 0.5% of placebo-treated participants (Supplemental Fig 3). The median time to onset of response to DAXI treatment was 3 days (range, 2-11 days).

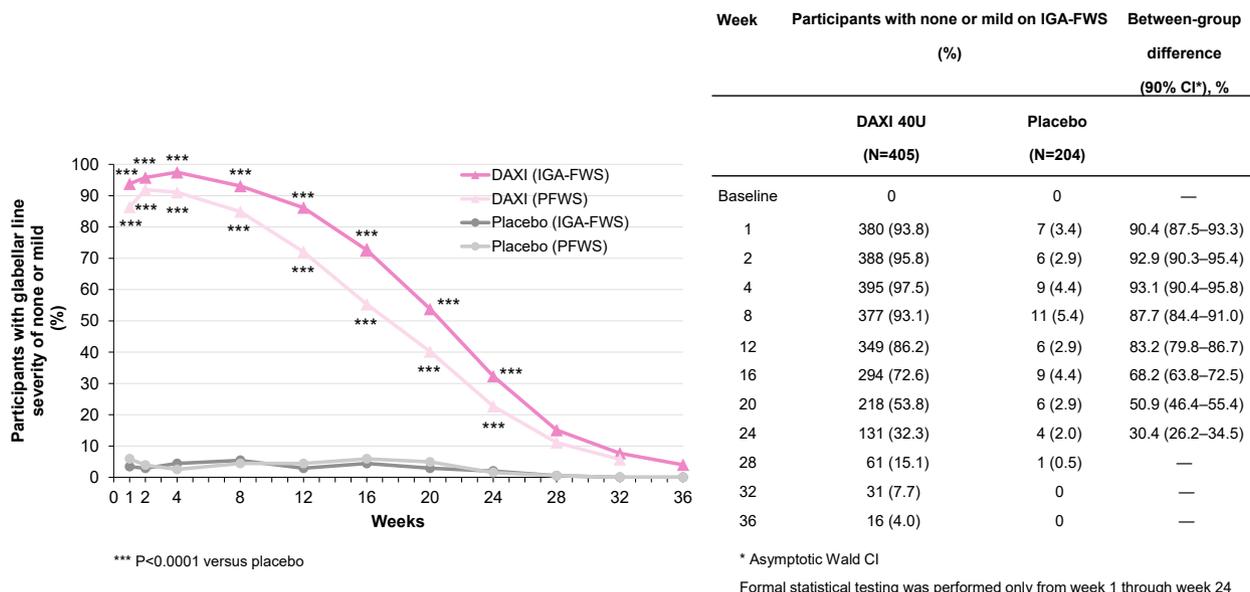
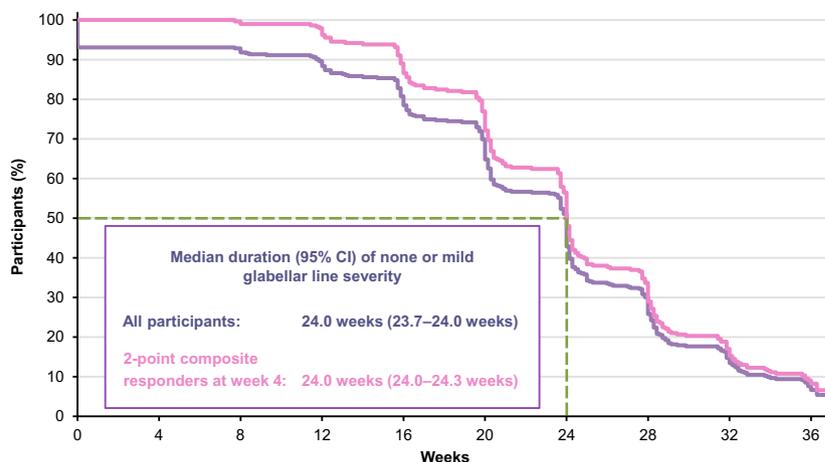


Fig 2. Proportion of participants with glabellar line severity of none or mild at maximum frown after treatment with 40 U DaxibotulinumtoxinA for Injection (DAXI) or placebo. Assessed by investigators using the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) scale or participants using the Patient Frown Wrinkle Severity (PFWS) scale. CI Confidence interval.



Participants with events (number at risk):	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36
All participants	28 (405)	0 (377)	5 (375)	14 (369)	39 (352)	54 (310)	86 (255)	65 (164)	47 (98)	24 (50)
2-point composite responders at week 4	0 (295)	0 (295)	3 (295)	8 (290)	28 (279)	42 (250)	69 (207)	53 (133)	38 (79)	18 (40)

Time to loss of none or mild glabellar line severity was the number of days since treatment until the first visit at which IGA-FWS and PFWS scores had both returned to moderate or severe levels after an improvement from baseline to none or mild levels had been observed at week 1, 2, or 4. If no such return to moderate or severe levels occurred, censoring occurred at the latest visit for which both IGA-FWS and PFWS data were available. In the absence of an improvement in both IGA-FWS and PFWS scores at weeks 1, 2 or 4, the time to return to moderate or severe levels was 0 days.

