A Phase 3, Open-label, Multi-center Trial to Evaluate the Long-term Safety and Efficacy of Repeat Treatments of DaxibotulinumtoxinA for Injection in Adults With Isolated Cervical Dystonia

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Introduction

Cervical Dystonia and Botulinum Toxin Treatment

• Cervical dystonia (CD), or spasmodic torticolis, is a chronic condition characterized by involuntary contractions of neck muscles, often associated with discomfort or pain.5

• Botulinum toxin injections are first-line treatment for CD with ~85% of patients receiving injections2

• Patients treated with currently approved botulinum toxin products typically receive re-treatment every 12–14 weeks.2

• 88% of patients report the reappearance of pre-existing symptoms between botulinum toxin injections9

• 71% of patients would like longer-lasting benefit.4

Patient Experiences With Botulinum Toxins Suggest Symptoms Re-emerge Before Being Re-treated8

DaxibotulinumtoxinA-1mnm for Injection (DAXI)

• DAXI is a long-acting formulation of botulinum toxin type A in development for the treatment of CD as well as other indications, including glabellar lines and upper limb spasticity.

• DAXI is composed of a purified 150-kD botulinum toxin formulated with a stabilizing peptide excipient that binds electrostatically to negatively charged sites on the neurotoxin.10

• In vitro data suggest that the peptide increases affinity of the botulinum toxin for cell membranes.11

• In a Phase 2, open-label, dose-escalation study of DAXI in patients with moderate-to-severe CD, DAXI demonstrated efficacy and extended duration of effect in adults with CD.8

• In the Phase 3, randomized, controlled, single-dose study, ASPEN-1, DAXI demonstrated efficacy and extended duration of effect in adults with CD.8

• Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total scores were significantly improved at Weeks 4 and 8 vs placebo (p<0.001, 125U vs placebo, p=0.002, 250U vs placebo).

• Median duration of effect was 24 weeks for the 125U dose and 20 weeks for the 250U dose.

• ASPEN-OLS is a Phase 3, open-label study to evaluate the long-term safety and efficacy of up to 4 repeat treatments of DAXI.

• DAXI has not yet been approved for CD.

ASPEN-OLS Methods and Study Design

• ASPEN-OLS was conducted across 65 sites in the USA, Canada, the UK, and the EU.

• Subjects were rolled over from the 36-week, double-blind, placebo-controlled, single-dose study, ASPEN-1 (n=1,279), or were enrolled de novo (n=186).

• Subjects received up to 4 DAXI treatment cycles in ASPEN-OLS:

  - Cycle 1: DAXI 125U or 250U was selected by the investigator according to predefined clinical criteria, including the subject’s CD severity and botulinum toxin treatment history.

  - Cycles 2–4: The investigator could administer the same dose as in Cycle 1 or increase or decrease the subject’s dose by 1 dose step per cycle based on clinical judgment of the subject’s response in the prior cycle.

• Investigation chose the Cycle 1 dose (125U or 250U) based on prior botulinum toxin dose and disease severity.

• Subsequent doses could increase or decrease based on clinical judgment.

• Doses administered:

  - Cycle 1: 31% of subjects received 125U; 69% of subjects received 250U.

  - Cycles 2–4: 77% of subjects received a dose of 250U or higher.

  - Only 13% of subjects remained on 125U for all treatment cycles.

• The average final dose across all subjects was 243 U.

• No consistent pattern was observed between doses.

• Subjects could not be re-treated past Week 40, due to a 52-week limit on study participation.

• Cycles 3 and 4 were artificially truncated to due to total study duration and are not included in these analyses; durations presented are Kaplan-Meier median estimates in weeks.

Summary of Safety

• ASPEN-OLS confirmed the safety profile of DAXI established in the ASPEN-1 pivotal study12 with no new tolerability or safety concerns reported.

• Higher doses of DAXI were well tolerated and not associated with increased risk of AEs.

• Overall incidence rate and rates of the most common preferred terms were generally stable across the 4 cycles.

• Treatment-related AEs occurred in 34.2% of subjects overall, which was consistent with ASPEN-1 (26.7%).

• The incidence of treatment-related AEs generally decreased with repeat treatment, from 21.0% in Cycle 1 to 13.8% in Cycles 2–4.

• The most frequently reported side effects related to the effects of the toxin itself were dysphagia and muscular weakness, which were observed in ASPEN-OLS at rates comparable with rates reported for other botulinum toxin type A treatments (dysphagia 10–25% and muscular weakness 2–8%).

• No treatment-related serious AEs were observed.

Summary of Efficacy

• ASPEN-OLS confirmed the efficacy and safety results observed in ASPEN-1 and demonstrated continued improvement of CD signs and symptoms with repeat dosing of DAXI.

• Improvement in TWSTRS total score from baseline was observed in all treatment cycles.

• In general, the degree of improvement numerically increased across treatment cycles.

• Doses were adjusted based on clinical judgment.

• With subsequent cycles, patients tended to receive higher doses, resulting in an average final dose of 243 U.

• Only 13% of patients remained on 125U for all treatments.

• Median duration of effect, defined by time to loss of 80% of peak treatment effect, ranged from 19.9 to 26.0 weeks across treatment Cycles 1 and 2 and DAXI doses, which is consistent with the duration observed in ASPEN-1 of 24.0 weeks for DAXI 125U and 20.3 weeks for DAXI 250U.

