Clinical trial results:
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 (ASPEN-OLS)

Summary

EudraCT number	2018-000447-11
Trial protocol	GB AT PL IT
Global end of trial date	25 May 2021

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	1720304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03617367
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Revance Therapeutics Inc
Sponsor organisation address	7555 Gateway Boulevard, Newark, California, United States, 94560
Public contact	Regulatory Affairs Manager, Revance Therapeutics Inc, +1 5107423557, jlintao@revance.com
Scientific contact	Senior Director, Clinical Development, Revance Therapeutics Inc, +1 5107423400, 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	25 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the long-term safety of multiple continuous treatments of daxibotulinumtoxinA (DAXI) for injection and to assess immunogenicity to botulinum neurotoxin type A (BoNTA) and revance novel excipient (RTP004) after multiple treatments of DAXI for injection.

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	05 September 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: 65
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czechia: 26
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 220
Worldwide total number of subjects	357
EEA total number of subjects	130

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)	240
From 65 to 84 years	117
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 64 sites in 9 countries (Austria, Canada, Czech Republic, France, Germany, Poland, Spain, United Kingdom, and the United States from 05 September 2018 to 25 May 2021. A total of 387 subjects were screened and 357 subjects were enrolled.

Pre-assignment

Screening details:

A total of 387 subjects were screened, of which 357 subjects were enrolled and treated. Few subjects had multiple movement within the arms in the treatment cycles so, only overall subjects data was planned, analysed and reported to avoid double-counting in disposition and baseline.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	DaxibotulinumtoxinA (DAXI)

Arm description:

Subjects received 4 continuous treatments of multi-dose of DAXI intramuscular (IM) injection (125 U, 200 U, 250 U, and 300 U). In cycle 1 subjects received DAXI IM injection (DAXI 125 U or 250 U) based on clinical factors, CD disease severity, and prior BoNT treatment history, using the dose selection criteria on Day 1. In treatment cycles 2 to 4, subjects received same DAXI dose received in cycle 1 (125 U or 250 U), or there was an increase or decrease in the DAXI dose by 1 predefined dose step per subsequent cycle based on the subject's treatment response in the prior cycle, as determined by the Investigator. The 2 additional DAXI doses for these dose steps were started in cycle 2: DAXI 200 U and DAXI 300 U. If subjects had received retreatment at 12 weeks during each of the first 2 cycles, a 3rd cycle could not have a duration greater than 28 weeks, and if subjects had received 12 weeks of treatment during each of the first 3 cycles, a 4 cycle could not go longer than 16 weeks.

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

Dosage and administration details:

Subjects received 4 multi-dose of DAXI IM injection (125 U, 200 U, 250 U, and 300 U).

Number of subjects in period 1	DaxibotulinumtoxinA (DAXI)
Started	357
Treatment Cycle 1	357
Treatment Cycle 2	329
Treatment Cycle 3	234 [1]
Treatment Cycle 4	65 [2]
Completed	297
Not completed	60

Consent withdrawn by subject	15
Adverse Event	2
Protocol violation	6
Death	1
Other	2
Lost to follow-up	6
Progressive disease	4
Lack of efficacy	24

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Few subjects had multiple movement within the arms in the treatment cycles.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Few subjects had multiple movement within the arms in the treatment cycles.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

Subjects received 4 continuous treatments of multi-dose of DAXI intramuscular (IM) injection (125 U, 200 U, 250 U, and 300 U). In cycle 1 subjects received DAXI IM injection (DAXI 125 U or 250 U) based on clinical factors, CD disease severity, and prior BoNT treatment history, using the dose selection criteria on Day 1. In treatment cycles 2 to 4, subjects received same DAXI dose received in cycle 1 (125 U or 250 U), or there was an increase or decrease in the DAXI dose by 1 predefined dose step per subsequent cycle based on the subject's treatment response in the prior cycle, as determined by the Investigator. The 2 additional DAXI doses for these dose steps were started in cycle 2: DAXI 200 U and DAXI 300 U. If subjects had received retreatment at 12 weeks during each of the first 2 cycles, a 3rd cycle could not have a duration greater than 28 weeks, and if subjects had received 12 weeks of treatment during each of the first 3 cycles, a 4 cycle could not go longer than 16 weeks.

Reporting group values	Overall Study	Total	
Number of subjects	357	357	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.6		
standard deviation	± 11.86	-	
Gender categorical Units: Subjects			
Female	238	238	
Male	119	119	
Race Units: Subjects			
White	342	342	
Black	6	6	
Asian	4	4	
American Indian or Alaska Native	1	1	
Native Hawaiian or other Pacific Islander	1	1	
Other	3	3	
Ethnicity Units: Subjects			
Hispanic or Latino	19	19	
Not Hispanic or Latino	333	333	
Not provided	5	5	

End points

End points reporting groups

Reporting group title	DaxibotulinumtoxinA (DAXI)
Reporting group description:	
Subjects received 4 continuous treatments of multi-dose of DAXI intramuscular (IM) injection (125 U, 200 U, 250 U, and 300 U). In cycle 1 subjects received DAXI IM injection (DAXI 125 U or 250 U) based on clinical factors, CD disease severity, and prior BoNT treatment history, using the dose selection criteria on Day 1. In treatment cycles 2 to 4, subjects received same DAXI dose received in cycle 1 (125 U or 250 U), or there was an increase or decrease in the DAXI dose by 1 predefined dose step per subsequent cycle based on the subject's treatment response in the prior cycle, as determined by the Investigator. The 2 additional DAXI doses for these dose steps were started in cycle 2: DAXI 200 U and DAXI 300 U. If subjects had received retreatment at 12 weeks during each of the first 2 cycles, a 3rd cycle could not have a duration greater than 28 weeks, and if subjects had received 12 weeks of treatment during each of the first 3 cycles, a 4 cycle could not go longer than 16 weeks.	
Subject analysis set title	Treatment Cycle 1: DAXI 125 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 125 U solution, IM injection in treatment cycle 1.	
Subject analysis set title	Treatment Cycle 2: DAXI 125 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 125 U solution, IM injection in treatment cycle 2.	
Subject analysis set title	Treatment Cycle 3: DAXI 125 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 125 U solution, IM injection in treatment cycle 3.	
Subject analysis set title	Treatment Cycle 4: DAXI 125 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 125 U solution, IM injection in treatment cycle 4.	
Subject analysis set title	Treatment Cycle 2: DAXI 200 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 200 U solution, IM injection in treatment cycle 2.	
Subject analysis set title	Treatment Cycle 3: DAXI 200 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 200 U solution, IM injection in treatment cycle 3.	
Subject analysis set title	Treatment Cycle 4: DAXI 200 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 200 U solution, IM injection in treatment cycle 4.	
Subject analysis set title	Treatment Cycle 1: DAXI 250 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 250 U solution, IM injection in treatment cycle 1.	
Subject analysis set title	Treatment Cycle 2: DAXI 250 U
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received DAXI 250 U solution, IM injection in treatment cycle 2.	
Subject analysis set title	Treatment Cycle 3: DAXI 250 U
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received DAXI 250 U solution, IM injection in treatment cycle 3.

Subject analysis set title	Treatment Cycle 4: DAXI 250 U
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received DAXI 250 U solution, IM injection in treatment cycle 4.

Subject analysis set title	Treatment Cycle 2: DAXI 300 U
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received DAXI 300 U solution, IM injection in treatment cycle 2.

Subject analysis set title	Treatment Cycle 3: DAXI 300 U
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received DAXI 300 U solution, IM injection in treatment cycle 3.

Subject analysis set title	Treatment Cycle 4: DAXI 300 U
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received DAXI 300 U solution, IM injection in treatment cycle 4.

Subject analysis set title	Treatment Cycle 1 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects who received treatment (DAXI 125U or DAXI 250U) in Cycle 1.

Subject analysis set title	Treatment Cycle 2 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in Cycle 2.

Subject analysis set title	Treatment Cycle 3 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in cycle 3.

Subject analysis set title	Treatment Cycle 4 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in cycle 4.

Primary: Number of Subjects with Drug-related Treatment-emergent Adverse Events (TEAEs) and Study Drug Discontinuation due to Drug-related TEAEs

End point title	Number of Subjects with Drug-related Treatment-emergent Adverse Events (TEAEs) and Study Drug Discontinuation due to Drug-related TEAEs[1]

End point description:

An AE was defined as any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, clinically significant abnormal laboratory finding, injury, or accident) that emerged or worsened following administration of the study drug; AEs were recorded until the end of study participation. The untoward medical occurrence may not necessarily have had a causal relationship to the administration of the study drug. A TEAE was one that occurred after any exposure to study drug. Number of subjects with drug-related TEAEs and study drug discontinuation due to drug-related TEAEs were reported. Safety population was defined as all enrolled subjects who receive at least one dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 52

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Treatment Cycle 1 Total	Treatment Cycle 2 Total	Treatment Cycle 3 Total	Treatment Cycle 4 Total
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	357	329	234	65
Units: subjects				
number (not applicable)				
Any treatment-related TEAE	75	56	46	9
TEAE that led to study drug discontinuation	1	0	2	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Developed Anti-drug Antibodies (ADAs) to RTP004 by Treatment Cycles and Dose

End point title	Number of Subjects who Developed Anti-drug Antibodies (ADAs) to RTP004 by Treatment Cycles and Dose[2]

End point description:

Subjects who developed ADAs (negative and positive) to analyte RTP004 were reported. Positive ADAs consisted of Treatment-induced, treatment unaffected, and treatment-boosted RTP004 ADAs. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	43	16	1
Units: subjects				
Treatment-induced ADA	0	0	0	0
Treatment-unaffected ADA	1	0	0	0
Treatment-boosted ADA	0	0	0	0
ADA-negative and treatment-induced negative	108	43	16	1

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	29	10	234
Units: subjects				
Treatment-induced ADA	1	0	0	2
Treatment-unaffected ADA	1	1	0	3
Treatment-boosted ADA	0	0	0	0
ADA-negative and treatment-induced negative	66	28	10	229

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	87	15	102
Units: subjects				
Treatment-induced ADA	0	1	0	0
Treatment-unaffected ADA	2	2	0	1
Treatment-boosted ADA	0	0	0	0
ADA-negative and treatment-induced negative	101	84	15	101

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	38		
Units: subjects				
Treatment-induced ADA	1	0		
Treatment-unaffected ADA	2	2		
Treatment-boosted ADA	0	0		
ADA-negative and treatment-induced negative	95	36		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Developed Anti-drug Antibodies (ADAs) to RTT150 by Treatment Cycles and Dose

End point title	Number of Subjects who Developed Anti-drug Antibodies (ADAs) to RTT150 by Treatment Cycles and Dose[3]

End point description:

Subjects who developed ADAs (negative and positive) to analyte RTT150 were reported. Positive ADAs consisted of Treatment-induced, treatment unaffected, and treatment-boosted RTT150 ADAs. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to Week 52

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	43	16	1
Units: subjects				
Treatment-induced ADA	1	0	0	0
Treatment-unaffected ADA	2	1	1	0
Treatment-boosted ADA	0	0	0	0
ADA-negative and treatment-induced negative	106	42	15	1

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	69	29	10	237
Units: subjects				
Treatment-induced ADA	1	0	0	0
Treatment-unaffected ADA	1	0	0	5
Treatment-boosted ADA	0	0	0	1
ADA-negative and treatment-induced negative	67	29	10	231

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	88	15	104
Units: subjects				
Treatment-induced ADA	1	1	1	0
Treatment-unaffected ADA	3	3	0	3
Treatment-boosted ADA	1	1	0	0
ADA-negative and treatment-induced negative	98	83	14	101

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100	39		

Units: subjects				
Treatment-induced ADA	0	0		
Treatment-unaffected ADA	2	2		
Treatment-boosted ADA	0	0		
ADA-negative and treatment-induced negative	98	37		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects who Developed Neutralizing Anti-drug Antibodies (ADAs) to RTT150 by Treatment Cycles and Dose

End point title	Number of Subjects who Developed Neutralizing Anti-drug Antibodies (ADAs) to RTT150 by Treatment Cycles and Dose[4]

End point description:

Subjects who developed NAbs (negative and positive) to analyte RTT150 were reported. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Treatment Cycle 1: Up to Week 36, Treatment Cycle 2: Up to Week 28, Treatment Cycle 3: Up to Week 16 and Treatment Cycle 4: Up to Week 16

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[5]	0[6]	0[7]	0[8]
Units: Subjects				
NAb positive				
NAb negative				

Notes:

[5] - No subjects were analysed at this timepoint (Week 36).

[6] - No subjects were analysed at this timepoint (Week 28).

[7] - No subjects were analysed at this timepoint (Week 16).

[8] - No subjects were analysed at this timepoint (Week 16).

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[9]	0[10]	0[11]	1
Units: Subjects				
NAb positive				0
NAb negative				1

Notes:

[9] - No subjects were analysed at this timepoint (Week 28).

[10] - No subjects were analysed at this timepoint (Week 16).

[11] - No subjects were analysed at this timepoint (Week 16).

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	0[12]	0[13]
Units: Subjects				
NAb positive	1	1		
NAb negative	0	0		

Notes:

[12] - No subjects were analysed at this timepoint (Week 16).

[13] - No subjects were analysed at this timepoint (Week 28).

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[14]	1		
Units: Subjects				
NAb positive		1		
NAb negative		0		

Notes:

[14] - No subjects were analysed at this timepoint (Week 16).

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change from Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score at Weeks 4 and 6 by Treatment Cycles and Dose

End point title	Average Change from Baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Total Score at Weeks 4 and 6 by Treatment Cycles and Dose

End point description:

The TWSTRS was an assessment scale used to measure the impact of CD on subjects and comprises 3 subscales: Severity (0–35), disability (0–30) and pain (0-20), each of which was scored independently. The total score from the 3 subscales gives the TWSTRS total score with a value from 0 to 85 (best to worst). The higher score indicates worst outcomes, and a negative change indicates better outcomes. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint. Here "99999" refers to data not available and we have added it as space-fillers.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and 6

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	107	41	15	1
Units: Score on scale				
arithmetic mean (standard deviation)	-15.0 (± 10.43)	-15.6 (± 12.26)	-15.0 (± 11.55)	-9.7 (± 99999)

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	29	8	243
Units: Score on scale				
arithmetic mean (standard deviation)	-19.5 (± 10.34)	-19.6 (± 11.07)	-13.9 (± 11.31)	-15.6 (± 10.26)

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	87	14	103
Units: Score on scale				
arithmetic mean (standard deviation)	-19.9 (± 10.78)	-18.1 (± 10.99)	-21.4 (± 12.63)	-15.2 (± 11.67)

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	39		
Units: Score on scale				
arithmetic mean (standard deviation)	-17.5 (± 11.71)	-20.9 (± 14.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Effect (Time to Loss of Efficacy Based on TWSTRS Total Score) by Treatment Cycles and Dose

End point title	Duration of Effect (Time to Loss of Efficacy Based on TWSTRS Total Score) by Treatment Cycles and Dose

End point description:

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). The peak treatment effect was defined as the average change from baseline at Weeks 4 and 6 in the TWSTRS total score. Duration of effect is only evaluable in Cycles 1 and 2; due to the 52-week limit on study participation, Cycles 3 and 4 are artificially truncated and therefore not provided valid estimates of duration. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here "99999" refers to data not available and we have added it as space-fillers. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 4 and 6

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	44	71	246
Units: weeks				
median (confidence interval 95%)	21.3 (19.3 to 24.4)	26.0 (20.1 to 32.1)	21.0 (19.0 to 24.0)	19.9 (17.1 to 20.9)

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 2: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	107	107		
Units: weeks				
median (confidence interval 95%)	20.1 (17.1 to 28.1)	20.1 (17.7 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at least "moderate" (a 2-point) improvement on Clinical Global Impression of Change (CGIC) at Week 4 or Week 6 of Each Treatment Cycle

End point title	Percentage of Subjects with at least "moderate" (a 2-point) improvement on Clinical Global Impression of Change (CGIC) at Week 4 or Week 6 of Each Treatment Cycle

End point description:

The CGIC was 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: -3 (very much worse), 0 (about the same), to +3 (very much better). The higher score indicates better outcomes. A 2+ point improvement was defined as a response of moderately better (+2) or very much better (+3) at Week 4 or Week 6. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 4 or 6

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	42	15	1
Units: Percentage of subjects				
number (not applicable)	75.7	79.5	75.0	100

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	29	8	244
Units: Percentage of subjects				
number (not applicable)	84.5	90.0	80.0	70.7

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	87	14	104
Units: Percentage of subjects				
number (not applicable)	86.0	77.3	80.0	76.6

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	39		
Units: Percentage of subjects				
number (not applicable)	76.0	84.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with at least "moderate" (a 2-point) improvement on Patient Global Impression of Change (PGIC) at Week 4 or Week 6 of Each Treatment Cycle

End point title	Percentage of Subjects with at least "moderate" (a 2-point) improvement on Patient Global Impression of Change (PGIC) at

	Week 4 or Week 6 of Each Treatment Cycle

End point description:

The PGIC was a questionnaire that captures the patient'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 2+ point improvement was defined as a response of moderately better (+2) or very much better (+3) at Week 4 or Week 6. The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "number of subjects analysed" refer to the subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Week 4 or 6

End point values	Treatment Cycle 1: DAXI 125 U	Treatment Cycle 2: DAXI 125 U	Treatment Cycle 3: DAXI 125 U	Treatment Cycle 4: DAXI 125 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	42	15	1
Units: Percentage of subjects				
number (not applicable)	69.4	68.2	43.8	100

End point values	Treatment Cycle 2: DAXI 200 U	Treatment Cycle 3: DAXI 200 U	Treatment Cycle 4: DAXI 200 U	Treatment Cycle 1: DAXI 250 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	29	8	244
Units: Percentage of subjects				
number (not applicable)	80.3	93.3	60.0	66.3

End point values	Treatment Cycle 2: DAXI 250 U	Treatment Cycle 3: DAXI 250 U	Treatment Cycle 4: DAXI 250 U	Treatment Cycle 2: DAXI 300 U
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103	87	14	104
Units: Percentage of subjects				
number (not applicable)	80.4	68.2	60.0	58.9

End point values	Treatment Cycle 3: DAXI 300 U	Treatment Cycle 4: DAXI 300 U		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	39		
Units: Percentage of subjects				
number (not applicable)	57.0	74.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Quality of Life (QOL) measured based on the Cervical Dystonia Impact Profile (CDIP-58) at Week 6

End point title	Percent Change from Baseline in Quality of Life (QOL) measured based on the Cervical Dystonia Impact Profile (CDIP-58) at Week 6

End point description:

The CDIP-58 assesses the health impact of CD. The CDIP-58 is composed of eight domains: head and neck (6 items; 6 to 30 points), pain and discomfort (5 items; 5 to 25 points), upper limb activities (9 items; 9 to 45 points), walking (9 items; 9 to 45 points), sleep (4 items; 4 to 20 points), annoyance (8 items; 8 to 40 points), mood (7 items; 7 to 35 points), and psychosocial functioning (10 items; 10 to 50 points). Subscale scores were transformed to a common theoretical range of 0 (no impact) to 100 (most impact). The safety population was defined as all enrolled subjects who received at least 1 dose of study drug. Here, "n= number analysed" signifies to subjects evaluable at given category.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Treatment Cycle 1 Total	Treatment Cycle 2 Total	Treatment Cycle 3 Total	Treatment Cycle 4 Total
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	357	329	234	65
Units: Percent Change				
arithmetic mean (standard deviation)				
Annoyance (n=309,273,201,56)	-29.46 (± 98.827)	-49.54 (± 57.094)	-40.35 (± 68.949)	-49.25 (± 54.633)
Head and neck symptoms (n=333,292,208,57)	-36.83 (± 35.884)	-46.13 (± 33.539)	-40.19 (± 37.735)	-48.60 (± 40.805)
Mood (n=273,242,179,51)	-29.09 (± 93.496)	-45.73 (± 73.222)	-45.42 (± 68.085)	-37.11 (± 139.591)
Pain and discomfort symptoms (n=326,284,204,55)	-36.82 (± 49.805)	-48.75 (± 48.029)	-39.24 (± 46.514)	-50.65 (± 37.450)
Psychosocial functioning (n=302,268,200,55)	-35.82 (± 58.520)	-48.75 (± 48.029)	-41.47 (± 65.214)	-47.73 (± 46.804)
Sleep (n=264,231,167,53)	-47.03 (± 78.131)	-56.09 (± 52.852)	-47.26 (± 59.372)	-56.84 (± 55.075)
Upper limb activity symptoms (n=313,277,199,56)	-26.84 (± 69.077)	-38.20 (± 62.693)	-36.31 (± 57.008)	-45.91 (± 43.393)
Walking (n=262,231,170,46)	-35.51 (± 95.256)	-36.20 (± 105.067)	-25.15 (± 110.519)	-16.07 (± 128.252)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 52	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Treatment Cycle 1 Total
Reporting group description: Total number of subjects who received treatment (DAXI 125U or DAXI 250U) in Cycle 1.	
Reporting group title	Treatment Cycle 2 Total
Reporting group description: Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in Cycle 2.	
Reporting group title	Treatment Cycle 3 Total
Reporting group description: Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in Cycle 3.	
Reporting group title	Treatment Cycle 4 Total
Reporting group description: Total number of subjects who received treatment (DAXI 125 U, DAXI 200 U, DAXI 250 U or DAXI 300 U) in Cycle 4.	

Serious adverse events	Treatment Cycle 1 Total	Treatment Cycle 2 Total	Treatment Cycle 3 Total
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 357 (0.56%)	6 / 329 (1.82%)	8 / 234 (3.42%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	0 / 234 (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
Squamous cell carcinoma of lung			

subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	0 / 234 (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
Head injury			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
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			
Intracranial aneurysm			
subjects affected / exposed	1 / 357 (0.28%)	0 / 329 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	0 / 234 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 357 (0.28%)	0 / 329 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Hiatus hernia			

subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	0 / 234 (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
Chronic kidney disease			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 357 (0.00%)	0 / 329 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 357 (0.00%)	1 / 329 (0.30%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Cycle 4 Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 65 (1.54%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Blood loss anaemia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			

subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 65 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment Cycle 1 Total	Treatment Cycle 2 Total	Treatment Cycle 3 Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 357 (17.65%)	48 / 329 (14.59%)	40 / 234 (17.09%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 357 (1.40%)	2 / 329 (0.61%)	3 / 234 (1.28%)
occurrences (all)	5	2	3
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 357 (3.08%)	9 / 329 (2.74%)	3 / 234 (1.28%)
occurrences (all)	11	9	4
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	9 / 357 (2.52%)	6 / 329 (1.82%)	7 / 234 (2.99%)
occurrences (all)	9	6	7
Injection site pain			
subjects affected / exposed	19 / 357 (5.32%)	9 / 329 (2.74%)	5 / 234 (2.14%)
occurrences (all)	19	10	6
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	15 / 357 (4.20%)	14 / 329 (4.26%)	12 / 234 (5.13%)
occurrences (all)	15	14	12
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 357 (1.12%)	1 / 329 (0.30%)	0 / 234 (0.00%)
occurrences (all)	4	1	0
Muscular weakness			
subjects affected / exposed	16 / 357 (4.48%)	17 / 329 (5.17%)	15 / 234 (6.41%)
occurrences (all)	16	18	15

Non-serious adverse events	Treatment Cycle 4 Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 65 (15.38%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2018	Protocol Amendment 1 •Modified Protocol title •Changed Medical Monitor •Modified Study design o Removed active comparator and changed dose range to fixed dose o Changed sample size from 600 to 290 subjects o Expanded participating countries to include Europe •Changed total number of sites from 50 to approximately 80 sites •Modified the study objectives •Modified primary, secondary, and exploratory endpoints •Modified screening window and modified screening period from 2 to 3 weeks •Modified schedule of assessments •Modified Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) scales from 9-point to 7-point scales •Updated safety evaluations (added Spirometry and Dysphagia Severity Scale) •Modified and updated Inclusion and exclusion criteria •Limited dose of drug to be injected into each targeted muscle to a minimum and maximum range •Modified scientific rationale to match updates •Modified dose justification •Updated the list of prohibited medications •Modified the injectable muscles and injection volume by muscle table (Appendix A) •Added appendices for Cervical Dystonia Impact Profile (CDIP-58), Treatment Satisfaction Questionnaire (TSQ), Work Productivity and Activity Impairment (WPAI), Questionnaire and Short Form-36 (SF-36) Survey.
27 March 2018	Protocol Amendment 2 •Clarified inclusion and exclusion criteria; added 1 exclusion criterion. •Clarified sections describing study intervention. •Updated secondary and exploratory endpoints. •Added more instructions for dose selection and clarified study product description. •Clarified that subjects could discontinue study product due to safety or at any time during the study as well as when there was no treatment benefit. •Clarified study assessment sections and moved some examples and scales to the appendices. •Reorganized the statistical analysis section to align with headings of ICH E9 guidance. •Added prior treatment experience, age, and gender as subgroup analyses in the exploratory endpoints. •Made wording changes to endpoints for clarification. •Changed sample size to approximately 300. •Clarified muscles for injections and added mandatory parameters. •Clarified BoNT, 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.

04 June 2018	Protocol Amendment 3 •Added more information about Study RT002-CL005 to the introduction. •Added dysphagia as a known potential risk. •Updated study design section for clarification. •Clarified and updated inclusion and exclusion criteria. •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 EOS Visit, TWSTRS, AE expectedness, follow-up of nonserious AEs, and follow-up of post-study SAEs. •In the statistical analysis section, added objectives with endpoints and clarified efficacy endpoints. •Updated information for key study personnel. •Updated study oversight text to reflect that the Data Safety Monitoring Board (DSMB) was to review unblinded data, as this was an open-label study.
27 June 2018	Protocol Amendment 4 •Increased sample size to approximately 350. •Clarified sample size justification and Increased sample size in 4.1 Overall design. •Clarified that a subject who has no reduction or an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 is the same as a subject who has a lack of efficacy. •Updated Figure 1. •Clarified major inclusion criteria. •Clarified that a subject who has no reduction or an increase from baseline in the average TWSTRS-total score at Weeks 4 and 6 is the same as a subject who has a lack of efficacy in 4.1. Overall design, and in 4.6 End of study definition and 7.2 Subject discontinuation/withdrawal from the study. •Updated 4.5 Justification for dose.
10 July 2019	Protocol Amendment 5 •Added National Clinical Trial Identified Number NCT03617367. •Added “Blood sample for antibody testing” at Week 4 after baseline injection and Week 4 after all retreatments. •Updated Medical Monitor’s information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported