



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
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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
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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
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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			
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			
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			
Units: Subjects			
Female	29	87	79
Male	17	38	51
Race			
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			
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 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 Units: years arithmetic mean full range (min-max)	-		
Gender categorical Units: Subjects			
Female	195		
Male	106		
Race Units: Subjects			
White	287		
Black	6		
Asian	3		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	1		
Other	3		
Ethnicity 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:	
<p>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.</p>	
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
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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
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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
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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
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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
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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
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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
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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
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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
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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)
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

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

Reporting group title	DAXI 125 U
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Reporting group description:

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

Reporting group title	DAXI 250 U
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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 subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2	2 / 125 (1.60%) 2	7 / 130 (5.38%) 7
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	4 / 125 (3.20%) 4	3 / 130 (2.31%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2018	<p>Modified the protocol title.</p> <ul style="list-style-type: none">• Changed the medical monitor.• Modified the study design:<ul style="list-style-type: none">o Changed sample size from 180 to 301 subjects.o Expanded participating countries to include Europe.• Changed the number of planned sites from 50 to approximately 80 sites.• Modified the study objectives.• Modified the primary, secondary, and exploratory endpoints.• Changed the number of scheduled visits from 17 to 12 visits.• Modified the screening period from 2 to 3 weeks.• Modified the schedule of assessments.• Modified the PGIC and CGIC scales from 9-point to 7-point scales.• Updated safety evaluations (added spirometry and DSS).• Modified and updated inclusion and exclusion criteria.• 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.• Modified the scientific rationale and dose justification to match updates.• Updated the list of prohibited medications.• 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	<ul style="list-style-type: none">• Clarified inclusion and exclusion criteria; added 1 exclusion criterion.• Clarified sections describing study intervention.• Updated secondary and exploratory endpoints.• Clarified study assessment sections and moved some examples and scales to the appendices.• Reorganized the statistical analysis section to align with headings of ICHe9 guidance.• Added prior treatment experience, age, and gender as sub-analyses to the primary endpoint as exploratory endpoints.• Made wording changes to endpoints and sample size justification for clarification.• Clarified muscles for injections.• 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	<ul style="list-style-type: none">• Added more information about Study RT002-CL005 to the introduction.• Added dysphagia as a known potential risk.• Updated study design section for clarification.• Clarified Inclusion Criterion #2.• Updated Exclusion Criteria #6, #8, #10, #14, #17, and #20.• Updated text about allowed concomitant medications; for focal dystonia treatments, amended time for stable dose requirement from 3 months to 4 weeks.• Amended recruitment and retention strategies section.• Clarified study intervention sections.• Amended pregnancy section.• Updated UPs section to align with guidance from regulatory authorities and added suspected unexpected serious adverse reaction (SUSAR) information.• Clarified sections about end-of-study (EOS), TWSTRS, AE expectedness, follow-up of non-SAEs, and follow-up of post-study SAEs.• In the statistical analysis section, added objectives with endpoints and clarified secondary efficacy endpoints.• Updated information for key study personnel.• Clarified instructions for injecting muscles.

27 June 2018	<ul style="list-style-type: none"> • Clarified inclusion criteria. • 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. • Added information to the justification for dosing, randomization, blinding sections for clarification. • Added the TWSTRS rater certification examination. • Added information to the sample size justification. • Updated information for key study personnel.
10 July 2019	<ul style="list-style-type: none"> • Added National Clinical Trial Identified Number: NCT03608397. • Added a blood sample for antibody testing at Week 2 and Week 4. • Updated Medical Monitor's information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported