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Efficacy and Safety of DaxibotulinumtoxinA for Injection in Cervical Dystonia

ASPEN-1 Phase 3 Randomized Controlled Trial

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Abstract

Background and Objectives

ASPEN-1 was a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, duration of response, and safety of 2 doses of DaxibotulinumtoxinA for Injection (DAXI), a novel botulinum toxin type A formulation in participants with cervical dystonia (CD).

Methods

Adults (aged 18–80 years) with moderate-to-severe CD (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] total score ≥20) were enrolled at 60 sites across 9 countries in Europe and North America. Participants were randomized (3:3:1) to single-dose intramuscular DAXI 125U, 250U, or placebo and followed for up to 36 weeks after injection. The primary end point was change from baseline in TWSTRS total score averaged across weeks 4 and 6. Key secondary end points included duration of effect, Clinical and Patient Global Impression of Change (CGIC, PGIC), TWSTRS subscale scores, and safety. Multiplicity-adjusted intent-to-treat hypothesis tests with multiple imputation were performed using ANCOVA and Cochran-Mantel-Haenszel analyses.

Results

Of 444 individuals screened, 301 were randomized to DAXI 125U (n = 125) or 250U (n = 130) or placebo (n = 46). DAXI 125U and 250U significantly improved the mean TWSTRS total score vs placebo (least squares mean [standard error] difference vs placebo: DAXI 125U, −8.5 [1.93], $p < 0.0001$; DAXI 250U, −6.6 [1.92], $p = 0.0006$). The median duration of effect (time from treatment until loss of ≥80% of the peak improvement in average TWSTRS total score achieved at weeks 4 and 6) was 24.0 (95% confidence interval 20.3–29.1) weeks with DAXI 125U and 20.3 (16.7–24.0) weeks with DAXI 250U. Significant improvements were also observed with DAXI in CGIC and PGIC responder rates and TWSTRS subscales. Treatment-related treatment-emergent adverse events (TEAEs) were reported by 29.6% of participants with DAXI 125U, 23.8% with DAXI 250U, and 17.4% with placebo, with injection site pain being the most common overall. The most frequently reported treatment-related TEAEs of interest in DAXI 125U, DAXI 250U, and placebo, respectively, were muscular weakness (4.8%, 2.3%, 0%), musculoskeletal pain (2.4%, 3.1%, 0%), and dysphagia (1.6%, 3.8%, 0%).

Discussion

This study demonstrated that DAXI, at doses of 125U and 250U, is an effective, safe, long-acting, and well-tolerated treatment for CD.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

ASPEN-1 Study Group coinvestigators are listed in Appendix 2 at links.lww.com/WNL/D375.

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Glossary

AE = adverse event; **BoNT** = botulinum toxin; **BoNTA** = BoNT type A; **CD** = cervical dystonia; **CGIC** = Clinical Global Impression of Change; **CI** = confidence interval; **DAXI** = DaxibotulinumtoxinA for Injection; **ITT** = intent-to-treat; **PGIC** = Patient Global Impression of Change; **SE** = standard error; **TEAE** = treatment-emergent AE; **TWSTRS** = Toronto Western Spasmodic Torticollis Rating Scale.

Trial Registration Information

ClinicalTrials.gov identifier (NCT03608397, submitted July 11, 2018) and EU Clinical Trials Register (ClinicalTrialsRegister.eu EudraCT identifier 2018-000446-19, submitted September 13, 2018). First participant enrolled on June 11, 2018. Trial registration was performed in accordance with the Food and Drug Administration Amendments Act (FDAAA 801), which stipulates that the responsible party register an applicable clinical trial not later than 21 calendar days after enrolling the first human participant (42 CFR 11.24).

Classification of Evidence

This study provides Class I evidence that in adults with moderate-to-severe idiopathic cervical dystonia, DAXI reduces dystonia more effectively than placebo.

Introduction

Cervical dystonia (CD) is a chronic condition characterized by involuntary contractions of the neck muscles resulting in abnormal head and neck postures, sometimes with overlying spasms or tremor.[1] CD may be associated with discomfort or pain and can be disabling.[2,3] In addition, CD can have a negative impact on a patient's mood and emotions, resulting in depression, social withdrawal, impaired sleep, poor health outcomes, and diminished quality of life.[1,4,5]

Botulinum toxins (BoNTs) are accepted as first-line therapy for the management of CD[6-8]; however, patient satisfaction with currently approved BoNTs is suboptimal.[9-11] Current product labeling, fear of immunogenicity, and reimbursement policies limit the retreatment interval to a minimum of 12 weeks.[11-14] However, it has been observed that, in clinical practice, patients experience a declining treatment effect at a mean of 9.5 weeks after injection and a mean time to symptom re-emergence of approximately 10.5 weeks.[10,15] These data correlate with reports of low patient satisfaction toward the end of the treatment cycle,[15] with many patients requesting earlier reinjection or a longer-lasting treatment.[10,15-17] Because of this, many patients experience a period of inadequate symptom relief before their next treatment.[12,18-20] A BoNT product that can provide a longer duration of efficacy would lessen this wearing off of treatment benefit and likely lead to greater patient quality of life and fewer treatments per year.

