# Clinical trial results:
# A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Trial to Evaluate the Efficacy and Safety of a Single Treatment of DaxibotulinumtoxinA for Injection in Adults with Isolated Cervical Dystonia (ASPEN-1)

## Summary

| | |
|---|---|
| EudraCT number | 2018-000446-19 |
| Trial protocol | AT PL FR GB IT |
| Global end of trial date | 16 June 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 May 2023 |
| First version publication date | 04 May 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 1720302 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03608397 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Revance Therapeutics Inc |
| Sponsor organisation address | 7555 Gateway Blvd. Newark, CA, United States, 94560 |
| Public contact | Regulatory Affairs Manager, Revance Therapeutics Inc, +1 5107423557, jlintao@revance.com |
| Scientific contact | Domenico Vitarella, Sr. Director, Clinical Development, Revance Therapeutics Inc, +1 510-742-3400, dvitarella@revance.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 June 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 16 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of a high and low dose of daxibotulinumtoxinA (DAXI) for injection (250 unit [botulinum toxin] [U]; 125 U) relative to placebo, and to each other, in adults with moderate to severe, isolated cervical dystonia (CD).

Protection of trial subjects:

This study was conducted in accordance with the accepted version of the Declaration of Helsinki, in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 June 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 61 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Czechia: 20 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | United States: 186 |
| Country: Number of subjects enrolled | Spain: 10 |
| Worldwide total number of subjects | 301 |
| EEA total number of subjects | 110 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 206 |
| From 65 to 84 years | 95 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at total of 60 sites in 9 countries from 20 June 2018 to 16 June 2020.

### Pre-assignment

Screening details:

A total of the 444 subjects were screened for this study, of which 301 were randomised and received study drug.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Subjects received placebo matched to DAXI 125 U, intramuscular (IM) injection, once on Day 1.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Placebo, 2.5 mL of reconstituted clear, colorless solution injection, administered via IM route.

| | |
|---|---|
| **Arm title** | DAXI 125 U |

Arm description:

Subjects received DAXI 125 U, IM injection, once on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | DAXI 125 U |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

DAXI 125 U, 2.5 mL of reconstituted clear, colorless solution injection, administered via IM route.

| | |
|---|---|
| **Arm title** | DAXI 250 U |

Arm description:

Subjects received DAXI 250 U, IM injection, once on Day 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | DAXI 250 U |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:
DAXI 250 U, 2.5 mL of reconstituted clear, colorless solution injection, administered via IM route.

| **Number of subjects in period 1** | Placebo | DAXI 125 U | DAXI 250 U |
|---|---|---|---|
| Started | 46 | 125 | 130 |
| Completed | 45 | 120 | 126 |
| Not completed | 1 | 5 | 4 |
| Consent withdrawn by subject | 1 | 3 | 2 |
| Adverse event, non-fatal | - | - | 1 |
| Death | - | 1 | - |
| Unspecified | - | - | 1 |
| Other-Unspecified | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo matched to DAXI 125 U, intramuscular (IM) injection, once on Day 1. | |
| Reporting group title | DAXI 125 U |
| Reporting group description: | |
| Subjects received DAXI 125 U, IM injection, once on Day 1. | |
| Reporting group title | DAXI 250 U |
| Reporting group description: | |
| Subjects received DAXI 250 U, IM injection, once on Day 1. | |

| Reporting group values | Placebo | DAXI 125 U | DAXI 250 U |
|---|---|---|---|
| Number of subjects | 46 | 125 | 130 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 34 | 82 | 90 |
| From 65-84 years | 12 | 43 | 40 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 56.5 | 57.4 | 58.5 |
| full range (min-max) | 29.0 to 80.0 | 18.0 to 80.0 | 30.0 to 79.0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 29 | 87 | 79 |
| Male | 17 | 38 | 51 |
| Race<br>Units: Subjects | | | |
| White | 43 | 118 | 126 |
| Black | 2 | 3 | 1 |
| Asian | 1 | 1 | 1 |
| American Indian or Alaska Native | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| Other | 0 | 2 | 1 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 4 | 4 | 7 |
| Not Hispanic or Latino | 41 | 119 | 123 |
| Not Provided | 1 | 2 | 0 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 301 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 206 | | |
| From 65-84 years | 95 | | |
| 85 years and over | 0 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| full range (min-max) | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 195 | | |
| Male | 106 | | |
| Race<br>Units: Subjects | | | |
| White | 287 | | |
| Black | 6 | | |
| Asian | 3 | | |
| American Indian or Alaska Native | 1 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Other | 3 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 15 | | |
| Not Hispanic or Latino | 283 | | |
| Not Provided | 3 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo matched to DAXI 125 U, intramuscular (IM) injection, once on Day 1. | |
| Reporting group title | DAXI 125 U |
| Reporting group description: | |
| Subjects received DAXI 125 U, IM injection, once on Day 1. | |
| Reporting group title | DAXI 250 U |
| Reporting group description: | |
| Subjects received DAXI 250 U, IM injection, once on Day 1. | |

### Primary: Average Change From Baseline in Total Score of Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at Weeks 4 and 6

| | |
|---|---|
| End point title | Average Change From Baseline in Total Score of Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) at Weeks 4 and 6 |
| End point description: | |
| The TWSTRS is a composite assessment scale that covers different features of CD. The scale evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain. The TWSTRS total score is the sum of the TWSTRS severity score (0–35), the TWSTRS disability score (0–30), and the TWSTRS pain score (0–20), and ranges from 0 to 85. The higher score indicates worst outcomes, and a negative change indicates better outcomes. The ITT population was defined as all subjects who were randomised and received study injections in this study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint. Average change from baseline data of Weeks 4 and 6 were presented. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Weeks 4 and 6 | |

| End point values | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 125 | 130 | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | -4.3 (± 1.82) | -12.7 (± 1.30) | -10.9 (± 1.25) | |

### Statistical analyses

| Statistical analysis title | DAXI 125 U vs. Placebo |
|---|---|
| Statistical analysis description: | |
| Statistical data of average change from baseline of Weeks 4 and 6 were reported. | |
| Comparison groups | Placebo v DAXI 125 U |

| | |
|---|---|
| Number of subjects included in analysis | 171 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 [1] |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean (LSM) Difference |
| Point estimate | -8.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.3 |
| upper limit | -4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.93 |

Notes:

[1] - p-value was based on average change from baseline of weeks 4 and 6 were as per ANCOVA model with terms for treatment.

| **Statistical analysis title** | DAXI 250 U vs. Placebo |
|---|---|

Statistical analysis description:

Statistical data of average change from baseline of Weeks 4 and 6 were reported.

| | |
|---|---|
| Comparison groups | Placebo v DAXI 250 U |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0006 [2] |
| Method | ANCOVA |
| Parameter estimate | LSM Difference |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | -2.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.92 |

Notes:

[2] - p-value was based on average change from baseline of weeks 4 and 6 were as per ANCOVA model with terms for treatment.

| **Statistical analysis title** | DAXI 250 U vs. DAXI 125 U |
|---|---|
| Comparison groups | DAXI 125 U v DAXI 250 U |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1902 [3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | LSM Difference |
| Point estimate | 1.8 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 4.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.4 |

Notes:

[3] - p-value was based on average change from baseline of weeks 4 and 6 were as per ANCOVA model with terms for treatment.

## Secondary: Change From Baseline in Total Score of TWSTRS at Weeks 2, 4, 6, 12, 16, 20, 24,28, 32 and 36

| | |
|---|---|
| End point title | Change From Baseline in Total Score of TWSTRS at Weeks 2, 4, 6, 12, 16, 20, 24,28, 32 and 36 |

End point description:

The TWSTRS is a composite assessment scale that covers different features of cervical dystonia (CD). The scale evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain. The TWSTRS total score is the sum of the TWSTRS severity score (0–35), the TWSTRS disability score (0–30), and the TWSTRS pain score (0–20), and ranges from 0 to 85. The higher score indicates worst outcomes and a negative change indicates better outcomes. The ITT population was defined as all subjects who were randomised and received study injections in this study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint and "n" refer to number of subjects who were subjects evaluable for given timepoints.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline, Weeks 2, 4, 6, 12, 16, 20, 24, 28, 32 and 36