References


Efficacy of DaxibotulinumtoxinA for Injection Over Successive Treatments in Adults With Isolated Cervical Dystonia in the Phase 3 ASPEN-1 and ASPEN-OLS Trials

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Introduction
Cervical Dystonia and Botulinum Toxin Treatment
- Cervical dystonia (CD), or spasmodic torticollis, is a chronic condition characterized by involuntary contractions of neck muscles, often associated with discomfort or pain.
- Botulinum toxin injections are first-line treatment for CD, with ~85% of patients receiving injections.
- Patients treated with currently approved botulinum toxin products typically receive re-treatment every 12-14 weeks.
- 88% of patients report the reappearance of pre-existing symptoms between botulinum toxin injections.
- 71% of patients would like longer-lasting treatments.

DaxibotulinumtoxinA (DAXI) for injection (DAXI)
- DAXI is a long-acting formulation of botulinum toxin type A developed for the treatment of CD, as well as other indications, including glabellar lines and upper lip lines.
- DAXI is composed of purified 195-104 botulinum toxin formulated with a stabilizing peptide agent that binds electrostatically to negatively charged surfaces on the neuron.
- In vitro data suggest that the peptide increases affinity of the botulinum toxin for cell membranes.
- In a Phase 2, open-label, dose-escalation study of DAXI in patients with moderate-to-severe CD, DAXI demonstrated efficacy and extended duration of effect in adults with CD.
- In the Phase 3, randomized, controlled, single-dose study, ASPEN-1, DAXI demonstrated efficacy and extended duration of effect in adults with CD.
- ASPEN-1 has not yet been approved for CD.

ASPEN-1 Study Design
- ASPEN-1 was a Phase 3, single-dose, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of DAXI for the treatment of CD over 36 weeks across 65 sites in the USA, Canada, the UK, and the EU.
- Subjects were enrolled de novo and received their first dose of DAXI at the investigator's discretion.
- DAXI was administered at week 0 and every 12 weeks.
- The primary endpoint was the symptom response in the TWSTRS total score.
- Treatment cycles were 4 weeks in length, with follow-up visits at weeks 4, 8, 12, 16, 20, and 24.
- The study was terminated at week 28 due to the demonstration of efficacy.

Dose Escalation for ASPEN-1 and ASPEN-OLS
- ASPEN-1
  - Randomized treatment assignment
  - Approximately equal subjects were dosed with 125U and 250U.
  - 130 subjects were dosed with 250U and 125 subjects were dosed with 125U.
- ASPEN-OLS
  - Investigators chose the Cycle 1 dose (125U or 250U) based on prior treatment and disease severity.
  - Subsequent doses could increase or decrease based on clinical judgment.
  - Doses administered:
    - Cycle 1: 36% of subjects received 250U; 64% of subjects received 125U.
    - Cycle 2: 35% of subjects received 250U; 65% of subjects received 125U.
  - 77% of subjects received a dose of 250U or higher during the 12-month treatment period.
- The average final dose across all subjects was 243U.

Change From Baseline in TWSTRS Total Score Averaged Over Weeks 4 and 6
- The median duration of effect across doses, defined as time to loss of 18% of peak treatment effect, ranged from 19 to 26 weeks in the evaluable cycles and was consistent with ASPEN-1.
- No consistent pattern was observed between doses.
- Subjects could not be re-treated post Week 40 due to the 52-week limit on study participation.
- Cycles 3 and 4 are not applicable because they are artificially truncated due to study closure time; durational analyses presented are Kaplan-Meier median estimates in weeks.

Duration of Response in ASPEN-1 and ASPEN-OLS
- The median duration of effect across doses, defined as time to loss of 18% of peak treatment effect, ranged from 19 to 26 weeks in the evaluable cycles and was consistent with ASPEN-1.
- No consistent pattern was observed between doses.
- Subjects could not be re-treated post Week 40 due to the 52-week limit on study participation.
- Cycles 3 and 4 are not applicable because they are artificially truncated due to study closure time; durational analyses presented are Kaplan-Meier median estimates in weeks.

Summary of Efficacy and Safety
- ASPEN-OLS confirmed the efficacy and safety results observed in ASPEN-1 and demonstrated continued improvement of CD signs and symptoms with repeat dosing of DAXI.
- With subsequent cycles, patients tended to receive higher doses, resulting in an average final dose of 248U; only 13% of patients remained on 125U for all treatments.
- Improvement in TWSTRS total score from baseline was observed in all treatment cycles.
- In general, the degree of improvement numerically increased across from ASPEN-1 to Cycle 4 of ASPEN-OLS.
- Similar trends for increasing change from baseline over successive cycles were seen for TWSTRS subscales of pain, disability, and severity.
- No new or worsened treatment-related AEs were reported across treatment cycles.

References
1. DAXI has not yet been approved for CD.
2. ASPEN-1 was a Phase 3, single-dose, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of DAXI for the treatment of CD over 36 weeks across 65 sites in the USA, Canada, the UK, and the EU.
3. ASPEN-OLS is a Phase 3, open-label study to evaluate the long-term safety and efficacy of up to 4 repeat treatments of DAXI.
4. ASPEN-1 has not yet been approved for CD.

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