DAXXIFY (DaxibotulinumtoxinA-Ianm for injection; DAXI; Revance Therapeutics, Inc., Nashville, TN) is a novel BoNT type A (BoNTA) formulation approved for the aesthetic treatment of glabellar lines[21-24] and is in clinical development for the treatment of CD and adult upper limb spasticity. DAXI consists of highly purified 150-kDa daxibotulinumtoxinA devoid of associated proteins, with a proprietary stabilizing excipient peptide (RTP004), that is highly positively charged and binds to negatively charged surfaces on the core neurotoxin with high avidity, and additional excipients, including polysorbate-20 (a surfactant), buffers, and a sugar, formulated in a lyophilized powder. Early preclinical data suggested DAXI could offer a significant duration advantage over currently available toxins and provided the impetus for the development programs in therapeutic and aesthetic indications.[25] In an open-label, phase 2 dose-escalation study of DAXI in patients with moderate-to-severe CD, 94% of patients achieved ≥20% reduction in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score.[26] The median duration of response was 25.3 weeks.[26] The ASPEN-1 study was a phase 3, double-blind, placebo-controlled study that evaluated the efficacy, duration of benefit, and safety of a single treatment of DAXI at either 125U or 250U compared with placebo in patients with moderate-to-severe CD. The primary objective was to evaluate the efficacy of 2 doses of DAXI compared with placebo in adults with moderate-to-severe idiopathic CD.

Methods

Study Design

ASPEN-1 was a multinational, randomized, double-blind, placebo-controlled phase 3 study conducted at 60 sites across 9 countries (Austria, Canada, Czech Republic, France, Germany, Poland, Spain, the United Kingdom, and the United States) from June 2018 to June 2020. Assessments were conducted at each study study site. From March 20, 2020, study sites were given the option of performing efficacy and safety assessments remotely owing to COVID-19 safety concerns.

Standard Protocol Approvals, Registrations, and Participant Consents

The study protocol (eSAP1, links.lww.com/WNL/D437) was approved by the appropriate ethics committee at each

participating study site, and the study was conducted according to the principles of the Declaration of Helsinki and applicable laws and regulations. Written informed consent was obtained from all participants. This study is registered at ClinicalTrials.gov (unique identifier: NCT03608397) and ClinicalTrialsRegister.eu (EudraCT unique identifier: 2018-000446-19), and the first participant was enrolled on June 11, 2018. Trial registration was performed in accordance with the Food and Drug Administration Amendments Act (FDAAA 801), which stipulates that the responsible party register an applicable clinical trial not later than 21 calendar days after enrolling the first human participant (42 CFR 11.24).

Study Population

Eligible participants were adults (age 18–80 years) with moderate-to-severe CD, defined as a TWSTRS total score of ≥20 (overall score range 0–85), with scores on the TWSTRS subscales for severity, disability, and pain of ≥15, ≥3, and ≥1, respectively. The main exclusion criteria were CD with predominant retrocollis or anterocollis posture, CD that was attributable to an underlying etiology (e.g., traumatic or tardive torticollis), or current treatment of dystonia in other body areas. Participants were excluded from the study, before randomization, if they had received any BoNT product within the 14 weeks preceding the screening visit; had historically required <100U of Botox® or its equivalent to effectively treat their CD symptoms; had a suboptimal response to their most recent BoNTA injection for CD as determined by the investigator; had a history of primary or secondary nonresponse to BoNTAs; or if they had known neutralizing antibodies to BoNTA. Participants were also excluded if they had severe dysphagia (grade 3 or 4 on the Dysphagia Severity Scale) before study entry.

Treatment Protocol

After screening, eligible participants were randomized in a 3:3:1 ratio to receive a single dose of DAXI 125U, DAXI 250U, or a placebo that consisted of the DAXI excipients (including RTP004, the surfactant polysorbate-20, histidine buffers, and trehalose) without the neurotoxin. Randomization was conducted using a computer-generated randomization schedule and stratified by prior BoNT treatment and geographic region with dynamic allocation of blocks by region. Treatment doses were prepared by a dedicated unblinded staff member while all participants, investigators, and study staff remained blinded to study drug allocation. The investigator identified the involved muscles for injection based on participant's clinical presentation, including the position of the head, neck, and shoulders; location of pain; and muscle hypertrophy. Both DAXI doses were reconstituted in 2.5 mL nonpreserved saline. The reconstituted study drug volume of 2.5 mL was divided and injected intramuscularly into involved muscles eligible for treatment according to the protocol-defined ranges specified for each muscle (eTable 1, links.lww.com/WNL/D374). The total volume was required to be injected. Use of electromyography, ultrasonography, or other imaging modalities to guide the injection of the study drug was at the discretion of the investigator.

Participants who were on a stable dose of medications for focal dystonia other than BoNT (e.g., anticholinergics, muscle relaxants, or benzodiazepines) for at least 4 weeks before baseline were to continue their use at the same dose during the study.

Outcome Measures

After study drug administration on day 1, participants were followed up at weeks 2, 4, 6, and 12 and every 4 weeks thereafter up to week 36 to capture the full duration of effect. Participants exited the study at week 6 if, in the judgment of the investigator, they did not experience initial treatment benefit. Participants who remained in the study after week 6 were allowed to exit before week 36 if they met predefined exit criteria (a TWSTRS total score that met or exceeded the TWSTRS total score indicating minimum residual benefit or experienced a significant recurrence in CD symptoms before reaching the minimum residual benefit and requested retreatment [with investigator agreement]). The minimum residual benefit for a TWSTRS score was defined as the TWSTRS total score that equated to a loss of 80% of the peak treatment effect. Each participant's minimum residual benefit was calculated using his/her TWSTRS total score at baseline, week 4, and week 6.

The primary efficacy end point was predefined as the change from baseline in TWSTRS total score averaged across weeks 4 and 6 (i.e., the time when treatment effect is expected to peak). Key secondary efficacy end points included the duration of effect, defined as the time in weeks from treatment to reach minimum residual benefit on the TWSTRS total score, and the percentage of responders (with improvement of ≥2 points) on the Clinical Global Impression of Change (CGIC) or Patient Global Impression of Change (PGIC) at week 4 or 6. The CGIC and the PGIC were each completed to rate global response to treatment on a 7-point scale from −3 (very much worse) to +3 (very much better). Change from baseline in TWSTRS subscale scores for motor severity (score range 0–35), disability related to CD (score range 0–30), and pain associated with CD (score range 0–20) averaged across weeks 4 and 6 were exploratory efficacy end points. The results from these end points are available at ClinicalTrials.gov (unique identifier: NCT03608397) and ClinicalTrialsRegister.eu (EudraCT unique identifier: 2018-000446-19). Additional end points available at ClinicalTrials.gov and/or ClinicalTrialsRegister.eu include the change from baseline in TWSTRS total score at each time point.

Safety assessments included adverse events (AEs), laboratory tests (hematology, chemistry, prothrombin time, and urinalysis), vital signs, physical and neurologic examinations, suicide assessment using the Columbia-Suicide Severity Rating Scale, severity of swallowing difficulties using the Dysphagia Severity Scale, pulmonary function by spirometry (not performed after March 20, 2020, owing to safety concerns regarding COVID-19), 12-lead ECGs, and injection site evaluations. Participants reported AEs spontaneously and in response to specific querying about AEs of interest.

Statistical Analysis

For the primary end point, the planned sample size of approximately 300 participants was estimated to provide at least 90% power to demonstrate a treatment difference between DAXI 125U and placebo, 90% power to demonstrate a treatment difference between DAXI 250U and placebo, and 80% power to demonstrate a difference between DAXI 125U and 250U for the primary end point. These estimates were calculated using a mean difference for the primary end point of 9.75 for DAXI 250U vs placebo and of 6 for DAXI 125U vs placebo, with a common standard deviation (SD) of 10.0 for each treatment group. Comparisons between treatment arms at the primary end point used an ANCOVA model with terms for treatment, region (pooled study center), and prior BoNT treatment experience and with baseline TWSTRS total score as a covariate.

Change from baseline in the TWSTRS total and subscale scores at all posttreatment time points was analyzed using a mixed model repeated measures analysis with fixed effect terms for treatment, prior BoNT treatment experience, pooled study center (region), visit, and treatment-by-visit interaction, and baseline TWSTRS score as a covariate with an unstructured covariance. For participants who exited the study before the final visit, change from baseline in TWSTRS total score was imputed with baseline score through week 36.

Kaplan-Meier analysis was performed to estimate the duration of effect. Participants who exited the study without reaching their minimum residual benefit level, including those who did not have initial treatment benefits, requested retreatment, or discontinued, were censored at their last study visit, and participants who did not reach their minimum residual benefit level or with no TWSTRS scores available after week 6 were assigned a duration equal to 0 weeks. A post hoc analysis was performed to describe the percentage of efficacy remaining on the TWSTRS total score for participants who requested retreatment before meeting their minimum residual benefit level. CGIC and PGIC responder rates were compared between treatment arms using a Cochran-Mantel-Haenszel test. A multiplicity adjustment was applied to the primary end point and key secondary end points to control the overall familywise error rate.

Efficacy analyses were performed using the intent-to-treat (ITT) population, which included all randomized participants who received study treatment and was analyzed according to randomization assignment. Safety analyses used the safety population, which included all randomized participants who received study treatment and was analyzed according to treatment received. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Data Availability

The data reported are part of a global, sponsor-led clinical development and registration program. Anonymized data not provided in this manuscript may be shared at the request of any qualified investigator.

Results

Participant Disposition and Baseline Characteristics

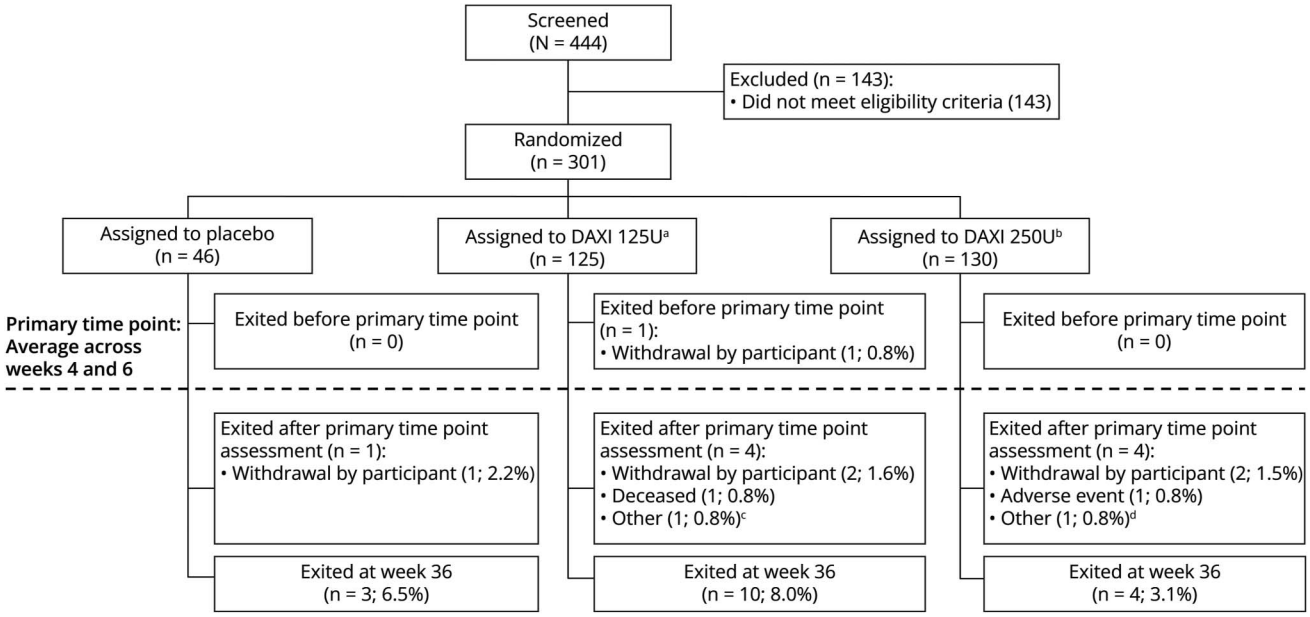
Of 444 participants screened, 143 patients did not meet the eligibility criteria and were excluded from the study. The remaining 301 patients were randomized to receive DAXI 125U (n = 125), DAXI 250U (n = 130), or placebo (n = 46) (Figure 1) and were included in the ITT population. The main reasons (≥5 patients) for exclusion from the study were an acute illness or medical condition that placed the participant at risk of increased risk of morbidity or was not stable (19 patients); previous neck surgery, phenol injection to the neck muscles, myotomy, or denervation surgery in the neck/shoulder region (13 patients); previous treatment with any BoNT product within 14 weeks before screening (8 patients); and screening 12-lead ECG with exclusionary conduction criteria of corrected QT interval (7 patients). The full list of reasons for exclusion is available in eTable 2 (links.lww.com/WNL/D374).

Eight participants randomized to DAXI received an incorrect dose (4 randomized to 125U received 250U and 4 randomized to 250U received 125U). These participants were analyzed according to their randomized treatment for all efficacy analyses (ITT population) and were included in the safety population according to the dose received (DAXI 125U, n = 125; DAXI 250U, n = 130; and placebo, n = 46). The COVID-19 pandemic had minimal impact on the study conduct and results. As of March 20, 2020, when study sites were given the option of remote assessments, only 8 (2.7%) participants remained in this study. In addition, all primary end point visits were completed before March 20, no participants discontinued because of COVID-19, no AEs were reported related to COVID-19, and all safety assessments were completed as scheduled.

Overall, 291 (96.7%) participants completed the study; 10 (3.3%) participants discontinued the study owing to withdrawn consent (6 participants), AE (1 participant), death unrelated to study treatment (1 participant), or other reasons (2 participants) (Figure 1). A total of 17 participants (5.6%) continued to week 36 without reaching their minimum residual benefit level (8.0%, 3.1%, and 6.5% of participants in the DAXI 125U, DAXI 250U, and placebo groups, respectively).

Demographic and baseline characteristics, including CD history, were similar across the 3 treatment groups (Table 1). No statistically significant differences in demographic or baseline characteristics were identified between the 2 DAXI dose groups. Most participants were female (64.8%) and White (95.3%), and the mean (SD) age was 57.7 (12.0) years. The mean duration of CD was 10.8 years, and most participants had received prior CD treatment with a BoNT (84.4%) or other medications (91.4%). Muscle relaxants were used by 18.3% of participants during the study. Baseline mean (SD) TWSTRS total scores were 45.3 (10.5) in the placebo group, 43.1 (9.4) in the DAXI 125U group, and 42.6 (8.6) in the DAXI 250U group.

Figure 1 Participant Disposition



DAXI = DaxibotulinumtoxinA for Injection; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. [a]Four participants randomized to DAXI 125U received DAXI 250U. [b]Four participants randomized to DAXI 250U received DAXI 125U. [c]Participant needed nonstudy botulinum toxin or oral dystonia medication. [d]Participant received prohibited medication (a Botox preparation).

Efficacy

The primary end point, change from baseline in TWSTRS total score averaged across weeks 4 and 6 (least squares mean (standard error [SE]) change −12.7 (1.30) with DAXI 125U, −10.9 (1.25) with DAXI 250U, and −4.3 (1.82) with placebo), showed a statistically significant improvement compared with placebo for both doses of DAXI (Figure 2). The least squares mean (SE) difference in TWSTRS total score vs placebo was −8.5 (1.93) for DAXI 125U ($p < 0.0001$) and −6.6 (1.92) for DAXI 250U ($p = 0.0006$). There was no statistically significant difference between the 2 DAXI dose groups ($p = 0.1902$). Treatment response was observed at the first follow-up visit; at week 2, the mean (SD) change from baseline in TWSTRS total score was −5.97 (8.44) for placebo and was −11.14 (10.33) for DAXI 125U and −8.01 (8.85) for DAXI 250U. There was no difference in efficacy between patients with and without prior BoNT treatment experience in either treatment arm ($p > 0.32$ for DAXI 125U and $p > 0.87$ for DAXI 250U).

The median (95% confidence interval [CI]) duration of effect, defined as time from treatment until loss of ≥80% of the peak effect (change from baseline in TWSTRS total score averaged across weeks 4 and 6), was 24.0 (20.3–29.1) weeks with DAXI 125U and 20.3 (16.7–24.0) weeks with DAXI 250U (Figure 3, A and B). A post hoc analysis of participants who requested retreatment before loss of 80% of peak effect (n = 45 (36.0%) and n = 27 (20.8%) for 125 and 250U, respectively) indicated that 45.2%–54.0% of efficacy still remained at the time of request.

In the CGIC and PGIC responder analyses, the percentages of participants achieving an improvement of ≥2 points (moderately better or very much better) at weeks 4 or 6 were significantly higher in both DAXI groups compared with placebo for both end points (Figure 4). The CGIC responder rate (95% CI), defined as an improvement of ≥2 points, was 60.8% (52.7%–69.9%) with DAXI 125U and 56.9% (48.4%–65.4%) with DAXI 250U vs 28.3% (15.2%–41.3%) with placebo ($p < 0.001$ for each DAXI dose vs placebo). The PGIC responder rate (95% CI), defined as an improvement of ≥2 points, was 53.6% (45.3%–62.8%) of participants with DAXI 125U and 50.8% (42.2%–59.4%) with DAXI 250U compared with 21.7% (9.8%–33.7%) with placebo ($p < 0.001$ for each DAXI dose vs placebo).

Change from baseline for each of the TWSTRS subscale scores (severity, disability, and pain), averaged across weeks 4 and 6, significantly improved with DAXI vs placebo (Figure 5).

Safety and Tolerability Measures

An overall summary of treatment-emergent adverse events (TEAEs) is listed in Table 2. Most TEAEs were mild or moderate, and there were no treatment-related serious TEAEs. A treatment-related severe event of neck pain was reported by 1 participant in the DAXI 125U group; the event started on study day 14 and resolved on the same day. One participant in the DAXI 250U group had a treatment-related TEAE of mild headache that led to study discontinuation. One death owing to unknown causes occurred in the DAXI 125U group and was deemed unrelated to study treatment.

Table 1 Demographic and Baseline Characteristics (ITT Population)

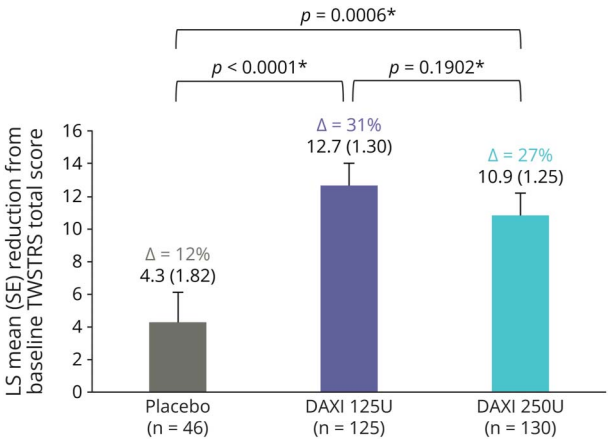
	Placebo (n = 46)	DAXI 125U (n = 125)	DAXI 250U (n = 130)	All participants (N = 301)
Age, y				
Mean (SD) [min–max]	56.5 (11.8) [29–80]	57.2 (13.4) [18–80]	58.6 (10.6) [30–79]	57.7 (12.0) [18–80]
≤50 y, n (%)	13 (28.3)	36 (28.8)	27 (20.8)	76 (25.2)
Female, n (%)	29 (63.0)	87 (69.6)	79 (60.8)	195 (64.8)
Race, n (%)				
White	43 (93.5)	119 (95.2)	125 (96.2)	287 (95.3)
Black	2 (4.3)	2 (1.6)	2 (1.5)	6 (2.0)
Asian	1 (2.2)	1 (0.8)	1 (0.8)	3 (1.0)
Other[a]	0	3 (2.4)	2 (1.5)	5 (1.7)
Prior treatment with BoNT[b]	39 (84.8)	110 (88.0)	111 (85.4)	260 (86.4)
Duration of CD, y, mean (SD)	11.3 (9.5)	10.8 (8.8)	10.5 (9.6)	10.8 (9.2)
Prior treatment with BoNT for CD[b]**, n (%)**	37 (80.4)	108 (86.4)	109 (83.8)	254 (84.4)
Other medications used for CD, n (%)	42 (91.3)	114 (91.2)	119 (91.5)	275 (91.4)
TWSTRS total score at baseline, mean (SD)	45.3 (10.5)	43.1 (9.4)	42.6 (8.6)	—

Abbreviations: BoNT = botulinum neurotoxin; CD = cervical dystonia; DAXI = DaxibotulinumtoxinA for Injection; ITT = intent-to-treat; max = maximum; min = minimum; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.
[a] Other includes American Indian or Alaska Native (1 in the DAXI 250U group), Native Hawaiian or other Pacific Islander (1 in the DAXI 125U group), and other (3 in the DAXI 125U group and 2 in the DAXI 250U group).
[b] Prior BoNT treatment was based on participant response at randomization in the electronic Case Report Form.

The most commonly reported treatment-related TEAEs for DAXI-treated participants were injection site pain (DAXI 125U, 8.0%; DAXI 250U, 4.6%; and placebo, 4.3%), headache (4.8%, 4.6%, and 2.2%), and injection site erythema (4.8%, 2.3%, and 2.2%). Commonly reported treatment-related TEAEs of interest were muscular weakness (DAXI 125U, 4.8%; DAXI 250U, 2.3%; and placebo, 0%), musculoskeletal pain (2.4%, 3.1%, and 0%), and dysphagia (1.6%, 3.8%, and 0%) (Table 2).

No safety findings were identified from other safety assessments.

Figure 2 Change From Baseline in TWSTRS Total Score Averaged Across Weeks 4 and 6

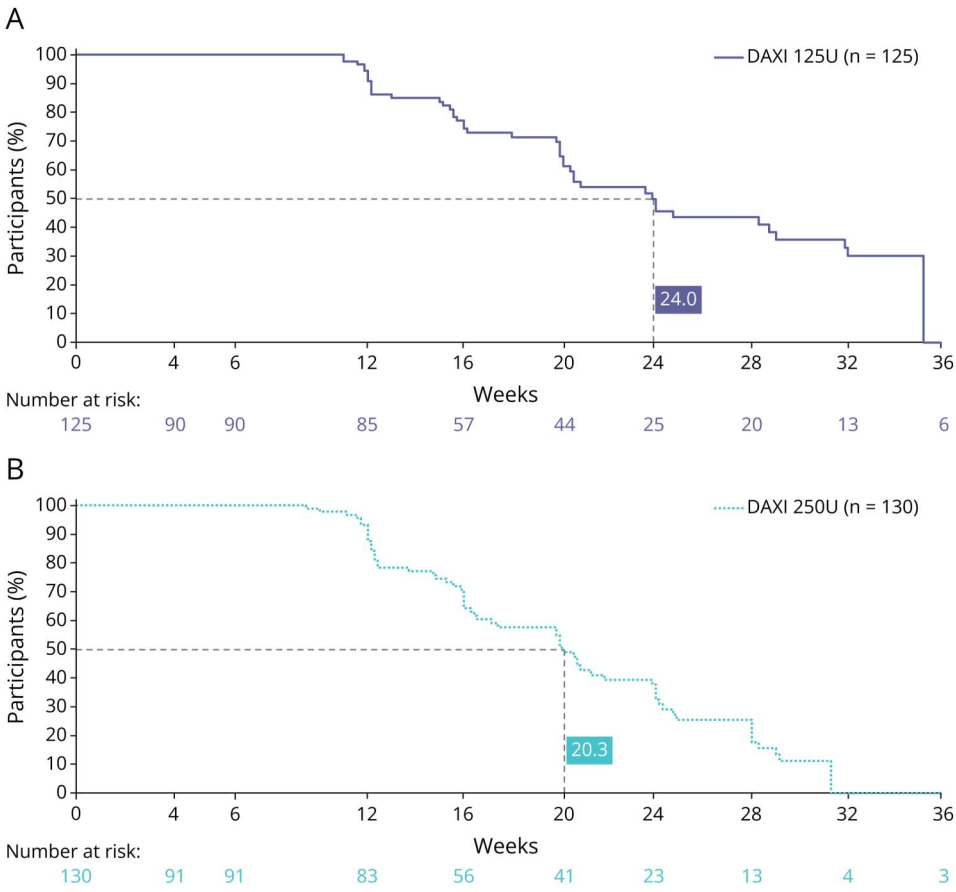


p Values based on an ANCOVA model with terms for treatment, pooled study center (region), prior botulinum toxin treatment experience, and baseline TWSTRS total score as a covariate. Multiple imputation was used for participants missing week 4 and week 6 TWSTRS total score data. DAXI = DaxibotulinumtoxinA for Injection; LS = least squares; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. Δ represents % change from baseline.

Discussion

The ASPEN-1 study demonstrates that DAXI, at either 125U or 250U, was an effective and well-tolerated treatment compared with placebo for reducing the signs and symptoms of CD. The primary study end point was met by each of the DAXI doses, with each achieving a statistically significant improvement vs placebo in the TWSTRS total score. The median time to loss of 80% treatment benefit with DAXI was 24.0 weeks for the 125U dose and 20.3 weeks for the 250U dose. With this long duration profile, the use of DAXI may extend the interval between treatments and potentially avoid significant symptom recurrence before the typical 12-week retreatment time point, addressing a clear unmet need among patients with CD and treating physicians. The apparent paradoxical difference suggesting longer duration of effect with lower dose was not statistically significant. The observed duration of effect is consistent with the 25-week median duration of response observed in the DAXI phase 2 dose-ranging study for CD[26] and is consistent with studies in other

Figure 3 Time to Loss of ≥80% of Peak Treatment Effect (Defined as TWSTRS Total Score Averaged Across Weeks 4 and 6) for (A) DAXI 125U and (B) DAXI 250U



DAXI = DaxibotulinumtoxinA for Injection; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

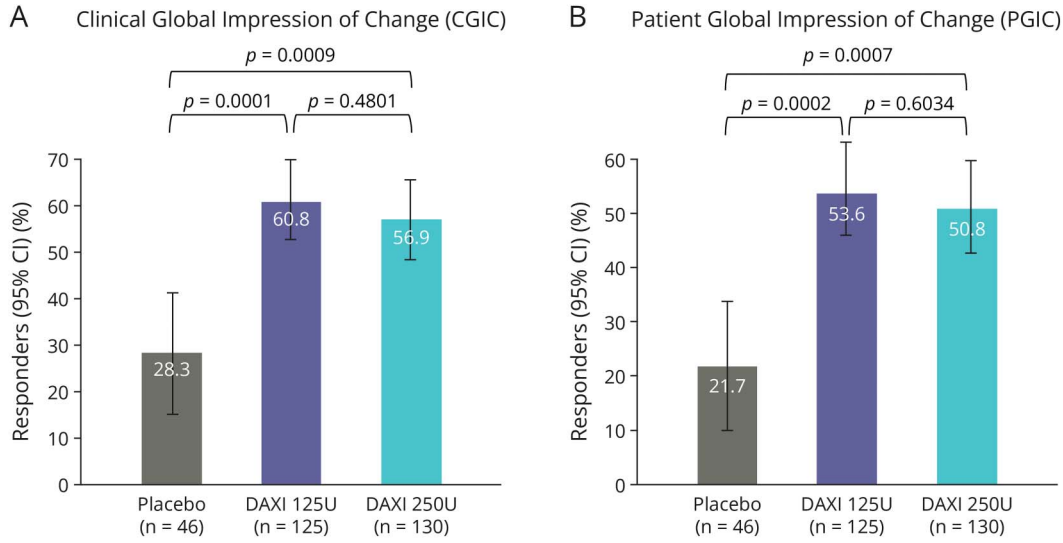
indications, with DAXI showing a 24-week to 28-week median duration of effect in the 3 phase 3 glabellar lines studies[21-23] and in a phase II study of upper limb spasticity.[27]

Defining duration as the time to loss of 80% of the peak treatment effect is an established method in which the time course of the clinical effect of a BoNT can be measured using a standardized assessment for treatment response.[28,29] In addition, this method allows for general comparisons to be made between BoNT products.[29] The duration of effect on CD symptoms seen with DAXI in both the phase 2 dose-ranging study for CD[26] and the current phase 3 study is substantially longer than the duration of efficacy reported from the pivotal trial of onabotulinumtoxinA, the most commonly used treatment for CD, in which most participants had returned to baseline status by 12 weeks with a median dose of 236U.[12] However, it should be acknowledged that time to loss of 80% of the peak treatment effect is not directly reflective of when patients may request retreatment in clinical practice. A detailed analysis of DAXI treatment over successive cycles will be available in the long-term open-label study (ASPEN-OLS; NCT03617367)[30] where patients received up to 4 continuous treatment cycles of DAXI and were reinjected when they lost 80% of their peak treatment effect or earlier, if clinically indicated. Participants enrolled in the current study could roll over to ASPEN-OLS, including those who requested reinjection.

The magnitude of mean change from baseline in TWSTRS total score at the primary time point (i.e., averaged across weeks 4 and 6) with each of the DAXI doses was −12.7 with DAXI 125U and −10.9 with DAXI 250U, which is similar to the responses seen in clinical trials for incobotulinumtoxinA[28] and abobotulinumtoxinA where TWSTRS total score at week 4 was the primary end point.[31] Participants who requested retreatment before loss of efficacy were observed to have approximately half of the peak effect still remaining at the time of their request. Consistent with the primary end point, improvements were also observed for the TWSTRS severity, disability, and pain subscales and for CGIC and PGIC responder rates when compared with placebo at weeks 4 and 6.

The TEAEs reported with DAXI in this study were typical of those reported in clinical trials of other BoNT products for CD.[12,18-20] There was no trend to increased frequency or severity of TEAEs at the higher DAXI dose. DAXI was associated with a low incidence of treatment-related dysphagia (1.6% and

Figure 4 Responders Achieving ≥2-Point Improvement at Weeks 4 or 6 for (A) Clinical Global Impression of Change (CGIC) and (b) Patient Global Impression of Change (PGIC)



CI = confidence interval; DAXI = DaxibotulinumtoxinA for Injection.

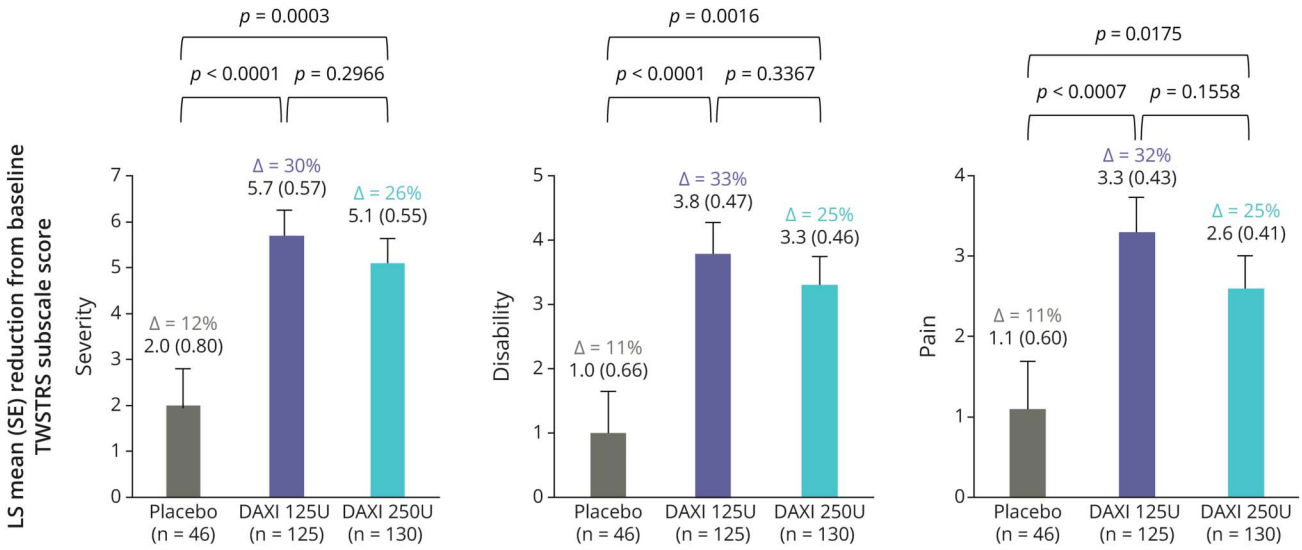
3.8% for 125U and 250U, respectively) and muscular weakness (4.8% and 2.3%). The incidence of dysphagia is considerably lower than has been reported in trials of onabotulinumtoxinA (19%), abobotulinumtoxinA (15%), incobotulinumtoxinA (13%–18%), and rimabobotulinumtoxinB (10%–25%).[12,18-20]

The unique characteristics of the RTP004 peptide excipient in the DAXI formulation may explain the consistently longer duration of effect seen with DAXI across a number of indications.[32] The strong net positive charge of the RTP004 peptide will facilitate binding to negatively charged extracellular elements, and RTP004 has been shown to increase binding of BoNTA to cell membranes and synaptosomes,[33,34] all of which may facilitate localization of BoNTA, thereby reducing diffusion away from the injection site, perhaps accounting for the low rate of local spread-related adverse events observed in ASPEN-1.[25,35] Increased binding affinity for the presynaptic nerve terminal may also prolong the time the neurotoxin molecule is associated with the neuronal membrane, increasing the probability of endocytosis of the neurotoxin. A greater amount of internalized neurotoxin will result in a prolongation of synaptic silencing.[32]

There was no statistically significant difference between the 2 DAXI doses for the primary end point or for any of the other end points analyzed in this study. Although it may seem surprising that the lower dose was associated with numerically greater outcomes compared with the higher dose, the lack of an observed dose response between 2 active doses has been reported previously in other randomized controlled trials in CD with other BoNTA products.[28,36] This may be due to random chance or, in part, the fixed-dose trial design in which patients are randomized to a treatment arm without consideration of disease severity, which will likely leave some patients overtreated and others undertreated in each study arm. In addition, both the dose that could be injected into various muscles and the selection of muscles that could be injected were limited in this study design.

There are some limitations to this study. As required per the trial design, participants were randomized to receive 1 of 2 fixed doses of DAXI, irrespective of their disease severity and were only evaluated through a single treatment cycle. In the clinical management of CD, dosing is generally optimized for each individual through trial and titration based on their clinical presentation and thereafter based on their response to previous treatments. This limitation was addressed, in part, by ASPEN-OLS, which enrolled participants who completed the current study or exited the study according to the predefined criteria. ASPEN-OLS was conducted to assess the long-term safety, efficacy, and immunogenicity of up to 4 continuous treatment cycles with DAXI, across 4 different doses. At the outset, investigators selected either 125U or 250U as the starting dose based on the participant's disease severity and prior toxin dose. They then used their judgment to increase or decrease subsequent doses across the 3 subsequent doses. Initial results from this study have been presented,[30] and further analysis of the results, where dosing could be titrated, may provide more information on dose response. In addition, consistent with many clinical trials in CD,[28,37,38] a standardized assessment for treatment response was used as the primary outcome measure, which is less commonly used in real-world clinical practice. Finally, consistent with previous registration trials of BoNTs,[28,37-39] patients with predominant retrocollis or anterocollis posture, previous

Figure 5 Change From Baseline in TWSTRS Subscale Scores Averaged Across Weeks 4 and 6



p Values based on a mixed model repeated measures analysis with fixed effect terms for treatment, prior botulinum neurotoxin treatment experience, pooled study center (region), visit, and treatment-by-visit interaction, and baseline TWSTRS subscale score as a covariate with an unstructured covariance. Δ represents % change from baseline. DAXI = DaxibotulinumtoxinA for Injection; LS = least squares; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

suboptimal response to BoNT, and history of severe dysphagia were excluded. Additional studies are required to provide insights into the use of DAXI in these patient subgroups.

In conclusion, the ASPEN-1 study demonstrated that DAXI is an efficacious and well-tolerated treatment for CD at both the 125U and 250U doses, with a median duration of effect of 24.0 and 20.3 weeks, respectively. The study confirms the

Table 2 Overall Summary of TEAEs (Safety Population)

	Placebo (n = 46)		DAXI 125U (n = 125)		DAXI 250U (n = 130)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n
Any TEAE	18 (39.1)	34	74 (59.2)	148	64 (49.2)	134
Treatment-related TEAE	8 (17.4)	11	37 (29.6)	54	31 (23.8)	49
Serious TEAE[a]	0	0	5 (4.0)	5	3 (2.3)	4
TEAE leading to study discontinuation[b]	0	0	0	0	1 (0.8)	1
Death[c]	0	0	1 (0.8)	1	0	0
Treatment-related TEAEs occurring in ≥3% of participants, n (%)						
Injection site pain	2 (4.3)		10 (8.0)		6 (4.6)	
Headache	1 (2.2)		6 (4.8)		6 (4.6)	
Injection site erythema	1 (2.2)		6 (4.8)		3 (2.3)	
Muscular weakness	0		6 (4.8)		3 (2.3)	
Musculoskeletal pain	0		3 (2.4)		4 (3.1)	
Dysphagia	0		2 (1.6)		5 (3.8)	

Abbreviations: DAXI = DaxibotulinumtoxinA for Injection; TEAE = treatment-emergent adverse event.
[a] No serious TEAEs were treatment related.
[b] One participant discontinued the study owing to a TEAE of mild headache.
[c] The death was owing to unknown causes and was considered unrelated to study drug.

results of the previous phase 2 study,[26] demonstrating DAXI to be a long-acting BoNT option that has the potential to address an unmet need in the treatment of CD.

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Joseph Jankovic, MD	Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Robert A. Hauser, MD	Department of Neurology, University of South Florida, Tampa, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Atul T. Patel, MD	Kansas City Bone & Joint Clinic, Overland Park, KS	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix 1 *(continued)*

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Domenico Vitarella, PhD	Revance Therapeutics, Inc.	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Roman G. Rubio, PhD	Revance Therapeutics, Inc.; Blue Obsidian Consulting, LLC	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/D375.

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