Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Daxxify

Active ingredient: DaxibotulinumtoxinA

Sponsor: Revance Australia Pty Ltd

June 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AESI	Adverse event of special interest
ARTG	Australian Register of Therapeutic Goods
BoNT	Botulinum neurotoxin
CDIP-58	Cervical Dystonia Impact Profile
CGIC	Clinical Global Impression of Change
CMI	Consumer Medicines Information
DAXI	daxibotulinumtoxinA
DP	drug product
DS	drug substance
GL	Glabellar lines
FDA	United States Food and Drug Administration
IGA-FWS	Investigator Global Assessment–Frown Wrinkle Severity
IM	Intramuscular
PFWS	Patient–Frown Wrinkle Severity
PI	Product Information
PGIC	Patient Global Impression of Change
PSUR	Periodic safety update report
RMP	Risk management plan
RT002	daxibotulinumtoxinA
RTP004	RTP004 peptide excipient
TEAEs	Treatment emergent adverse events
TGA	Therapeutic Goods Administration
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale

Daxxify (daxibotulinumtoxinA) submission

Type of submission:	New biological entity
Product name:	Daxxify
Active ingredient:	DaxibotulinumtoxinA
Decision:	Approved
Date of decision:	3 December 2024
Date of entry onto ARTG:	17 December 2024
ARTG number:	420430
, *Black Triangle Scheme*	Yes
Sponsor's name and address:	Revance Australia Pty Ltd, Suite 1, Level 3, 62 Lygon Street, Carlton South VIC 3053, Australia
Dose form:	Powder for Injection
Strength:	100 Units of daxibotulinumtoxinA per vial
Container:	single-dose vial
Pack size:	1 vial per carton
Approved therapeutic use for the current submission:	• The temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. • The treatment of cervical dystonia in adult patients.
Route of administration:	intramuscular injection

Dosage:

Indication	Diluent * Added to 100 Unit Vials	Resulting dose in Units per 0. 1 mL
Glabellar Lines, Adults	1. 2 mL	8 Units
Cervical Dystonia, Adults	1. 0 mL 2. 0 mL	10 Units 5 Units

* 0. 9% Sodium Chloride Injection, USP

For further information regarding dosage, refer to the Product Information.

Pregnancy category:	Category B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Daxxify (daxibotulinumtoxinA) – proposed indication

This AusPAR describes the submission by Revance Australia Pty Ltd to register Daxxify (daxibotulinumtoxinA) for the following proposed indication:[1]

> *The temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.*
>
> *The treatment of cervical dystonia in adult patients*

DaxibotulinumtoxinA is a purified Clostridium botulinum type A neurotoxin derived from the Hall strain of *Clostridium botulinum.*

Glabellar lines

Glabellar lines (GL) refer to the presence of one or more vertical lines that develop between the eyebrows upon frowning, and in some cases may be present at rest. Glabellar lines result from the contraction of the horizontally oriented corrugator muscles bilaterally and the vertically oriented central procerus muscle. [2]

Cervical dystonia

Cervical dystonia (CD, also referred to as spasmodic torticollis) is a chronic neurologic disorder characterised by involuntary patterned contractions of cervical musculature resulting in abnormal movements or postural changes of the head, neck, and shoulders. In isolated CD, there is no evidence for any identifiable cause for the dystonic symptoms. The pattern of neck muscle involvement in patients with CD is variable, leading to clinically heterogeneous directional presentations, such as rotational torticollis, laterocollis, retrocollis, or anterocollis. Most cases of CD are idiopathic, though genetic susceptibility is presumed to play an important role. Rare cases are monogenetic. [3]

Current treatment options for glabellar lines and cervical dystonia

Treatment of GL is performed for cosmetic reasons. Botulinum neurotoxin (BoNT) products registered in Australia for the treatment of GL include:

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Jean Carruthers, 'Overview of botulinum toxin for cosmetic indications', UpToDate, Feb 25, 2025.

[3] Andres Deik, 'Cervical dystonia: Etiology, clinical features, and diagnosis', UpToDate, Apr 23, 2024.

- Botox (botulinum toxin type A, onabotulinumtoxinA): for the temporary improvement in the appearance of upper facial rhytides (glabellar lines, crow's feet and forehead lines) in adults.
- Dysport (clostridium botulinum type A toxin - haemagglutinin complex): for the treatment of moderate to severe glabellar lines and/or lateral canthal lines (crow's feet) in adults.
- Xeomin (incobotulinumtoxinA): for the treatment of upper facial lines in adults (glabellar frown lines, lateral periorbital lines (crow's feet), horizontal forehead lines).
- Nuceiva (prabotulinumtoxinA): for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients.
- Letybo (letibotulinumtoxinA): indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.

Treatment of cervical dystonia is symptomatic, and can include BoNT injections, oral medications, and deep brain stimulation for refractory cases. BoNT products registered in Australia for the treatment of CD (or spasmodic torticollis) include Botox, Dysport, and Xeomin.

Clinical rationale for the use of Daxxify for glabellar lines and cervical dystonia

BoNT cleaves a key protein of the neuroexocytosis apparatus on peripheral cholinergic nerve endings, preventing acetylcholine release, thereby inhibiting muscle contraction and wrinkle formation. [4,5,6]

Regulatory status

Australian regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

International regulatory status

At the time this submission was being evaluated by the TGA:

USA: The GL indication was submitted on 24 November 2019 and approved 7 September 2022. The CD indication was submitted on 19 October 2022 and approved 11 August 2023. The approved indications are:

> *Daxxify is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.*
>
> *Daxxify is indicated for the treatment of cervical dystonia in adult patients.*

[4] Morbiato, L.; Carli, L.; Johnson, E.A.; Montecucco, C.; Molgo, J.; Rossetto, O. Neuromuscular Paralysis and Recovery in Mice Injected with Botulinum Neurotoxins A and C. Eur. J. Neurosci. 2007, 25, 2697–2704.

[5] Pirazzini, M.; Rossetto, O.; Eleopra, R.; Montecucco, C. Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology. Pharmacol Rev. 2017, 69, 200-235.

[6] Simpson, L. The Life History of a Botulinum Toxin Molecule. Toxicon. 2013, 68, 40–59

Registration timeline

Table 1 captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Registration timeline for Daxxify (DaxibotulinumtoxinA) PM-2023-03624-1-1

Description	Date
Submission dossier accepted and evaluation commenced	30 November 2023
Evaluation completed	22 July 2024
Registration decision (Approved)	3 December 2024
Registration in the ARTG completed	17 December 2024
Number of working days from submission dossier acceptance to registration decision*	256 days

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

DaxibotulinumtoxinA drug substance (DS) is a purified *Clostridium botulinum* type A neurotoxin derived from the Hall strain of *Clostridium botulinum*.

Daxxify is formulated as a lyophilised drug product (DP) with a novel peptide excipient, RTP004, which functions to stabilise daxibotulinumtoxinA. Daxxify is free of human albumin or animal-based components. Reconstitution of the DP is carried out with a commercially sourced sterile saline. The dosage form contains approximately 100 U of daxibotulinumtoxinA per 2 mL vial (borosilicate glass vial with butyl rubber stopper).

The physicochemical and biological properties of the DP relevant to the safety, clinical performance and manufacturability of the DP were identified and appropriately characterised or controlled in accordance with ICH guidelines.

The proposed drug DS and DP specifications are acceptable.

The compatibility of reconstituted DP with both the commercial vial and in-use syringe containers (polycarbonate and polypropylene) was demonstrated in in-use stability and in-use microbial studies.

Based on the submitted stability data, the recommended shelf life and storage conditions are:

- DS shelf life: 48 months; storage condition: ≤ -65°C.
- DP shelf life: 36 months; storage condition: 20 to 25°C or 2 to 8°C; protected from light.

The novel excipient, RTP004 acetate (RTP004), is a single-chain synthetic peptide consisting of 35 L-amino acids, which is used in the final DP formulation as a stabiliser of the active ingredient daxibotulinumtoxinA. Characterisation of the peptide's stabiliser properties has been adequately demonstrated and its manufacturing process has been successfully validated.

The Product Information (PI) and labels are acceptable from a quality perspective.

Nonclinical evaluation summary

The submitted nonclinical data consisted of studies in rodents, rabbits, pigs, dogs and monkeys, with pivotal safety studies conducted in compliance with Good Laboratory Practice requirements, and generally conformed to relevant ICH guidelines. Non-clinical studies were conducted to establish the safety and toxicity profile of both daxibotulinumtoxinA and the new peptide excipient, RTP004. Possible differences in potency, safety, local or systemic spread and antigenicity (ability to generate neutralising antibodies) after intramuscular injections of daxibotulinumtoxinA was assessed compared to Botox.

Pharmacological studies in mouse hind limb paralysis models confirmed daxibotulinumtoxinA acts on the neuromuscular junction producing the desired (reversible) effect of muscle paralysis. Time course of onset (ca. 2-3 days) and maximum paralytic efficacy were comparable to Botox. DaxibotulinumtoxinA exhibited a greater duration of paralytic efficacy at a similar dose (up to 126%) with mice taking about twice as long (by 92%) to return to baseline cf. Botox. Investigations showed less local diffusion from the injection site cf. Botox (2. 5:1 dose ratio required for significant comparable paralysis of adjacent muscle).

Whilst no dedicated safety pharmacology studies were conducted with daxibotulinumtoxinA, no adverse effects on ECG parameters were seen in a repeat-dose toxicity study in monkeys. RTP004 also had no effect on ECG parameters in the repeat-dose toxicity study in monkeys and on CNS function in a single dedicated safety pharmacology study in rats. Given the low expected systemic exposures, no adverse effects on cardiovascular, central nervous system and respiratory function are expected in patients with the proposed clinical use.

No pharmacokinetic studies were conducted with daxibotulinumtoxinA and/or RTP004 given the low IM doses and the low systemic exposure in animals. However, distribution studies in rats following IM injections of ^{125}I-daxibotulinumtoxinA (^{125}I-DAXI) showed no difference for ^{125}I-DAXI (or related radioactivity) with or without RTP004 in the RT002 formulation in the local tissue distribution, area of distribution (within the injected thigh muscle) or on tissue distribution of radioactivity throughout the body of rats.

Toxicity findings in the repeat-dose toxicity studies with daxibotulinumtoxinA in rats and monkeys by IM injection and in mice by the SC route were expected for this type of product, and were mainly restricted to the injected muscle (i. e. , local muscle paralysis, resulting in reduced mobility and muscular tone, muscle atrophy, weakness, paralysis of the dosed hindlimb and at most dose levels, reductions in body weights). All of these findings are well known class effects of BoNT agents. There were no clinically relevant toxicity findings in the single and repeat-dose toxicity studies with RTP004.

No genotoxicity or carcinogenicity studies were conducted with Daxxify, which is consistent with the guideline for a product of this nature. RTP004 was not mutagenic in a bacterial mutation assay and was negative in both in vitro (lymphocytes) and in an in vivo chromosome aberration assay (bone marrow cells).

Fertility was reduced ≥10 U/kg and 30 U/kg in male and female rats, respectively, due to the poor clinical condition of animals (associated with limited use of the hindlimb, reductions in body weight gain and food intake). Adverse effects on embryofetal development in rats (but not rabbits) with daxibotulinumtoxinA were limited to decreased fetal body weight and skeletal ossification sites at 30 U/kg (24-times the maximum recommended human dose) and attributed to maternotoxicity. DaxibotulinumtoxinA was not teratogenic. In addition, it had no effect on pre- and postnatal development despite maternotoxicity at ≥3 U/kg. All findings were consistent with those reported for other BoNT agents as a class. Pregnancy Category B3 is considered appropriate. RTP004 resulted in no reproductive toxicity.

Nonclinical data submitted for RTP004 supports its use as a new (novel) excipient in Daxxify.

There are no non-clinical objections to the registration of Daxxify.

Clinical evaluation summary

DaxibotulinumtoxinA was known as RT002 during clinical development and is also referred to as DAXI in this report. The clinical development program included:

- Dose-finding studies:
  - GL: RT002-CL001 (GL-Mexico) and RT002-CL002 (GL-Belmont).
  - CD: RT002-CL005.
- Pivotal efficacy/safety studies:
  - GL: Studies 1620301 (SAKURA-1) and 1620302 (SAKURA-2).
  - CD: Study 1720302 (ASPEN-1).
- Other efficacy/safety studies:
  - GL: Study 1620303 (SAKURA-OLS).
  - CD: Study 1720304 (ASPEN-OLS).

None of the main efficacy/safety studies evaluated an active comparator.

The evaluation of efficacy in the GL program was informed by FDA guidance,[7] research reported in the literature, and experience from other BoNT products approved for the treatment of GL. The main clinical studies evaluated Investigator Global Assessment–Frown Wrinkle Severity (IGA-FWS) and Patient–Frown Wrinkle Severity (PFWS). The IGA-FWS and PFWS are 4-point scales, where rating scores of 0, 1, 2, and 3 correspond to None, Mild, Moderate, and Severe, respectively. In the pivotal studies, success was defined as achievement of a score of 0 or 1 and a 2-grade improvement from the baseline, on both the investigator assessment and the subject self-assessment scales concurrently (2-point composite responder rate). In addition to the 2-point composite responder rate, efficacy analyses assessed the proportion of subjects with glabellar line severity rated as None or Mild, and time to return to a rating of Moderate or Severe.

The evaluation of efficacy in the CD program was based primarily on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The TWSTRS is a composite assessment scale which covers different features of CD. The TWSTRS-Total score is the sum of the TWSTRS-Severity score (0-35, clinician-rated), the TWSTRS-Disability score (0–30, patient-rated), and the TWSTRS-Pain score (0–20, patient-rated), with a maximum score of 85 reflecting maximum severity.

Pharmacology

No pharmacokinetic or pharmacodynamic studies were submitted. This is acceptable for a BoNT product given the local administration into the target muscle, low/undetectable systemic exposure, and well-established mechanism of action of BoNT.

[7] U.S. Food and Drug Administration, 'Guidance Document: Upper Facial Lines: Developing Botulinum Toxin Drug Products' August 2014.

Dose selection

Glabellar lines

Study RT002-CL002 (GL-Belmont)

This was a Phase 2, randomised, double-blind, placebo-controlled, dose-finding study that evaluated DAXI at single doses of 20, 40, and 60 U compared with placebo and Botox at dose of 20 U in 250 subjects with moderate to severe GL.

The primary efficacy outcome was a ≥1-point improvement from baseline on the IGA-FWS at maximum frown at Week 24 post-treatment. There was a statistically significant greater proportion of responders in each DAXI group compared with the placebo group, with a small increase in responders in the 60 U group compared with the 40 U group (Table 2). Considering the small difference in responders in the 60 U group compared with the 40 U group, the proportion of treatment-related adverse events in each group, and the number of eyelid ptosis cases, the 40 U dose was selected as the optimal dose to be evaluated in Phase 3 studies.

Table 2: Study RT002-CL-002 (GL-Belmont). Results in support of DAXI dose selection

Treatment	N	Responder Rate[a] Week 4 (%)	Responder Rate[a] Week 24 (%)	Treatment-Related AEs (% subjects)	Eyelid Ptosis (n)
DAXI 60 U	53	100	35. 7	30. 2	4
DAXI 40 U	53	100	32. 1	22. 7	0
DAXI 20 U	54	98. 1	16. 8	24. 1	0
Placebo	54	5. 9	2. 5	13. 1	0
OnabotA 20 U	54	96. 3	20. 4	27. 9	1

AE = adverse event; DAXI = daxibotulinumtoxinA; IGA-FWS = Investigator Global Assessment-Frown Wrinkle Severity; OnabotA = onabotulinumtoxinA.

a. Response rate was based on ≥ 1-point improvement from baseline on the IGA-FWS at maximum frown at the specified week.

Cervical Dystonia

Study RT002-CL005

This was a Phase 2, multicentre, open-label, dose escalation study to evaluate the safety and preliminary efficacy of DAXI in adult subjects with moderate to severe isolated CD. The study enrolled 37 subjects in 3 treatment cohorts in a sequential, dose escalating fashion (Cohort 1 up to 200 U, Cohort 2 200 to 300 U, Cohort 3 300 to 450 U), with the actual dose administered to each patient based on the investigator's clinical judgement. 33 subjects completed the study: 12 in Cohort 1, 10 in Cohort 2, and 11 in Cohort 3.

The primary efficacy endpoint was the change from baseline in TWSTRS-total score at Week 4. At Week 4, the overall mean change from baseline in TWSTRS-total score was -16. 8 (-20. 2 in Cohort 1, -12. 4 in Cohort 2, and -17. 8 in Cohort 3). A dose response trend was not evident on the primary endpoint or other endpoints, including Cervical Dystonia Impact Profile (CDIP-58), Clinical Global Impression of Change (CGIC), or Patient Global Impression of Change (PGIC). The Sponsor postulated that a possible explanation for the lack of dose response was that the selection of dose for each patient was influenced by the investigator's clinical judgment.

The pivotal study, ASPEN-1, evaluated two doses of DAXI (125 U, 250 U) compared to placebo.

Efficacy

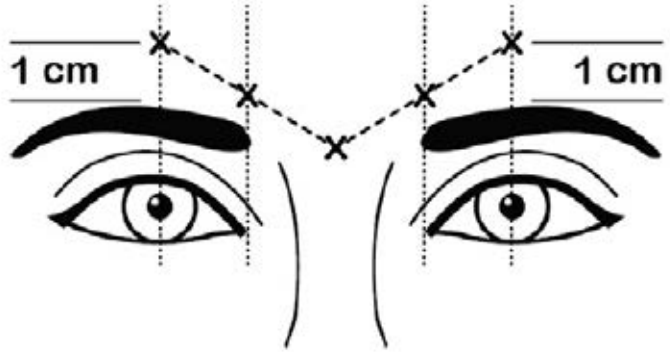
Glabellar lines

Study 1620301 (SAKURA-1)

This was a Phase 3, randomised, double-blind, placebo-controlled, multicentre study conducted at 15 sites in the USA from December 2016 to November 2017. The primary objective was to evaluate the efficacy and safety of a single treatment of DAXI for the treatment of moderate to severe GL compared to placebo.

The study included healthy adults aged 18 to 75 years with moderate or severe GL during maximum frown based on the IGA-FWS and PFWS. Subjects were randomly assigned in a 2:1 ratio to DAXI for injection (40 U) or placebo, and were followed for a minimum of 24 weeks and up to a maximum of 36 weeks post-treatment. A trained physician administered a single dose of DAXI for injection (40 U) or placebo to subjects as five IM injections of 0. 1 mL each in the glabellar region: 2 injections into each corrugator muscle and 1 injection in the procerus muscle (Figure 1).

Figure 1: Study 1620301 (SAKURA-1) Injection Sites



The primary efficacy endpoint was the proportion of subjects who achieved a 2-point composite response at Week 4. In the final SAP, there were two hypothesis-tested secondary endpoints: proportion of subjects rated “none” or “mild” by the Investigator (IGA-FWS), and proportion of subjects rated “none” or “mild” by both the subject (PFWS) and the Investigator (IGA-FWS).

The primary endpoint was analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by trial centre using a two-sided test with a Type I error rate of 0. 05. The two secondary endpoints were analysed sequentially (IGA-FWS first, then composite) at seven sequential study time points of Week 2, 4, 8, 12, 16, 20, and 24. All other efficacy endpoints were analysed descriptively.

303 subjects were randomised to treatment, 201 to DAXI and 102 to placebo. Overall, 275 (90. 8%) subjects completed the study. The majority of subjects were female (86. 5%), white (83. 8%), with a mean age of 50. 3 years. Approximately half of all subjects had been previously treated with BoNT with a mean time since last injection of 29. 1 months. At baseline, 62. 4% of subjects had moderate GL and 37. 6% had severe GL at maximum frown based on IGA-FWS. 60. 7% of subjects had moderate GL and 39. 3% had severe GL at maximum frown based on PFWS.

The primary endpoint was met (Table 3). The key secondary outcomes are presented in Figure 2 and Figure 3.

Table 3: Study 1620301 (SAKURA-1) Proportion of subjects who achieved a 2-point Composite Response at Maximum Frown at Week 4 (Worst/Best Outcome Imputation; ITT Population)

	Placebo (N=102)	DAXI for Injection 40 U (N=201)	Difference[a] (95% CI)[b]
n (%)	0	148 (73. 6%)	74. 2% (68. 2%, 80. 2%)
p-value[c]			<0. 0001

CI = confidence interval; IGA-FWS = Investigator Global Assessment-Frown Wrinkle Severity; ITT = Intent-to treat; PFWS = Patient Frown Wrinkle Severity. Response was defined as achieving a score of 0 or 1 (none or mild) and an improvement of at least 2 points from baseline on both IGA-FWS and PFWS scales concurrently at the visit. Percentages were based on N.

a Difference was calculated as DAXI for injection 40 U minus placebo using the Mantel-Haenszel estimate of the common risk difference.

b The 95% CI was the stratified Newcombe confidence limits for the common risk difference.

c The p-value was based on the Cochran-Mantel-Haenszel test, stratifying by trial centre.

Figure 2: Proportion of Subjects Who Achieved a Score of 0 or 1 (None or Mild) on IGA-FWS at Maximum Frown Over Time (Worst/Best Outcome Imputation; ITT Population). The 90% CI is displayed at each visit.

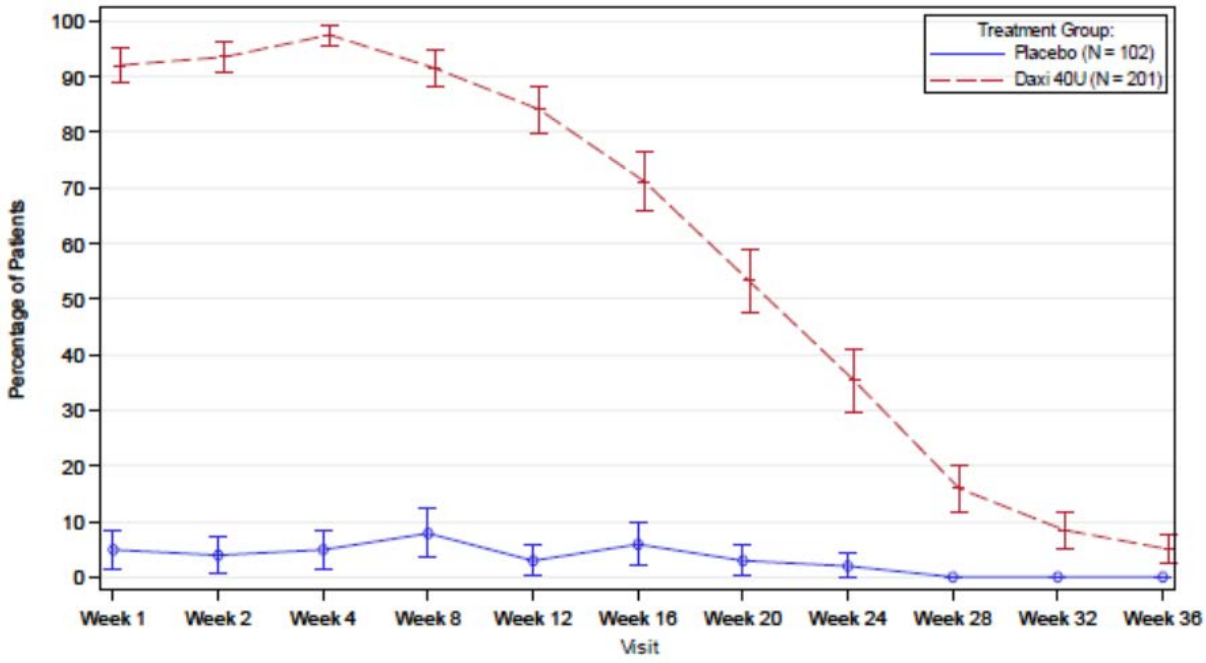
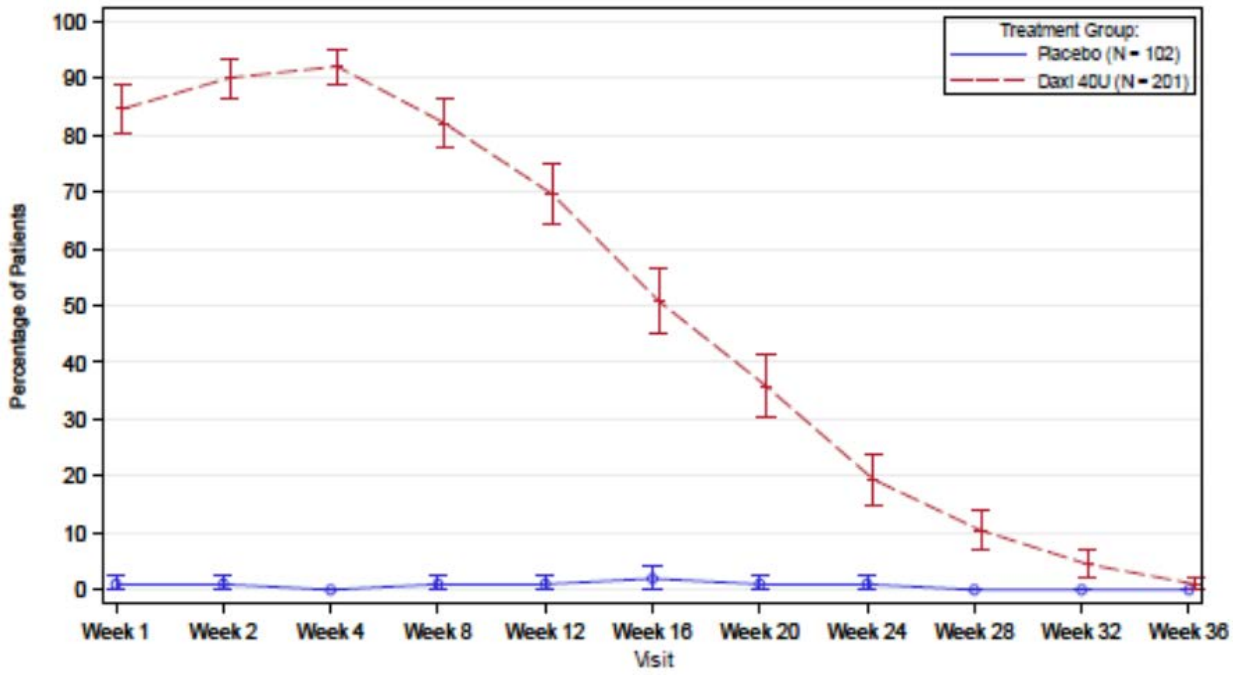


Figure 3: Proportion of Subjects Who Achieved a Score of 0 or 1 (None or Mild) on Both IGA-FWS and PFWS at Maximum Frown Over Time (Worst/Best Outcome Imputation; ITT Population). The 90% CI is displayed at each visit.



The median time to return to moderate or severe GL on both IGA-FWS and PFWS was 24 weeks in all DAXI subjects, as well as for those who achieved a 2-point composite response at Week 4. The median time to return to baseline or worse than baseline on both IGA-FWS and PFWS was ~28 weeks in all DAXI subjects and 28 weeks in subjects who achieved a 2-point composite response at Week 4.

Study 1620302 (SAKURA-2)

This was a Phase 3, randomised, double blind, placebo controlled, multicentre study conducted at 15 sites in the USA (9) and Canada (6) from November 2016 to November 2017. The study design was similar to SAKURA-1, including the dose and efficacy endpoints.

The primary efficacy outcome is shown in Table 4 and key secondary efficacy outcomes in Figure 4 and Figure 5.

The median time to return to moderate or severe GL on both IGA-FWS and PFWS was ~24 weeks in all DAXI subjects, as well as for those who achieved a 2-point composite response at Week 4. The median time to return to baseline or worse than baseline on both IGA-FWS and PFWS was ~26 weeks in all DAXI subjects and 28 weeks in subjects who achieved a 2-point composite response at Week 4.

Table 4: Study 1620302 (SAKURA-2) Proportion of subjects who achieved a 2-point composite response at maximum frown at Week 4 (Worst/Best Outcome Imputation; ITT Population)

	Placebo (N=102)	DAXI for Injection 40 U (N=204)	Difference[a] (95% CI)[b]
n (%)	1 (1. 0%)	151 (74. 0%)	72. 9% (66. 6%, 79. 1%)
p-value[c]			<0. 0001

Response was defined as achieving a score of 0 or 1 (none or mild) and an improvement of at least 2 points from baseline on both IGA-FWS and PFWS scales concurrently at the visit. Percentages were based on N.

a Difference was calculated as DAXI for injection 40 U minus placebo using the Mantel-Haenszel estimate of the common risk difference.

b The 95% CI was the stratified Newcombe confidence limits for the common risk difference.

c The p-value was based on the Cochran-Mantel-Haenszel test, stratifying by trial centre.

Figure 4: Study 1620302 (SAKURA-2): Proportion of subjects who achieved a score of 0 or 1 (None or Mild) on IGA-FWS at maximum frown over time (Worst/Best Outcome Imputation; ITT Population)

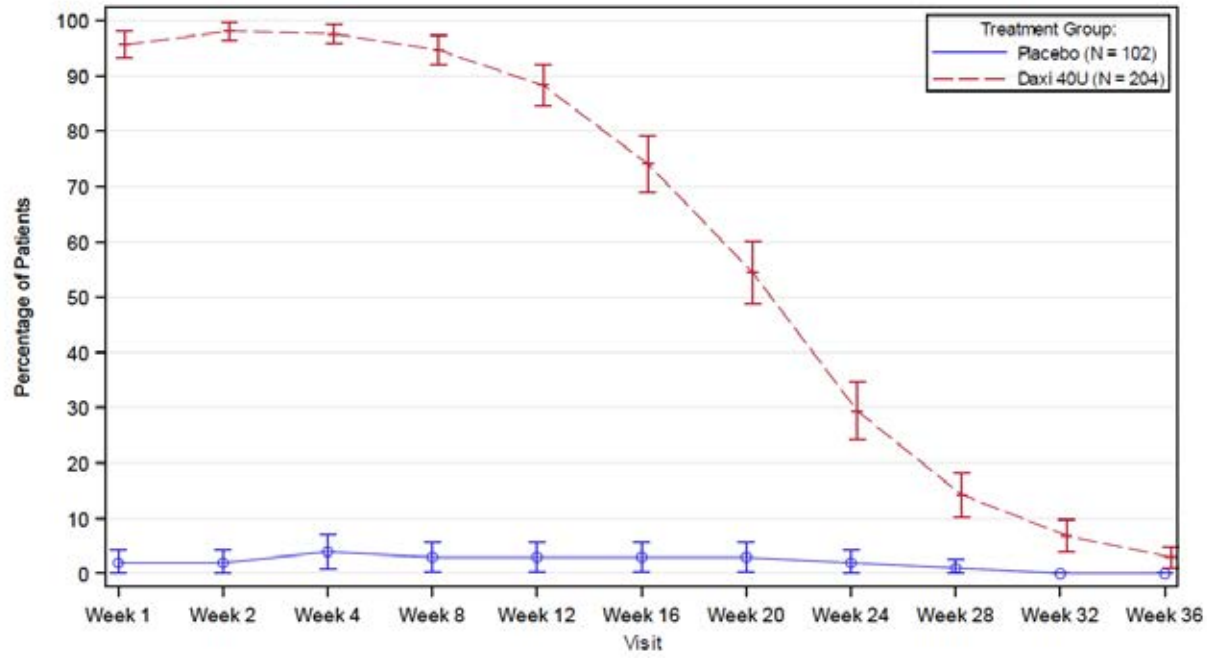
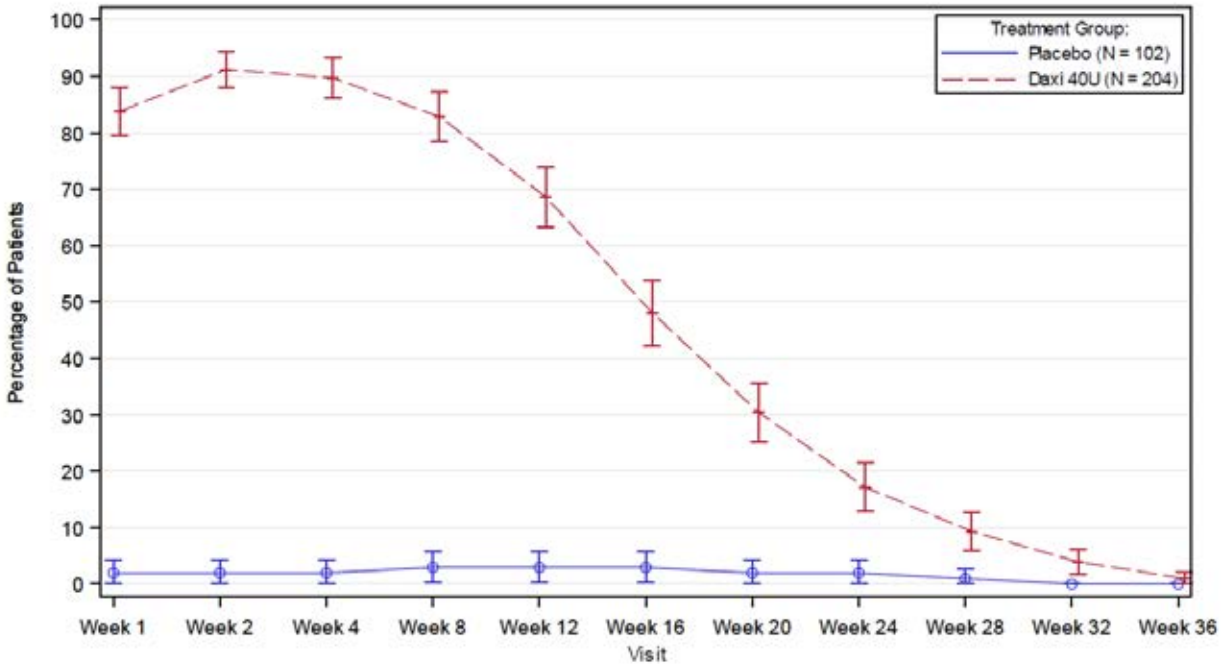


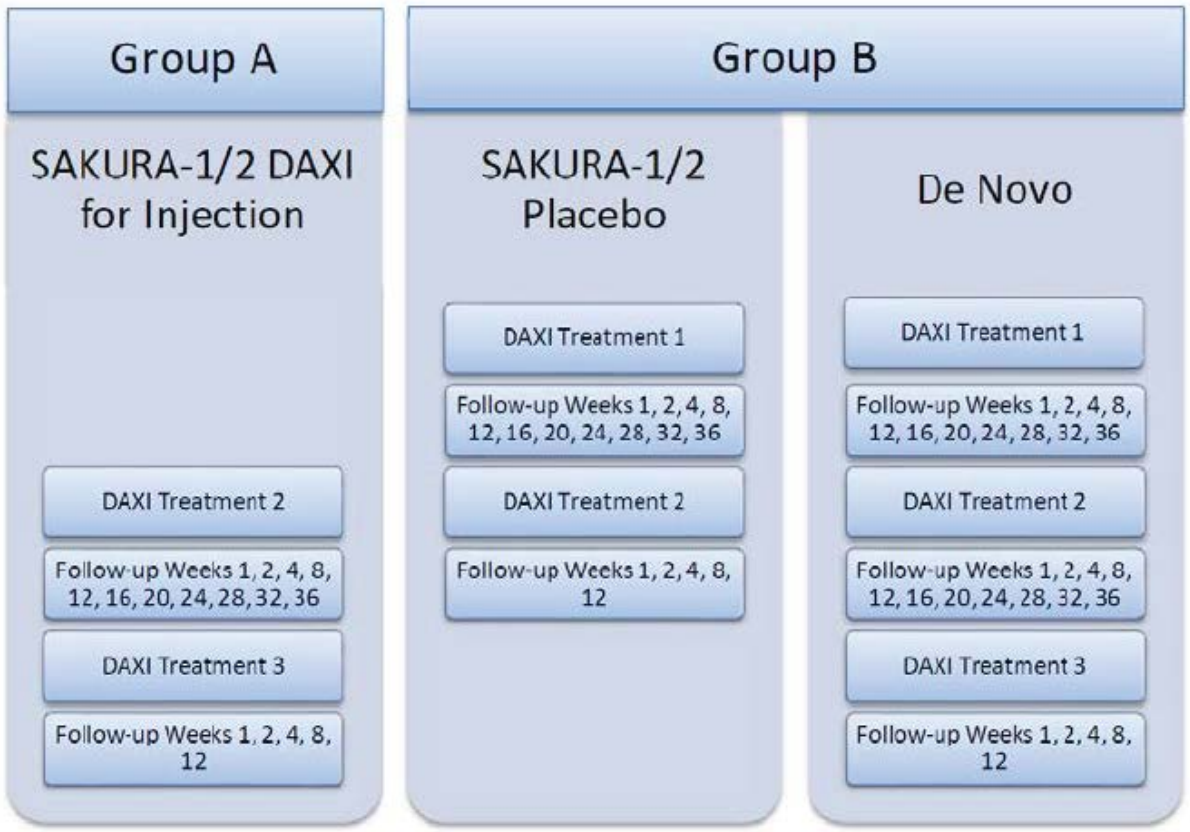
Figure 5 Study 1620302 (SAKURA-2): Proportion of subjects who achieved a score of 0 or 1 (None or Mild) on both IGA-FWS and PFWS at maximum frown over time (Worst/Best Outcome Imputation; ITT Population)



Study 1620303 (SAKURA-OLS)

This was a Phase 3, open-label, multicentre study to assess the safety of single and repeat administration of DAXI in subjects with moderate to severe GL. It was conducted at 65 centres in the US and Canada from December 2016 to October 2018, and included subjects who completed SAKURA-1 and SAKURA-2 and also newly enrolled adult subjects (Figure 6).

Figure 6: Study 1620303 (SAKURA-OLS) design



All subjects received a single dose of 40 U DAXI into 5 injection sites (Figure 1) on Study Day 1. The criteria for re-treatment included a minimum period of 12 weeks between treatments, and return of IGA-FWS and PFWS to baseline. A subset of subjects received 3 treatments based on a pre-determined cut-off date of subject enrolment, including rollover subjects who received their first DAXI treatment in SAKURA-1 or SAKURA-2 and received 2 cycles of treatment in the OLS study, and de novo subjects who received all 3 treatment cycles in the OLS study.

2691 subjects were enrolled and treated in SAKURA-OLS, including 311 subjects (Group A) who received their first dose of DAXI in SAKURA-1 or SAKURA-2, and 2380 subjects (Group B) who received their first dose of DAXI in SAKURA-OLS. The majority of subjects were female (88. 6%), Caucasian/White (89. 4%), with a mean age of 49. 5 years. 39. 9% had been previously treated with BoNT with a mean time since last injection of 32. 06 months.

In SAKURA-OLS, 2380 subjects received treatment 1, 882 subjects received treatment 2, and 568 subjects received treatment 3.

The primary objective of the study was safety; efficacy outcomes were descriptive.

The proportion of subjects who achieved a 2-point composite response at maximum frown at each visit over time is shown in Table 5.

Table 5: Study 1620303 (SAKURA-OLS): Proportion of subjects who achieved a 2-point composite response at maximum frown at each visit over time (Safety Evaluable Population) – First reference point (OLS baseline)

	Treatment 1 (N=2380)		Treatment 2[a] (N=882)		Treatment 3 (N=568)	
	N1	n (%)	N1	n (%)	N1	n (%)
Week 1	2304		1480 (62. 2%)		833	
Week 2	2334		1761 (74. 0%)		840	
Week 4	2332		1743 (73. 2%)		866	
Week 8	2302		1330 (55. 9%)		858	
Week 12	2270		786 (33. 0%)		853	
Week 16	2142		454 (19. 1%)		681	
Week 20	1942		218 (9. 2%)		634	
Week 24	1614		135 (5. 7%)		536	
Week 28	1202		66 (2. 8%)		415	
Week 32	882		34 (1. 4%)		286	
Week 36	653		13 (0. 5%)		194	

IGA-FWS = Investigator Global Assessment-Frown Wrinkle Severity; OLS = open-label safety; PFWS = Patient Frown Wrinkle Severity.

N was the number of evaluable subjects in the analysis population. N1 was the number of subjects with an IGA-FWS and PFWS score at maximum frown at the given visit. n was the number of subjects with a 2-point composite response at maximum frown at the given visit.

Percentages were based on the number in the population, N.

a Rollover subjects (n=134) were only followed through Week 12. The number in the population after Week 12 was 748 and was used for percentages starting at Week 16.

The median time to return to moderate or severe GL on IGA-FWS and PFWS from OLS baseline was ~24. 0 weeks after receiving the first and second administrations of DAXI. The median time to return to baseline, or worse than OLS baseline, on both IGA-FWS and PFWS was ~28. 0 weeks after receiving the first and second administrations of DAXI.

For Group B (received treatment 1 in SAKURA-OLS), the median time to re-treatment was ~24 weeks after treatment 1 and ~28 weeks after treatment 2. For Group A (received treatment 1 in SAKURA-1 or SAKURA-2), the median time to re-treatment after treatment 2 was ~26 weeks.

Cervical Dystonia

Study 1720302 (ASPEN-1)

This was a Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of a single treatment of DAXI for injection in adults with isolated CD. It was conducted at 60 sites in 9 countries [Austria (1), Canada (1), Czech Republic (4), France (3), Germany (5), Poland (6), Spain (3), UK (1) and USA (36)] from June 2018 to June 2020.

The primary objective was to compare the efficacy of a high and low dose of DAXI for injection (250 U; 125 U) relative to placebo, and to each other, in adults with moderate to severe isolated

CD. All subjects received a single treatment at baseline and then had follow up visits at Weeks 2, 4, 6, 12, and then every 4 weeks thereafter up to Week 36.

The study included healthy adults aged 18 to 80 years who met the diagnostic criteria for isolated CD (idiopathic; dystonic symptoms localised to the head, neck, shoulder areas) with at least moderate severity at baseline, defined as a TWSTRS total score of at least 20, with at least 15 on the TWSTRS-Severity subscale, at least 3 on the TWSTRS-Disability subscale, and at least 1 on the TWSTRS-Pain subscale.

Subjects were allowed to be on a stable dose of medications (if any) used for focal dystonia treatment (e. g. anticholinergics, muscle relaxants, benzodiazepines) for at least 4 weeks prior to baseline (Study Day 1) and continuing through end of study. Subjects previously treated with BoNT therapy were required to have a washout period of at least 14 weeks.

Subjects were randomised 3:3:1 to one of the following treatments:

- DAXI 250 U in 2. 5 mL
- DAXI 125 U in 2. 5 mL
- Placebo in 2. 5 mL

The investigator identified the involved muscles for injection based on the subject's clinical presentation (e. g. subject's head, neck, and shoulder positions; localisation of pain; and muscle hypertrophy). The following muscles could be selected: sternocleidomastoid, levator scapulae, scalenus complex, splenius complex, splenius capitis, splenius cervices, trapezius, and longissimus. The entire 2. 5 mL solution of reconstituted study drug for each subject was to be divided and injected into the selected muscles. The volume injected into each involved muscle was restricted to a pre-defined range, which corresponded to a specific dose range per muscle for DAXI for injection 250 U, DAXI for injection 125 U, and placebo, respectively. Use of electromyography, ultrasonography, or other imaging modalities to guide injection of the investigational product was optional.

The primary efficacy endpoint was the average change from baseline in TWSTRS-Total Score at Week 4 and 6. The secondary efficacy endpoints included:

- Change from baseline in TWSTRS total score (all post-treatment time points).
- Duration of effect, defined as time (number of weeks) from treatment to loss of at least 80% of the peak treatment effect achieved at Weeks 4 and 6.
- Percentage of subjects with at least "moderate" (2-point) improvement on Clinical Global Impression of Change (CGIC) at Week 4 or 6.
- Percentage of subjects with at least "moderate" (2-point) improvement on Patient Global Impression of Change (PGIC) at Week 4 or 6.

301 subjects were randomised, 130 to DAXI 250 U, 125 to DAXI 125 U, and 46 to placebo. Overall, the mean age was 57. 7 years, with 74. 8% of subjects >50 years old. Over half of subjects were female (64. 8%) and postmenopausal (52. 5%). Most subjects were white (95. 3%). Most subjects (86. 4%) had received prior treatment with BoNT. The median duration of CD was 8. 6 years.

For the primary endpoint, a statistically significant improvement in the average change from baseline in TWSTRS-Total Score at Week 4 and 6 was demonstrated for both dose groups compared with placebo (Table 6). No dose-response relationship was demonstrated.

The duration of effect was defined as the time from treatment until loss of at least 80% of the peak treatment effect. The median (95% CI) duration of effect in the DAXI 125 U and DAXI 250 U groups was 24. 0 (20. 3, 29. 1) weeks and 20. 3 (16. 7, 24. 0) weeks, respectively (Figure 7).

60. 8% of subjects in the DAXI 125 U group and 56. 9% of subjects in the DAXI 250 U group had a CGIC response indicating improvement (moderately better or very much better at Week 4 or Week 6), compared with 28. 3% of subjects in the placebo group. 53. 6% of subjects in the DAXI 125 U group and 50. 8% of subjects in the DAXI 250 U group had a PGIC response indicating improvement (moderately better or very much better at Week 4 or Week 6), compared with 21. 7% of subjects in the placebo group.

Table 6: Primary endpoint ASPEN-1. TWSTRS Total Score, ANCOVA of average change from baseline at Weeks 4 and 6 with multiple imputation (ITT Population)

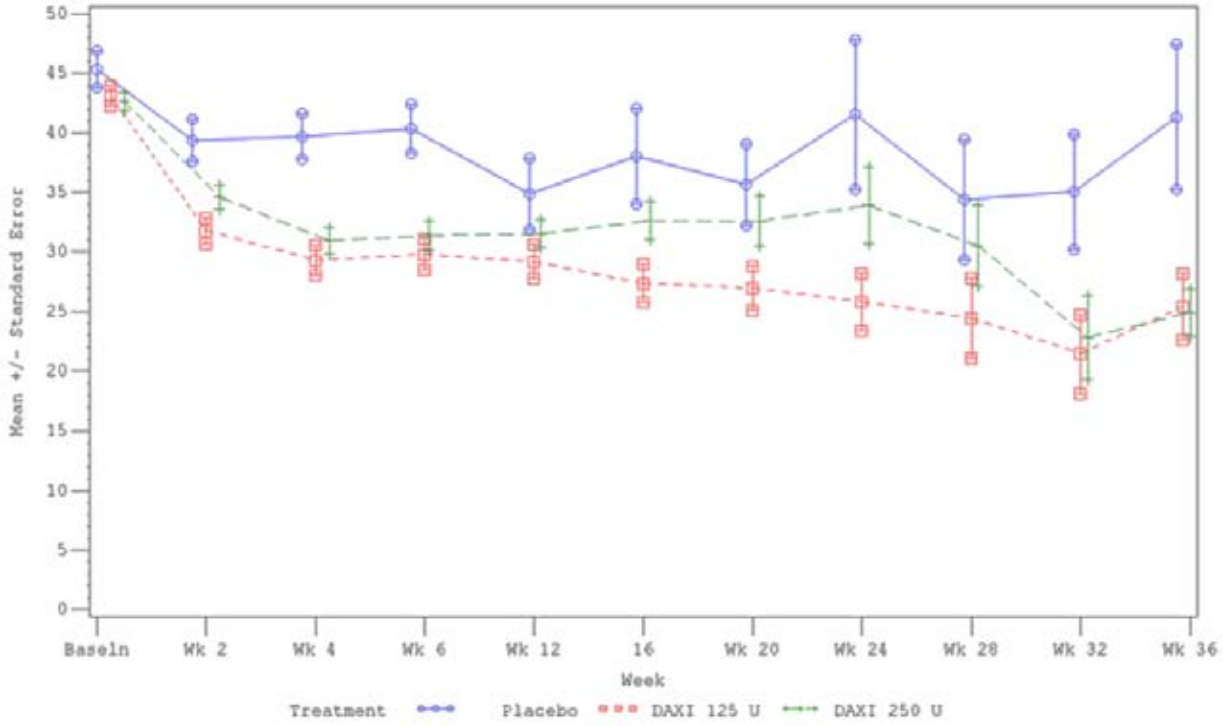
Visit	Statistic	Placebo (N = 46)	DAXI 125 U (N = 125)	DAXI 250 U (N = 130)
Baseline	n	46	125	130
	Mean	45.3	43.1	42.6
	SE	1.54	0.84	0.76
Average of Weeks 4 and 6	n	46	125	130
	Mean	40.0	29.8	31.3
	SE	1.93	1.24	1.12
Average change from baseline at Weeks 4 and 6	n	46	125	130
	Mean	-5.3	-13.3	-11.3
	SE	1.46	1.07	0.98
Percent change from baseline[a]		-11.7%	-30.9%	-26.5%
LS mean (SE) change from baseline		-4.3 (1.82)	-12.7 (1.30)	-10.9 (1.25)
LS mean difference (SE) (versus placebo)			-8.5 (1.93)	-6.6 (1.92)
95% CI of LS mean difference (versus placebo)			(-12.3, -4.7)	(-10.4, -2.9)
p-value (versus placebo)[b]			< 0.0001	0.0006
LS mean difference (SE) (versus DAXI 125 U)				1.8 (1.40)
95% CI of LS mean difference (versus DAXI 125 U)				(-0.9, 4.6)
p-value (versus DAXI 125 U)[b]				0.1902

ANCOVA = analysis of covariance; BoNT = botulinum neurotoxin; CI = confidence interval; DAXI = daxibotulinumtoxinA; ITT = intent-to-treat; LS = least squares; n = number of subjects in category; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. Notes: The average of subject's individual values at Week 4 and Week 6 was used to compute the summary statistics. LS mean, LS mean difference, 95% CI of LS mean difference, and p-value for average change from baseline at Weeks 4 and 6 were based on an ANCOVA model with terms for treatment, pooled study centre (region), prior BoNT treatment experience, and with baseline TWSTRS total score as a covariate. Multiple imputation was used for subjects missing both Week 4 and Week 6 TWSTRS data. Treatments presented in the table were based on planned treatment.

a The percent change in total TWSTRS score from baseline to the average of Weeks 4 and 6 was hand-calculated as follows: 100% × (mean change from baseline to the average of Weeks 4 and 6)/(mean baseline score).

b The test for DAXI 125 U versus placebo was done only if the test for DAXI 250 U versus placebo was statistically significant, and the test for DAXI 250 U versus DAXI 125 U was done only if the test for DAXI 125 U versus placebo was statistically significant.

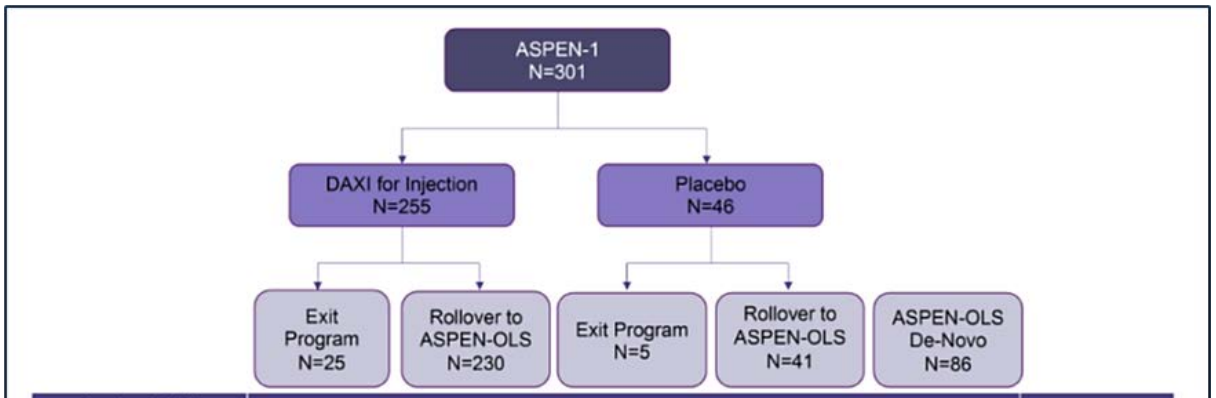
Figure 7: TWSTRS Total Score (Mean ± SE) by visit (ITT Population, ASPEN-1)



Study 1720304 (ASPEN-OLS)

This was a Phase 3 open-label, multicentre trial to evaluate the long-term safety and efficacy of repeat treatments of daxibotulinumtoxinA for injection in adults with isolated CD. ASPEN-OLS was an extension study for subjects completing ASPEN-1, but also enrolled de-novo subjects (Figure 8). The primary objectives were to evaluate the long-term safety of multiple continuous treatments of DAXI, and to assess immunogenicity after multiple treatments.

Figure 8: Study 1720304 (ASPEN-OLS) design



Number of DAXI Treatments in OLS Study	Number of Subjects Receiving DAXI for Injection					Total (n=357)
One	--	20	n/a	2	6	28
Two	--	59	n/a	18	18	95
Three	--	111	n/a	15	43	169
Four	--	40	n/a	6	19	65

ASPEN-OLS included healthy adults aged 18 to 80 years who met the diagnostic criteria for isolated CD (idiopathic; dystonic symptoms localised to the head, neck, shoulder areas) with at least moderate severity at baseline (Study Day 1), defined as a TWSTRS total score of at least 20, with at least 15 on the TWSTRS severity subscale, at least 3 on the TWSTRS disability subscale,

and at least 1 on the TWSTRS pain subscale (minimum TWSTRS subscale criteria were applicable only to subjects not previously enrolled in ASPEN-1. De-novo subjects could be BoNT treatment-naïve or have had past BoNT treatment.

The study was not randomised or blinded. At the Baseline Visit (Study Day 1) of Treatment Cycle 1 (Cycle 1), the investigator selected an open-label dose of DAXI for injection (125 U or 250 U) for the subject based on clinical factors, CD disease severity, and prior BoNT treatment history, using the following dose selection criteria.

To be eligible for the low dose (125 U) arm, a subject must have met 1 of the following criteria:

- Must have had a prior clinical experience with a BoNT dose that was <190 U of onabotulinumtoxinA (Botox) or incobotulinumtoxinA (Xeomin®) equivalent, OR
- Would qualify for a dose that was < 190 U of onabotulinumtoxinA or incobotulinumtoxinA equivalent, based on the clinical judgment of the investigator.

To be eligible for the high dose (250 U) arm, a subject must have met 1 of the following criteria:

- Must have had prior clinical experience with a BoNT dose that was ≥ 190 U of onabotulinumtoxinA or incobotulinumtoxinA equivalent, OR
- Would qualify for a BoNT dose that was ≥ 190 U of onabotulinumtoxinA or incobotulinumtoxinA equivalent, based on the clinical judgment of the investigator.

Subjects could receive up to 4 treatment cycles over the course of the study. Criteria for retreatment are described below. The study allowed investigators to adjust the DAXI dose by 50 U or 75 U in subsequent treatment cycles, such that the study evaluated doses of 125 U, 200 U, 250 U, and 300 U. The rationale for studying multiple doses of DAXI in this study was based on the consideration that the clinical application of BoNT for CD requires individualised treatment to achieve optimal outcome and minimise adverse events such as dysphagia.

The primary endpoints related to safety and immunogenicity. Secondary efficacy endpoints included average change in TWSTRS total score at Weeks 4 and 6 of each treatment cycle, inter-treatment time interval or duration of effect, percentage of subjects with at least moderate (2-point) improvement on CGIC at Week 4 or Week 6, percentage of subjects with at least moderate (2-point) improvement on PGIC at Week 4 or Week 6, and changes in quality of life measures based on CDIP-58.

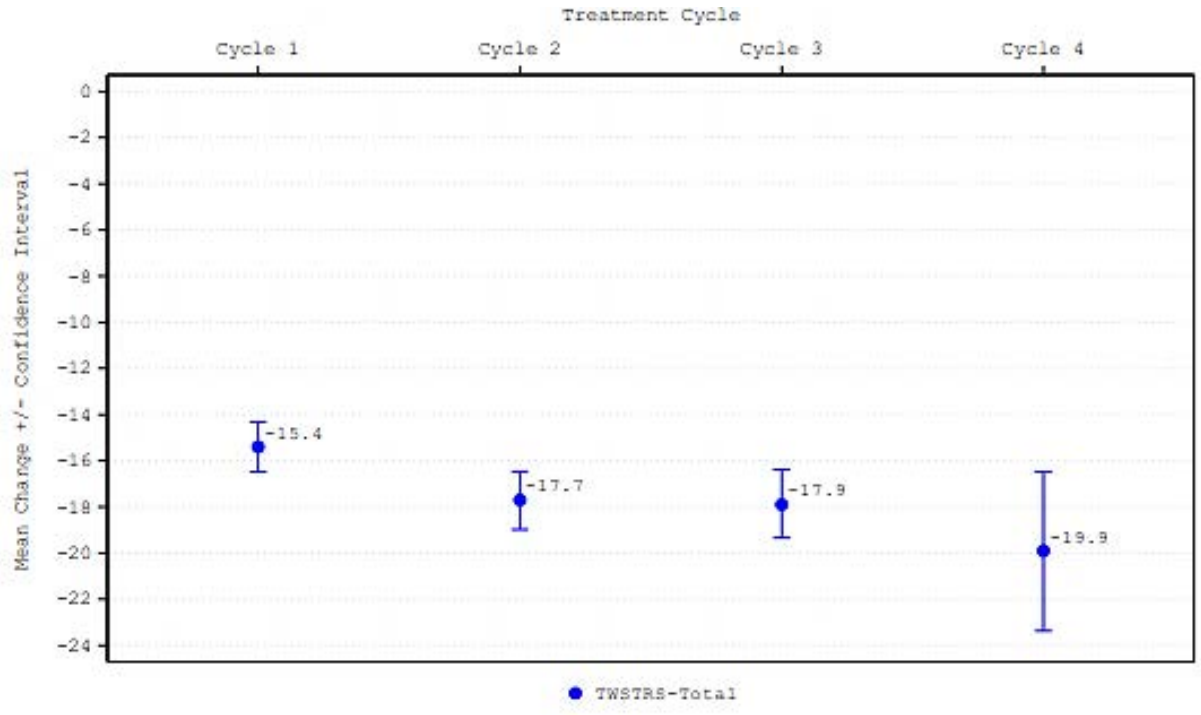
The duration of effect was defined as the time in weeks after each treatment until loss of at least 80% of the peak treatment effect. The peak treatment effect was defined as the average change from baseline at Week 4 and Week 6 in the TWSTRS total score. The score that was consistent with the loss of at least 80% of the peak treatment effect was called the target TWSTRS score. When a subject's TWSTRS total score was the same or higher than his/her target TWSTRS score from Cycle 1, there was sufficient return of CD symptoms to warrant retreatment. Due to significant symptom recurrence (e. g. pain), some subjects may have requested retreatment before their TWSTRS total score reached/exceeded their target TWSTRS score. In this case, the investigator must have agreed that retreatment was clinically indicated for the subject to receive another treatment.

357 subjects received at least 1 treatment in ASPEN-OLS. 329 subjects received treatment 2, 234 received treatment 3, and 65 received treatment 4. Subjects were allowed to shift to higher or lower doses from treatment cycle to treatment cycle. Most shifts in dose levels were to higher dose groups over cycles (64 subjects from 125 U to 200 U, 31 subjects from 200 U to 250 U, and 131 subjects from 250 U to 300 U). There were some shifts to lower dose groups (9 subjects from 300 U to 250 U, 17 subjects from 250 U to 200 U, and 1 subject from 200 U to 125 U).

Overall, the mean age was 57. 6 years. The majority of subjects were female (66. 7%) and White (95. 8%).

The study showed a reduction (improvement) in the average change in TWSTRS total score from baseline at Weeks 4 and 6 for each treatment cycle, with a mean (percent) reduction of 15. 4 (35. 54%) in Cycle 1, 17. 7 (41. 22%) in Cycle 2, 17. 9 (39. 72%) in Cycle 3, and 19. 9 (41. 25%) in Cycle 4 (Figure 9).

Figure 9: Mean Change in TWSTRS Total Score from Baseline for the Average of Weeks 4 and 6 for Each Treatment Cycle Overall (ASPEN-OLS, Safety Population)



Note: The average of each subject's individual values at Week 4 and Week 6 was used to compute the summary statistics. The error bars represent the 95% CIs of the mean change from baseline in TWSTRS total score at Weeks 4 and 6.

The duration of effect was defined as the time in weeks after each treatment until loss of at least 80% of the peak treatment effect based on TWSTRS total score (loss of efficacy). Within each cycle the median duration of effect was similar at about 20 weeks, and was mostly similar across dose groups.

Safety

Safety data for the treatment of GL and CD were presented separately, as the dosage regimens and injection sites differ substantially.

Glabellar lines

The safety evaluation for GL included the following studies:

- Pooled pivotal studies – Study 1620301 (SAKURA-1) and Study 1620302 (SAKURA-2)
- Open label repeat-dose safety study – Study 1620303 (SAKURA-OLS)
- Supportive studies – Study RT002-CL001 (GL-Mexico) and Study RT002-CL002 (GL-Belmont)

A total of 3,139 subjects received at least 1 dose of study drug in the 5 GL clinical studies; of these, 2,994 subjects were exposed to DAXI at any dose, with a total of 4,444 treatments. A total of 2,839 subjects received the proposed dose of 40 U; of these, 1,957 received a single 40 U dose, 314 received 2 consecutive doses, and 568 subjects received 3 consecutive doses.

Pooled pivotal studies (SAKURA-1, SAKURA-2)

Treatment emergent adverse events (TEAEs) in the pooled pivotal studies are summarised in Table 7 and Table 8. SAEs reported in DAXI-treated subjects (bone marrow failure, sepsis, uterine perforation, and uterine leiomyoma) were all assessed as unrelated to study treatment. Overall, 63 (15. 5%) subjects treated with DAXI and 10 (4. 9%) treated with placebo reported AESIs; of the 63 DAXI subjects, 40 (9. 9%) reported adverse event of special interest (AESIs) which were considered related to treatment (Table 9).

Table 7: Overview of Subjects with TEAEs (SAKURA-1 and -2 Pooled Population)

	Placebo N = 203 n (%) [E]	DAXI 40 U N = 406 n (%) [E]
Total subjects with at least 1 TEAE	49 (24.1) [74]	166 (40.9) [294]
Total subjects with at least 1 related[a] TEAE	18 (8.9) [25]	78 (19.2) [104]
Total subjects with at least 1 serious TEAE	2 (1.0) [2]	4 (1.0) [4]
Total subjects with at least 1 related[a] serious TEAE	0	0
Total subjects with at least 1 TEAE of special interest[b]	10 (4.9) [10]	63 (15.5) [73]
Total subjects with at least 1 TEAE of special interest[c]	0 [0]	23 (5.7) [35]
Total subjects with at least 1 TEAE Leading to Study Discontinuation	0 [0]	0 [0]
Total subjects with at least 1 TEAE resulting in death	0 [0]	0 [0]
Total subjects with at least 1 Injection Site Reaction (ISR)	3 (1.5) [3]	6 (1.5) [6]

n = number of subjects with adverse events. Percentages are based on the number in the analysis group, N. The Pooled Population includes all randomised subjects who received at least one dose of study treatment in SAKURA-1 or SAKURA-2 and had at least one post-treatment safety assessment. DAXI = daxibotulinumtoxinA for injection, [E] = number of events, MedDRA = Medical Dictionary for Regulatory Activities, PDSOT = potential distant spread of toxin, TEAE = treatment-emergent adverse event, U = units. a Related = possible, probable, or definite. b PDSOT events as determined by a pre-specified list of preferred terms and a system organ class. c PDSOT events as determined by the investigator.

Table 8: TEAEs reported in ≥1% of subjects by MedDRA SOC and PT (SAKURA-1 and -2 Pooled Population)

MedDRA System Organ Class Preferred Term	Placebo N = 203 n (%) [E]	DAXI 40 U N = 406 n (%) [E]
Any adverse event	28 (13.8) [35]	100 (24.6) [122]
Eye disorders	0 [0]	9 (2.2) [9]
Eyelid ptosis	0 [0]	9 (2.2) [9]
General disorders and administration site conditions	12 (5.9) [15]	22 (5.4) [25]
Injection site erythema	4 (2.0) [4]	5 (1.2) [5]
Injection site oedema	3 (1.5) [3]	5 (1.2) [5]
Injection site pain	8 (3.9) [8]	15 (3.7) [15]
Infections and infestations	11 (5.4) [12]	39 (9.6) [45]
Influenza	2 (1.0) [2]	6 (1.5) [6]
Nasopharyngitis	6 (3.0) [7]	17 (4.2) [21]
Upper respiratory tract infection	3 (1.5) [3]	11 (2.7) [13]
Urinary tract infection	0 [0]	5 (1.2) [5]
Investigations	3 (1.5) [3]	2 (0.5) [3]
Prothrombin time prolonged	3 (1.5) [3]	2 (0.5) [3]
Nervous system disorders	5 (2.5) [5]	37 (9.1) [40]
Headache	5 (2.5) [5]	37 (9.1) [40]

MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects with adverse events, U = units. Percentages are based on the number in the analysis group, N. The Pooled Population includes all randomised subjects who received at least one dose of study treatment in SAKURA-1 or SAKURA-2 and had at least one post-treatment safety assessment. [E] = number of adverse events, regardless of causality.

Table 9: Treatment-related AESIs – Potential Distant Spread of Toxin (SAKURA-1 and -2 Pooled Population)

Preferred Term[a]	Placebo N=203	DAXI 40 U N=406
Any adverse event, n (%)	4 (2. 0)	40 (9. 9)
Eyelid ptosis	0	9 (2. 2)
Vision blurred	0	1 (0. 2)
Facial paresis	0	4 (1. 0)
Headache	4 (2. 0)	26 (6. 4)
Hemiparesis	0	1 (0. 2)
Brow ptosis	0	3 (0. 7)

n = number of subjects with adverse events. Percentages are based on the number in the analysis group, N.

a Treatment-emergent adverse events are selected based upon a predetermined list of preferred terms.

SAKURA-OLS

This was a large open-label study of 2,691 subjects who could receive up to 3 treatments of 40 U DAXI for moderate to severe GL. 2,380 subjects received Treatment 1, 882 subjects received Treatment 2, and 568 subjects received Treatment 3. Subjects were followed for up to 86 weeks.

Overall, 1,043 (38. 8%) subjects in SAKURA-OLS reported at least one TEAE, with similar profiles in Group A (received DAXI in SAKURA-1 or SAKURA-2) and Group B (received first dose of DAXI in SAKURA-OLS). TEAEs reported in >2% of subjects included headache (5. 9% of subjects), nasopharyngitis (4. 4%), injection site pain (3. 9%), injection site erythema (3. 3%), injection site oedema (2. 8%), erythema (2. 1%). Eyelid ptosis was reported in 35 (1. 3%) subjects. Most of the injection site reaction AEs were mild or moderate in severity. The rates of these AEs remained stable or decreased across successive treatment cycles.

There were 5 AEs which led to study discontinuation: optic neuritis, humerus fracture, brow spocking, basal cell carcinoma and bile duct cancer. Only brow spocking was considered related to treatment. 31 SAEs were reported. The most common SAE reported was breast cancer (2 [<0. 1%] subjects), while all other SAEs reported occurred in only one subject (<0. 1%). There was one death due to a homicide, considered unrelated to study drug.

There were 74 TEAEs that were deemed of special interest as potentially related to the distant spread of toxin in 65 (2. 4%) subjects, including eyelid ptosis (29 [1. 1%] subjects), headache (18 [0. 7%] subjects), brow ptosis (8 [0. 3%] subjects), and facial paresis (7 [0. 3%] subjects).

Cervical Dystonia

The safety evaluation for CD included the following studies:

- Pivotal study – Study 1720302 (ASPEN-1)
- Open label repeat-dose safety study – Study 1720304 (ASPEN-OLS)
- Dose-finding study – Study RT002-CL005.

ASPEN-1

This was a randomised, double-blind single-treatment study: 130 subjects received DAXI 250 U, 125 subjects received DAXI 125 U, and 46 subjects received placebo. TEAEs were reported more frequently with DAXI compared to placebo, but the profile was similar across the 2 DAXI dose groups (Table 10). The most commonly reported TEAEs in the DAXI groups were headache and injection site pain (Table 11). AEs related to distant spread of toxin reported in ≥2% of subjects in the All DAXI group were headache (4. 3% All DAXI, 5. 4% DAXI 250 U, 3. 2% DAXI 125 U), dysphagia (2. 7% All DAXI, 3. 8% DAXI 250 U, 1. 6% DAXI 125 U), and muscular weakness (2. 4% All DAXI, 0. 8% DAXI 250 U, 4. 0% DAXI 125 U).

Eight (3. 1%) DAXI-treated subjects reported SAEs, none of which were assessed as treatment-related. In the DAXI 125 U group, 5 (4. 0%) subjects reported SAEs of depression, urinary tract infection, cholelithiasis, renal tubular injury, and death (in 1 subject each). The death in the DAXI 125 U group occurred on Study Day 86, and the family declined to reveal the cause of death to the investigator. In the DAXI 250 U group, 3 (2. 3%) subjects reported SAEs of tachycardia and ventricular extrasystoles (both in 1 subject), abdominal pain (in 1 subject), and transient global amnesia (in 1 subject).

Table 10: Overall Summary of TEAEs, ASPEN-1, Safety Population

Category	Placebo (N = 46) n (%) E	DAXI 125 U (N = 125) n (%) E	DAXI 250 U (N = 130) n (%) E	All DAXI (N = 255) n (%) E
Subjects with any TEAE	18 (39.1) 34	74 (59.2) 148	64 (49.2) 134	138 (54.1) 282
Subjects with any treatment-related TEAE	8 (17.4) 11	37 (29.6) 54	31 (23.8) 49	68 (26.7) 103
Subjects with any serious TEAE	0	5 (4.0) 5	3 (2.3) 4	8 (3.1) 9
Subjects with any treatment-related serious TEAE	0	0	0	0
Subjects with any TEAE of special interest as reported by the investigator[a]	4 (8.7) 4	14 (11.2) 17	13 (10.0) 17	27 (10.6) 34
Subjects with any TEAE related to distant spread of toxin[b]	3 (6.5) 4	14 (11.2) 18	18 (13.8) 26	32 (12.5) 44
Subjects with any potential distant spread of toxin TEAE[c]	1 (2.2) 1	9 (7.2) 11	10 (7.7) 13	19 (7.5) 24
Subjects with any TEAE related to potential anaphylactic reaction[d]	0	7 (5.6) 10	4 (3.1) 4	11 (4.3) 14
Death[e]	0	1 (0.8) 1	0	1 (0.4) 1
Subjects with any TEAE that led to study discontinuation[f]	0	0	1 (0.8) 1	1 (0.4) 1

a These TEAEs of special interest were identified by the investigator in the AE eCRF. b These TEAEs related to distant spread of toxin were identified by the investigator on the AE eCRF. c Potential distant spread of toxin TEAEs were identified by SMQs. d TEAEs related to potential anaphylactic reaction were identified by SMQs. e The death was considered by the investigator as unrelated to study drug. f Subject 21418-03 in the DAXI 250 U group discontinued the study on Study Day 61 due to a TEAE of mild headache possibly related to study drug; this event began on Study Day 11 and resolved on Study Day 22.

Table 11: TEAEs reported in ≥3% of subjects in the all DAXI group by SOC and PT ASPEN-1, Safety Population

System Organ Class Preferred Term	Placebo (N = 46) n (%)	DAXI 125 U (N = 125) n (%)	DAXI 250 U (N = 130) n (%)	All DAXI (N = 255) n (%)
Subjects with any TEAE	18 (39.1)	74 (59.2)	64 (49.2)	138 (54.1)
Musculoskeletal and connective tissue disorders	2 (4.3)	15 (12.0)	12 (9.2)	27 (10.6)
Musculoskeletal pain	0	5 (4.0)	5 (3.8)	10 (3.9)
Muscular weakness	0	6 (4.8)	3 (2.3)	9 (3.5)
Neck pain	2 (4.3)	5 (4.0)	4 (3.1)	9 (3.5)
General disorders and administration site conditions	3 (6.5)	14 (11.2)	9 (6.9)	23 (9.0)
Injection site pain	2 (4.3)	10 (8.0)	7 (5.4)	17 (6.7)
Injection site erythema	1 (2.2)	6 (4.8)	3 (2.3)	9 (3.5)
Nervous system disorders	1 (2.2)	11 (8.8)	9 (6.9)	20 (7.8)
Headache	1 (2.2)	11 (8.8)	9 (6.9)	20 (7.8)
Infections and infestations	2 (4.3)	2 (1.6)	7 (5.4)	9 (3.5)
Upper respiratory tract infection	2 (4.3)	2 (1.6)	7 (5.4)	9 (3.5)

ASPEN-OLS

This was an open label study which was an extension study of ASPEN-1 (272 patients) and also enrolled de novo patients (86 patients). Subjects could receive up to 4 treatment cycles over the course of the study. 357 (99. 7%) subjects received treatment in Cycle 1, 329 (91. 9%) subjects received treatment in Cycle 2, 234 (65. 4%) subjects received treatment in Cycle 3, and 65 (18. 2%) subjects received treatment in Cycle 4.

The DAXI dose was selected by the investigator, with a dose of 125 U or 250 U in cycle 1. Doses in subsequent treatment cycles could be 125 U, 200 U, 250 U or 300 U. Subjects were allowed to shift to higher or lower doses from treatment cycle to treatment cycle. 44 subjects received a high dose (250 U or 300 U) for 4 treatments.

DAXI was generally well tolerated, with no clear pattern of increased TEAEs observed with higher doses. The most common AEs reported were dysphagia (10. 4%), muscular weakness (9. 5%), injection site pain (7. 6%), headache (5. 9%), neck pain (5. 3%), and upper respiratory tract infection (5. 0%). The incidence of AEs reflecting potential spread of toxin was 21. 9% in the high dose high frequency group, 17. 9% in the high dose low frequency group, 30. 6% in the low dose high frequency group, and 19. 6% in the low dose low frequency group.

Immunogenicity

In the pivotal GL studies, ≤1. 5% of subjects developed treatment-related antibodies to DAXI and RT004. No subject developed neutralising antibodies and presence of ADAs had no demonstrable effect on efficacy. In SAKURA-OLS, a total of 19 (0. 7%) subjects developed treatment induced (n=18, 0. 7%) or treatment boosted (n=1, <0. 05%) anti-DAXI binding antibodies during the study. Treatment-related anti-DAXI antibody responses were reported in 10 (0. 4%), 4 (0. 5%), and 5 (0. 9%) subjects who received 1, 2, or 3 DAXI treatments, respectively.

In ASPEN-1, treatment-induced DAXI ADAs were reported in 6 (2. 7%) evaluable DAXI-treated subjects. In ASPEN-OLS, treatment-induced DAXI ADAs were reported in 2/346 (0. 6%) subjects. There was no trend observed with time in study or with higher DAXI dose in the percentage of subjects with post-baseline positive DAXI ADAs or neutralising antibodies.

Risk management plan

The sponsor submitted Core RMP version 2. 0 (date 19 October 2023; data lock point 28 June 2021) and Australia specific annex version 1. 0 (date 19 October 2023) with the initial application. The summary of safety concerns is presented in Table 12. The proposed pharmacovigilance plan and risk minimisation measures are acceptable.

Table 12: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Potential distant spread of toxins	P	-		-
Important potential risks	Hypersensitivity		-		-
Missing information	Use in pregnancy or lactation	P*	-		-

*follow-up forms

The Daxxify Core Risk Management Plan (RMP) version 2. 0 (dated 11 June 2024; data lock point 28 June 2021), with Australian Specific Annex (version 1. 0, dated 11 June 2024), included with

submission PM-2023-03624-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six-monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII. B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must be submitted within ninety calendar days of the data lock point for that report.

Daxxify (daxibotulinumtoxinA) is to be included in the Black Triangle Scheme. The PI and CMI for Daxxify must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.

Risk-benefit analysis

Efficacy

Glabellar lines

The efficacy of DAXI 40 U for the treatment of moderate to severe GL was demonstrated in two pivotal randomised, double-blind, placebo-controlled, single treatment studies which shared similar design. Both studies demonstrated similar efficacy for DAXI 40 U compared to placebo. The primary efficacy endpoint was the proportion of subjects who achieved a 2-point composite response at Week 4, requiring both the subject and the investigator to record at least a 2-point response, in line with regulatory guidance published by the FDA. The difference in the proportion of subjects who reported a 2-point composite response at maximum frown at Week 4 between DAXI and placebo was 74. 2% in SAKURA-1 and 72. 9% in SAKURA-2. In both studies, the median time to return to moderate or severe GL on both IGA-FWS and PFWS was ~24 weeks for DAXI subjects.

The efficacy of single and repeat treatments with DAXI 40 U was evaluated in SAKURA-OLS, an open-label study which enrolled subjects from SAKURA-1 and SAKURA-2 plus 2,380 new subjects. Subjects enrolled from the pivotal studies could receive up to 2 treatments in SAKURA-OLS and new subjects could receive up to 3 treatments, subject to a pre-determined cut-off date. The criteria for re-treatment included a minimum period of 12 weeks between treatments, and return of IGA-FWS and PFWS to baseline. Efficacy as measured by 2-point composite response at maximum frown at 4 weeks post-treatment was consistent across treatments 1, 2, and 3. The

proportion of subjects achieving a 2-point composite response after each treatment in SAKURA-OLS was similar to SAKURA-1 and SAKURA-2.

In SAKURA-OLS, the median time to return to moderate or severe GL on IGA-FWS and PFWS from OLS baseline was ~24. 0 weeks after receiving the first and second administrations of DAXI. For Group B (received treatment 1 in SAKURA-OLS), the median time to retreatment was ~24 weeks after treatment 1 and ~28 weeks after treatment 2. For Group A (received treatment 1 in SAKURA-1 or SAKURA-2), the median time to re-treatment was ~26 weeks after treatment 2.

There was no active comparator study, which limited comparative conclusions regarding duration of effect and frequency of re-treatment relative to other BoNT products.

Cervical Dystonia

In the pivotal study, a statistically significant improvement in the average change from baseline in TWSTRS-Total Score at Week 4 and 6 was demonstrated for both dose groups (125 U and 250 U) compared with placebo. No dose-response relationship was demonstrated. The Phase 3 open-label, multiple dose study evaluated doses of 125 U and 250 U for the first treatment cycle, based on prior BoNT experience or the clinical judgment of the investigator. The investigator could then adjust the dose by 50 U or 75 U for subsequent treatments, such that the study evaluated doses of 125 U, 200 U, 250 U, and 300 U. Most shifts in dose levels were to higher dose groups over cycles. The rationale for studying multiple doses of DAXI in this study was based on the consideration that the clinical application of BoNT for CD requires individualised treatment to achieve optimal outcome and minimise adverse events such as dysphagia. This approach is similar to that of other BoNT approved for the treatment of CD.

The evaluation concluded that the doses evaluated in the pivotal study have been adequately justified and that efficacy of the proposed doses (125 U to 250 U) have been satisfactorily demonstrated. The proposed dose range provides flexibility to individualise the treatment based on the muscles involved.

Safety

Glabellar lines

The safety database for the GL indication is large, with 2,839 subjects treated with the proposed dose of DAXI 40 U. The two pivotal studies evaluated a single treatment and the open-label study evaluated patients treated up to 3 times over ~1 year.

The DAXI safety profile was similar across the studies and consistent with the known safety profile of BoNT. Common AEs reported included headache, nasopharyngitis, injection site pain, and upper respiratory tract infection. Eyelid ptosis was reported in ~2% of subjects, comparable to rates reported for other BoNT products. AEs were generally mild and transient and resolved without treatment. There were no cases of anaphylaxis but ~3. 4% of DAXI patients were identified as having TEAEs potentially related to hypersensitivity.

Cervical Dystonia

The dose of DAXI for CD (125 U to 250 U) is notably higher than the dose used for GL (40 U). The most commonly reported TEAEs in the All DAXI group were headache (7. 8%) and injection site pain (6. 7%). TEAEs related to distant spread of toxin reported in ≥2% of subjects in the All DAXI group were headache (4. 3% All DAXI, 5. 4% DAXI 250 U, 3. 2% DAXI 125 U), dysphagia (2. 7% All DAXI, 3. 8% DAXI 250 U, 1. 6% DAXI 125 U), and muscular weakness (2. 4% All DAXI, 0. 8% DAXI 250 U, 4. 0% DAXI 125 U).

In the open-label, multiple dose study ASPEN-OLS, the most common AEs reported were dysphagia (10. 4%), muscular weakness (9. 5%), injection site pain (7. 6%), headache (5. 9%), neck pain (5. 3%), and upper respiratory tract infection (5. 0%). There was no clear pattern of increased TEAEs observed with higher doses, but the variation in doses used over the course of ASPEN-OLS limits the assessment of the relative safety of the different doses evaluated in that study.

Uncertainties and limitations of the data

The main GL and CD efficacy studies did not include an active comparator, so they do not directly inform comparative efficacy and duration of effect relative to other BoNT products.

Both DAXI doses evaluated in the pivotal CD study (125 U and 250 U) were superior to placebo, but a dose-response was not demonstrated. The open-label, multiple dose study evaluated doses of 125 U to 300 U. The proposed dose range of 125 U to 250 U is consistent with the established individualised treatment approach for BoNT for the treatment of CD.

No paediatric data were submitted. The proposed indications are only for adults.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Daxxify (daxibotulinumtoxinA) for the following indications:

> *The temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.*
>
> *The treatment of cervical dystonia in adult patients*

Specific conditions of registration

Batch Release Testing and Compliance with the Certified Product Details Conditions of Registration for Daxxify

- All batches of Daxxify supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details.
- When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product.

Product Information and Consumer Medicines Information

For the most recent Product Information (PI) and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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