| **End point values** | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 123 | 128 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=46, 123, 127) | -5.97 (± 8.442) | -11.14 (± 10.325) | -8.01 (± 8.849) | |
| Week 4 (n=46, 123, 127) | -5.63 (± 9.226) | -13.67 (± 11.960) | -11.54 (± 10.921) | |
| Week 6 (n=46, 123, 128) | -5.02 (± 11.450) | -13.16 (± 12.533) | -11.19 (± 12.295) | |
| Week 12 (n=21, 91, 94) | -11.05 (± 10.323) | -13.53 (± 10.935) | -10.85 (± 9.630) | |
| Week 16 (n=15, 65, 60) | -8.53 (± 8.404) | -14.24 (± 9.902) | -10.76 (± 11.606) | |
| Week 20 (n=11, 47, 41) | -8.17 (± 8.695) | -12.96 (± 11.230) | -10.92 (± 10.624) | |
| Week 24 (n=7, 28, 23) | -5.89 (± 7.738) | -13.77 (± 10.963) | -9.41 (± 13.630) | |
| Week 28 (n=4, 19, 15) | -8.68 (± 4.460) | -15.38 (± 10.048) | -9.68 (± 15.921) | |
| Week 32 (n=4, 13, 7) | -8.05 (± 5.645) | -16.81 (± 10.651) | -16.99 (± 12.936) | |
| Week 36 (n=3, 11, 4) | -7.60 (± 6.643) | -13.59 (± 7.702) | -16.40 (± 10.072) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Effect

| End point title | Duration of Effect |
|---|---|

End point description:

Duration of effect was defined as time in weeks from treatment to loss of at least 80 percent (%) of the peak treatment effect achieved at Weeks 4 and 6 (that is, the target TWSTRS score). The TWSTRS-total score that was consistent with loss of at least 80% of the peak treatment effect called the target TWSTRS score. The ITT population was defined as all subjects who were randomised and received study injections in this study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 36

| **End point values** | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 16 | 43 | 62 | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 20.1 (16.1 to 24.4) | 24.0 (20.3 to 29.1) | 20.3 (16.7 to 24.0) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With at Least 2-point Improvement on Clinical Global Impression of Change (CGIC) Scale at Week 4 or 6

| End point title | Percentage of Subjects With at Least 2-point Improvement on Clinical Global Impression of Change (CGIC) Scale at Week 4 or 6 |
|---|---|

End point description:

Improvement is defined as a response of moderately better (+2) or very much better (+3) at Week 4 or Week 6. The CGIC is a questionnaire that captures the clinician’s overall impression of the subject’s response to study treatment. The clinician’s selected response maps to a 7-point scale: negative (-) 3 (very much worse), 0 (about the same), to positive (+) 3 (very much better). The higher score indicates better outcomes. The ITT population was defined as all subjects who were randomised and received study injections in this study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

| End point type | Secondary |
|---|---|

| End point timeframe: |
|---|
| At Week 4 or 6 |

| **End point values** | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 124 | 130 | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 28.3 (15.2 to 41.3) | 60.8 (52.7 to 69.9) | 56.9 (48.4 to 65.4) | |

**Statistical analyses**

| **Statistical analysis title** | DAXI 125 U vs. Placebo |
|---|---|
| Comparison groups | Placebo v DAXI 125 U |
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0001 |
| Method | Cochran-Mantel-Haenszel |

| **Statistical analysis title** | DAXI 250 U vs. Placebo |
|---|---|
| Comparison groups | Placebo v DAXI 250 U |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0009 |
| Method | Cochran-Mantel-Haenszel |

| **Statistical analysis title** | DAXI 250 U vs. DAXI 125 U |
|---|---|
| Comparison groups | DAXI 125 U v DAXI 250 U |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4801 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: Percentage of Subjects With at Least 2-point Improvement on Patient Global Impression of Change (PGIC) at Week 4 or 6

| End point title | Percentage of Subjects With at Least 2-point Improvement on |
|---|---|

| | |
|---|---|
| | Patient Global Impression of Change (PGIC) at Week 4 or 6 |

End point description:

Improvement is defined as a response of moderately better (+2) or very much better (+3) at Week 4 or Week 6. The PGIC is a questionnaire that captures the subject's overall impression of their response to study treatment. The subject's selected response maps to a 7-point scale: -3 (very much worse), 0 (about the same), to +3 (very much better). A higher score indicates better outcomes. The ITT population was defined as all subjects who were randomised and received study injections in this study. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

At Week 4 or 6

| **End point values** | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 124 | 130 | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 21.7 (9.8 to 33.7) | 53.6 (45.3 to 62.8) | 50.8 (42.2 to 59.4) | |