Fig 3. Glabellar line severity of none or mild at maximum frown was maintained for a median of 24.0 weeks in participants treated with DaxibotulinumtoxinA for Injection and also 24.0 weeks in participants treated with DaxibotulinumtoxinA for Injection who were 2-point composite responders at week 4, according to observed (ie, not imputed) data from both investigators and participants on the Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) scale and the Patient Frown Wrinkle Severity (PFWS) scale. CI, Confidence interval.

Duration of response

With DAXI treatment, the median duration over which none or mild glabellar line severity was

maintained was 24.0 weeks (Fig 3, Supplemental Table IV), and the median time to return to baseline levels was 27.1 weeks (28.0 weeks in the subgroup of



Fig 4. Study participant showing a 2-point reduction in glabellar line severity at maximum frown at weeks 1 and 4 according to both investigator and participant ratings. A reduction of at least 1 point was sustained through week 24. Investigators used the Investigator Global Assessment—Frown Wrinkle Severity (*IGA-FWS*) scale and participants used the Patient Frown Wrinkle Severity (*PFWS*) scale.

2-point composite responders at week 4; Supplemental Fig 4, Supplemental Table IV). Representative photographs illustrate the prolonged response achieved (Fig 4).

Patient satisfaction

The proportion of participants reporting they were very satisfied, satisfied, or somewhat satisfied with their treatment at week 4 was greater in the DAXI group than in the placebo group (95.7% vs 5.1%; Supplemental Fig 5). Whereas most participants in the DAXI group were very satisfied, most participants in the placebo group were very dissatisfied or dissatisfied.

Safety and tolerability

Adverse events occurred with an incidence of 40.9% with DAXI and 24.1% with placebo, with treatment-related adverse events occurring at an incidence of 19.2% and 8.9%, respectively (Table I). Treatment-related adverse events were predominantly mild, and none were severe, serious, or the cause of discontinuations. The most common treatment-related event was headache (6.4% vs 2.0%), followed by injection site events (pain, erythema, or edema, which occurred at least as frequently with placebo as with DAXI) and unilateral eyelid ptosis (2.2% vs 0.0%). No participant showed neutralizing antibodies to daxibotulinumtoxinA, and

results of other safety evaluations were largely normal.

DISCUSSION

These pooled results from 2 phase 3 studies are highly consistent with the findings from an earlier dose-ranging study⁴ and show that DAXI offers high response rates and a prolonged duration of response in the treatment of glabellar lines—maintaining none or mild glabellar line severity for a median of 24.0 weeks and taking a median of 27.1 weeks to return to baseline severity levels—longer than would be anticipated with the US Food and Drug Administration (FDA)-approved doses of currently available BoNTAs. Also, compared with placebo, DAXI treatment was associated with a significantly higher proportion of participants showing improvement in glabellar line severity at all mandatory study time points and higher satisfaction ratings.

The 2-point composite response used as the primary efficacy outcome in this study is a stringent measure of efficacy that is mandated by the US FDA.⁹ This standardized measure helps minimize the placebo response rate and increase the signal-to-noise ratio in clinical trials. However, it is of secondary importance in clinical practice compared with the more frequently cited “achieving none or mild glabellar lines” outcome. The maintenance of none or mild glabellar line severity may provide greater

Table I. Adverse events, with worst severity reported for each participant

Adverse events	DaxibotulinumtoxinA	
	40 U (n = 406), No. (%)	Placebo (n = 203), No. (%)
All adverse events		
Any	166 (40.9)	49 (24.1)
Mild	124	36
Moderate	36	11
Severe	6	2
Leading to discontinuation	0 (0.0)	0 (0.0)
Serious*	4 (1.0)	2 (1.0)
Deaths	0 (0.0)	0 (0.0)
Treatment-related [†] adverse events		
Any	78 (19.2)	18 (8.9)
Mild	62	14
Moderate	16	4
Severe	0	0
Serious	0 (0.0)	0 (0.0)
Treatment-related [†] adverse events with incidence of $\geq 1\%$ in any group		
Headache	26 (6.4) [‡]	4 (2.0)
Mild	22	2
Moderate	4	2
Severe	0	0
Injection site pain	15 (3.7)	8 (3.9)
Mild	10	5
Moderate	5	3
Severe	0	0
Injection site erythema	5 (1.2)	4 (2.0)
Mild	5	4
Moderate	0	0
Severe	0	0
Injection site edema	6 (1.5)	3 (1.5)
Mild	6	3
Moderate	0	0
Severe	0	0
Unilateral eyelid ptosis	9 (2.2) [§]	0 (0.0)
Mild	6	0
Moderate	3	0
Severe	0	0

*Sepsis, uterine perforation, uterine leiomyoma, bone marrow failure in DaxibotulinumtoxinA for Injection group; anxiety, recurrent leiomyosarcoma in placebo group.

[†]Possibly, probably, or definitely related.

[‡]Median duration of headache: 2 days. Calculations of duration exclude start day and include end day.

[§]Median duration of eyelid ptosis: 58 days. Calculations of duration exclude start day and include end day.

value to clinicians in describing duration of effect, because the return of moderate or severe glabellar lines will likely trigger a patient's desire for repeat treatment. The incidence of patients maintaining none or mild glabellar line severity ≥ 4 months after

40 U DAXI treatment in the SAKURA⁷ and dose-ranging studies⁴ was markedly higher than that reported after onabotulinumtoxinA^{4,10} or abobotulinumtoxinA treatment.¹¹

Because of the significant formulation differences between BoNTAs and the lack of an international reference standard to define BoNTA potency units, units of BoNTAs are not interchangeable with those of other BoNTAs.^{12,13} Although it might be tempting to assume that a 40-U dose of DAXI is simply twice the 20-U dose of onabotulinumtoxinA—potentially accounting for the extended duration of DAXI—both doses actually contain an identical quantity of the 150-kDa neurotoxin (0.18 ng in 40 U DAXI [Data on file, Revance Therapeutics, Inc.] and 0.18 ng¹³ in 20 U onabotulinumtoxinA). Thus, the relatively greater duration of response with 40 U DAXI is more likely attributable to its unique formulation and not a difference in the amount of core neurotoxin.

It has been postulated whether, if it were safe to do so, using a BoNTA at doses higher than the US FDA-approved dose for glabellar lines might prolong the duration of response. Although few well-controlled studies have been published that evaluate BoNTA dose versus duration of response, available data in women, who represent most of the patients receiving such treatment, suggest that increasing the dose of onabotulinumtoxinA above the approved 20-U dose is not associated with a meaningful improvement in duration, with no statistically significant differences observed in relapse rates between doses of 20 U, 30 U, and 40 U.¹⁴ Double-blind, placebo-controlled, dose-ranging studies with abobotulinumtoxinA for the treatment of glabellar lines identified the subsequently approved 50-U dose as optimal, with a similar duration of effect observed at both 50-U and 75-U doses.^{15,16} However, results from an open-label, single-arm study have suggested that a 120-U dose of abobotulinumtoxinA prolonged the duration of response beyond that previously obtained with 50 U.¹⁷

Although dose-response relationships have been reported at lower doses of BoNTA than the approved dose,^{14,18} the approved doses of onabotulinumtoxinA and abobotulinumtoxinA have been shown to provide the optimal balance of safety and efficacy. Furthermore, it does not appear that higher doses are routinely being administered in clinical practice in an attempt to prolong the duration of clinical effect, because the mean onabotulinumtoxinA dose for glabellar treatment in women is reported to be 17 U,¹⁹ which is lower than the approved 20-U dose.

DAXI was generally well tolerated. Neutralizing antibodies to daxibotulinumtoxinA did not develop in any participant, and no new safety signals were observed with this novel formulation. Although making meaningful comparisons of data across different trials is not possible given that this usually involves an abundance of uncontrolled variables, the incidences of eyelid ptosis and headache with DAXI are generally similar to those reported with other BoNTAs.^{4,10,11,20,21}

It might be anticipated that a BoNTA with a longer than usual duration of response could have adverse events with a longer than usual duration. Although there are inherent difficulties in attempting comparisons across studies, the limited data that are available suggest that the duration of adverse events with DAXI is consistent with that from other products; for example, the duration of eyelid ptosis with 40 U DAXI in our study was a median of 58 days, which appears to be comparable with the duration of 51 days reported with 20 U onabotulinumtoxinA⁴ and the range of 39 to 85 days reported with 50 U abobotulinumtoxinA.²²

As with other similar phase 3 studies with other BoNTAs,¹⁰ our study population was predominantly women and white, and a limitation of the study is therefore that further research may be needed to confirm the widespread applicability of the findings to men and nonwhites. It will also be interesting to evaluate the effect of repeat dosing with DAXI. This will be possible once results are available from a long-term open-label safety study (NCT03004248) that has already been completed.

CONCLUSION

These findings demonstrate that DAXI offers high response rates in the treatment of glabellar lines and a prolonged duration of response (median ≥ 24 weeks). No new safety signals were observed. Once approved, DAXI will provide an alternative treatment option for patients seeking a long duration of efficacy from their regular BoNTA treatment.

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