**Statistical analyses**

| **Statistical analysis title** | DAXI 125 U vs. Placebo |
|---|---|
| Comparison groups | Placebo v DAXI 125 U |
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0002 |
| Method | Cochran-Mantel-Haenszel |

| **Statistical analysis title** | DAXI 250 U vs. Placebo |
|---|---|
| Comparison groups | Placebo v DAXI 250 U |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0007 |
| Method | Cochran-Mantel-Haenszel |

| **Statistical analysis title** | DAXI 250 U vs. DAXI 125 U |
|---|---|
| Comparison groups | DAXI 125 U v DAXI 250 U |

| | |
|---|---|
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6034 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

| | |
|---|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |

End point description:

A TEAE was any untoward medical occurrence (example, sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) that emerged or worsened following administration of study drug and until end of study participation. The untoward medical occurrence might not necessarily have a causal relationship to the administration of the investigational product. SAE: event resulted in any of following: Death; life-threatening; persistent or significant disability/incapacity or substantial disruption of the subject's ability to carry out normal life functions; required in-patient hospitalisation or prolonged hospitalisation; congenital anomaly/birth defect; did not meet any of above serious criteria, but based upon appropriate clinical judgment could have jeopardised subject or required medical or surgical intervention to prevent one of outcomes listed above. Safety population: All randomised subjects who received study injections.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Week 36

| End point values | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 125 | 130 | |
| Units: subjects | | | | |
| TEAEs | 18 | 74 | 64 | |
| SAE | 0 | 5 | 3 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Serum Neutralizing Antibodies for DAXI

| | |
|---|---|
| End point title | Number of Subjects With Serum Neutralizing Antibodies for DAXI |

End point description:

Positive neutralising antibodies for DAXI were reported in this endpoint. The safety population was defined as all randomised subjects who received study injections. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline up to Week 36

| End point values | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 125 | 130 | |
| Units: subjects | 0 | 0 | 1 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Clinically Significant Changes in Pulmonary Function by Spirometry

| End point title | Number of Subjects With Clinically Significant Changes in Pulmonary Function by Spirometry |
|---|---|

End point description:

The safety population was defined as all randomized subjects who received study injections.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline up to Week 36

| End point values | Placebo | DAXI 125 U | DAXI 250 U | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 46 | 125 | 130 | |
| Units: subjects | 0 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Baseline up to Week 36 | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |
| **Reporting groups** | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo matched to DAXI 125 U, IM injection, once on Day 1. | |
| Reporting group title | DAXI 125 U |
| Reporting group description: Subjects received DAXI 125 U, IM injection, once on Day 1. | |
| Reporting group title | DAXI 250 U |
| Reporting group description: Subjects received DAXI 250 U, IM injection, once on Day 1. | |

| Serious adverse events | Placebo | DAXI 125 U | DAXI 250 U |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 5 / 125 (4.00%) | 3 / 130 (2.31%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 125 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 125 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 125 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 125 (0.00%) | 1 / 130 (0.77%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 125 (0.80%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 125 (0.80%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 125 (0.80%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal tubular injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 125 (0.80%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 125 (0.80%) | 0 / 130 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| **Non-serious adverse events** | Placebo | DAXI 125 U | DAXI 250 U |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 42 / 125 (33.60%) | 41 / 130 (31.54%) |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 11 / 125 (8.80%) | 9 / 130 (6.92%) |
| occurrences (all) | 1 | 11 | 10 |
| General disorders and administration site conditions | | | |
| Injection site pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 10 / 125 (8.00%) | 7 / 130 (5.38%) |
| occurrences (all) | 2 | 12 | 9 |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 6 / 125 (4.80%) | 3 / 130 (2.31%) |
| occurrences (all) | 1 | 6 | 3 |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 125 (1.60%) | 5 / 130 (3.85%) |
| occurrences (all) | 0 | 2 | 6 |
| Nausea | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 125 (0.80%) | 1 / 130 (0.77%) |
| occurrences (all) | 2 | 1 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 5 / 125 (4.00%) | 5 / 130 (3.85%) |
| occurrences (all) | 0 | 5 | 5 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 6 / 125 (4.80%) | 3 / 130 (2.31%) |
| occurrences (all) | 0 | 6 | 3 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 5 / 125 (4.00%) | 4 / 130 (3.08%) |
| occurrences (all) | 2 | 6 | 4 |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 125 (2.40%) | 4 / 130 (3.08%) |
| occurrences (all) | 1 | 3 | 6 |
| Back pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 125 (0.80%) | 2 / 130 (1.54%) |
| occurrences (all) | 2 | 1 | 2 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 46 (4.35%)<br>2 | 2 / 125 (1.60%)<br>2 | 7 / 130 (5.38%)<br>7 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 46 (0.00%)<br>0 | 4 / 125 (3.20%)<br>4 | 3 / 130 (2.31%)<br>3 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 February 2018 | Modified the protocol title.<br>• Changed the medical monitor.<br>• Modified the study design:<br>o Changed sample size from 180 to 301 subjects.<br>o Expanded participating countries to include Europe.<br>• Changed the number of planned sites from 50 to approximately 80 sites.<br>• Modified the study objectives.<br>• Modified the primary, secondary, and exploratory endpoints.<br>• Changed the number of scheduled visits from 17 to 12 visits.<br>• Modified the screening period from 2 to 3 weeks.<br>• Modified the schedule of assessments.<br>• Modified the PGIC and CGIC scales from 9-point to 7-point scales.<br>• Updated safety evaluations (added spirometry and DSS).<br>• Modified and updated inclusion and exclusion criteria.<br>• Limited the dose of drug to be injected into each targeted muscle to minimum and maximum ranges; modified the Injectable Muscles and Injection Volume by Muscle Table.<br>• Modified the scientific rationale and dose justification to match updates.<br>• Updated the list of prohibited medications.<br>• Added the Cervical Dystonia Impact Profile (CDIP)-58, Treatment Satisfaction Questionnaire (TSQ), Work Productivity and Activity Impairment (WPAI) questionnaire, and Short Form-36 Survey (SF-36) survey. |
| 26 March 2018 | • Clarified inclusion and exclusion criteria; added 1 exclusion criterion.<br>• Clarified sections describing study intervention.<br>• Updated secondary and exploratory endpoints.<br>• Clarified study assessment sections and moved some examples and scales to the appendices.<br>• Reorganized the statistical analysis section to align with headings of ICHe9 guidance.<br>• Added prior treatment experience, age, and gender as sub-analyses to the primary endpoint as exploratory endpoints.<br>• Made wording changes to endpoints and sample size justification for clarification.<br>• Clarified muscles for injections.<br>• Clarified BoNT and BoNTA and made global terminology changes for clarification: DAXI to DAXI for injection, total TWSTRS score to TWSTRS-total score, medical judgment to clinical judgment. |
| 16 May 2018 | • Added more information about Study RT002-CL005 to the introduction.<br>• Added dysphagia as a known potential risk.<br>• Updated study design section for clarification.<br>• Clarified Inclusion Criterion #2.<br>• Updated Exclusion Criteria #6, #8, #10, #14, #17, and #20.<br>• Updated text about allowed concomitant medications; for focal dystonia treatments, amended time for stable dose requirement from 3 months to 4 weeks.<br>• Amended recruitment and retention strategies section.<br>• Clarified study intervention sections.<br>• Amended pregnancy section.<br>• Updated UPs section to align with guidance from regulatory authorities and added suspected unexpected serious adverse reaction (SUSAR) information.<br>• Clarified sections about end-of-study (EOS), TWSTRS, AE expectedness, follow-up of non-SAEs, and follow-up of post-study SAEs.<br>• In the statistical analysis section, added objectives with endpoints and clarified secondary efficacy endpoints.<br>• Updated information for key study personnel.<br>• Clarified instructions for injecting muscles. |

| | |
|---|---|
| 27 June 2018 | • Clarified inclusion criteria.<br>• Clarified that a subject who had no reduction or an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 was the same as a subject who had a lack of efficacy.<br>• Added information to the justification for dosing, randomization, blinding sections for clarification.<br>• Added the TWSTRS rater certification examination.<br>• Added information to the sample size justification.<br>• Updated information for key study personnel. |
| 10 July 2019 | • Added National Clinical Trial Identified Number: NCT03608397.<br>• Added a blood sample for antibody testing at Week 2 and Week 4.<br>• Updated Medical Monitor’s information. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported