Clinical trial results:
Prospective, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial With an Open-label Period to Investigate the Efficacy and Safety of NT201 in the Unilateral and Bilateral Treatment of Essential Tremor of the Upper Limb

Summary

EudraCT number	2021-001988-24
Trial protocol	PL
Global end of trial date	21 November 2023

Results information

Result version number	v1
This version publication date	05 December 2024
First version publication date	05 December 2024

Trial information

Trial identification

Sponsor protocol code	M602011069

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04766723
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merz Pharmaceuticals GmbH
Sponsor organisation address	Eckenheimer Landstrasse 100, Frankfurt, Germany, 60318
Public contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.de
Scientific contact	Public Disclosure Manager, Merz Pharmaceuticals GmbH, +49 69 1503 1, clinicaltrials@merz.de

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 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine whether a single treatment with administration of NT 201 (botulinum toxin) was superior to placebo (no medicine) for one-sided treatment of essential tremor in the arm (Unilateral Period).

Protection of trial subjects:

The study was conducted in accordance with GCP as required by ICHGCP, applicable regulatory requirements in the USA, Canada, and Poland, and standard operating procedures for clinical investigation and documentation in force at Merz Pharmaceuticals GmbH, hereinafter referred to as Merz. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 38
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Poland: 35
Worldwide total number of subjects	78
EEA total number of subjects	35

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)	29

From 65 to 84 years	47
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 15 investigational sites in the United States, Poland and Canada.

Pre-assignment

Screening details:

A total of 114 subjects were screened, out of which 78 subjects were randomized, and 77 subjects were treated in this study.

Period 1

Period 1 title	Unilateral Treatment: Cycle 1 (24 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Unilateral Treatment Period: NT 201

Arm description:

Subjects were randomized to receive unilateral intramuscular injections of NT 201 into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, IncobotulinumtoxinA, Xeomin, Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received solution for the injection from the reconstituted powder of NT 201 (130-165 units [U]) into the muscles of motor-dominant upper limb on Day 1 in Cycle 1 (Cycle length = 24 Weeks) according to the semi-flexible dosing scheme.

Arm title	Unilateral Treatment Period: Placebo

Arm description:

Subjects were randomized to receive unilateral intramuscular injections of placebo into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).

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:

Subjects received solution for the injection from the reconstituted placebo (with an injection volume corresponding to 130-165 U for treatment with NT201), into the muscles of the motor-dominant upper limb on Day 1 in Cycle 1 (Cycle length = 24 Weeks) according to the semi-flexible dosing scheme.

Number of subjects in period 1	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo
Started	51	27
Completed	48	26
Not completed	3	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	-
Other	1	1

Period 2

Period 2 title	Bilateral treatment: Cycle 2 (12 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bilateral Treatment Period: NT 201

Arm description:

Subjects received NT201 or placebo in the unilateral treatment period, transitioned to bilateral treatment period and who were eligible for re-injection, received bilateral intramuscular injections of NT 201 into the muscles of both upper limbs on Day 1 of Cycle 2 (Cycle length = 12 weeks).

Arm type	Experimental
Investigational medicinal product name	NT 201
Investigational medicinal product code	
Other name	IncobotulinumtoxinA, IncobotulinumtoxinA, Xeomin, Botulinum toxin type A (150 kiloDalton), free from complexing proteins
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received solution for the injection from the reconstituted powder of NT 201 (130-165 U per upper limb or 260-330 U per both upper limbs), into the muscles of both upper limbs on Day 1 in Cycle 2 (Cycle length = 12 Weeks) according to the semi-flexible dosing scheme.

Number of subjects in period 2[1]	Bilateral Treatment Period: NT 201
Started	72
Completed	71
Not completed	1
Consent withdrawn by subject	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Among the 74 subjects who completed unilateral treatment period (Cycle 1), 2 subjects did

not meet all re-injection criteria for Cycle 2 and therefore discontinued the study after end of Cycle 1 (no need for re-injection was reported as reason for both subjects). Therefore, only 72 subjects entered the bilateral treatment period (Cycle 2).

Baseline characteristics

Reporting groups	
Reporting group title	Unilateral Treatment Period: NT 201
Reporting group description:	
Subjects were randomized to receive unilateral intramuscular injections of NT 201 into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).	
Reporting group title	Unilateral Treatment Period: Placebo
Reporting group description:	
Subjects were randomized to receive unilateral intramuscular injections of placebo into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).	

Reporting group values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo	Total
Number of subjects	51	27	78
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)	18	11	29
From 65-84 years	32	15	47
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	25	12	37
Male	26	15	41

End points

End points reporting groups

Reporting group title	Unilateral Treatment Period: NT 201
Reporting group description:	
Subjects were randomized to receive unilateral intramuscular injections of NT 201 into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).	
Reporting group title	Unilateral Treatment Period: Placebo
Reporting group description:	
Subjects were randomized to receive unilateral intramuscular injections of placebo into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).	
Reporting group title	Bilateral Treatment Period: NT 201
Reporting group description:	
Subjects received NT201 or placebo in the unilateral treatment period, transitioned to bilateral treatment period and who were eligible for re-injection, received bilateral intramuscular injections of NT 201 into the muscles of both upper limbs on Day 1 of Cycle 2 (Cycle length = 12 weeks).	

Primary: Unilateral Treatment Period: Change From Baseline to Week 6 in Maximum Tremor Amplitude of the Wrist

End point title	Unilateral Treatment Period: Change From Baseline to Week 6 in Maximum Tremor Amplitude of the Wrist
End point description:	
TremorTek kinematic analytic investigational device is combination of computer software and wearable movement sensors that allows to collect motion data when placed on individual's arm to quantify tremor in various muscle groups that impact shoulder, elbow, wrist. This assessment system was used to measure maximum angular tremor amplitude at wrist of injected limb (unit: degrees). Angular tremor amplitude was measure of tremor severity. Reduction of maximum angular tremor amplitude at wrist of injected limb represented tremor improvement. Full analysis set for unilateral treatment period (FAS-UP) was subset of subjects in safety evaluation set (SES-UP, that is, all subjects who received NT201/placebo during unilateral treatment period) for whom at least one score of tremor amplitude at wrist level (injected UL) at study baseline and at least at one post-baseline score was available. "N"= subjects who were evaluable for this endpoint. The analysis was performed by randomized treatment.	
End point type	Primary
End point timeframe:	
Baseline up to Week 6	

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	26		
Units: degrees of arc				
least squares mean (standard error)	-0.25 (± 0.140)	-0.46 (± 0.180)		

Statistical analyses

Statistical analysis title	Unilateral Treatment Period: NT 201 vs Placebo
Comparison groups	Unilateral Treatment Period: NT 201 v Unilateral Treatment Period: Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Least Square Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.196

Notes:

[1] - Analysis of covariance adjusting for baseline value and study site.

Secondary: Unilateral Treatment Period: Change From Baseline to Week 6 in TETRAS ADL Functional Impact Score

End point title	Unilateral Treatment Period: Change From Baseline to Week 6 in TETRAS ADL Functional Impact Score

End point description:

TETRAS ADL Functional Impact score was the sum of the following three ADL items: occupational impairment (item 10), overall disability (item 11), and social impact (item 12) of ET. The items are rated on a 5-point response scale each ranged from 0 (normal status/impact) to 4 (severe status/impact). The ADL Functional Impact score ranged from 0 to 12. Higher scores indicated greater tremor severity. The FAS-UP was the subset of subjects in the SES-UP (all subjects who received NT201 or placebo during the unilateral treatment period) for whom at least one score of tremor amplitude at wrist level (injected UL) at the study baseline and at least at one post-baseline score was available. The analysis was performed by randomized treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 6

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.2 (± 1.87)	-1.3 (± 1.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Unilateral Treatment Period: Change From Baseline to Week 6 in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Dominant Upper Limb (UL) Score as Assessed by Investigator

End point title	Unilateral Treatment Period: Change From Baseline to Week 6 in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Dominant Upper Limb (UL) Score as Assessed by Investigator

End point description:

The Essential Tremor Rating Assessment Scale (TETRAS) was a validated clinical scale for the assessment of essential tremor severity. The TETRAS performance subscale was utilized by the qualified investigators to assess the tremor severity. The TETRAS Performance dominant UL score included TETRAS Performance items 4 (including subitems a, b, c for 3 manoeuvres), 6 to 8 of dominant UL. Each individual item score ranged from 0 to 4. The performance dominant UL score ranged from 0 to 24. Higher scores=more severe tremor. The FAS-UP was the subset of subjects in the SES-UP (all subjects who received NT201 or placebo during the unilateral treatment period) for whom at least one score of tremor amplitude at wrist level (injected UL) at the study baseline and at least at one post-baseline score was available. The analysis was performed by randomized treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 6

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: score on a scale				
arithmetic mean (standard deviation)	-2.3 (± 2.60)	-0.9 (± 1.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Unilateral Treatment Period: Change From Baseline to Week 6 in the TETRAS Performance Activities of Daily Living (ADL) UL Score as Assessed by Investigator

End point title	Unilateral Treatment Period: Change From Baseline to Week 6 in the TETRAS Performance Activities of Daily Living (ADL) UL Score as Assessed by Investigator

End point description:

TETRAS ADL subscale was another component of TETRAS. ADL subscale of TETRAS was completed by study subjects through an interview procedure to assess impact of tremor on activities of daily living. TETRAS ADL UL score was the sum of eight ADL items (on UL tremor [items 2-9]). Items were rated on a 5-point response scale each ranged from 0 (normal status/impact) to 4 (severe status/impact). The ADL UL score ranged from 0 to 32. Higher scores = greater tremor severity. The FAS-UP was subset of subjects in the SES-UP (all subjects who received NT201 or placebo during the unilateral treatment period) for whom at least one score of tremor amplitude at wrist level (injected UL) at the study baseline and at least at one post-baseline score was available. The analysis was performed by randomized treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 6

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: score on a scale				
arithmetic mean (standard deviation)	-3.7 (± 5.00)	-3.8 (± 4.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Unilateral Treatment Period: Subject's Global Impression of Change Scale (GICS) Score of Motor-dominant UL at Week 6

End point title	Unilateral Treatment Period: Subject's Global Impression of Change Scale (GICS) Score of Motor-dominant UL at Week 6

End point description:

The GICS was used to evaluate overall clinical impression of change after treatment by the subject. The response option was a common 7-point Likert scale ranged from 4 to +4, with the following values: +4 (very much improved); +3 (much improved); +2 (improved); +1 (minimally improved); 0 (no change); -1 (minimally worse); -2 (worse); -3 (much worse); 4 (very much worse). The FAS-UP was the subset of subjects in the SES-UP (all subjects who received NT201 or placebo during the unilateral treatment period) for whom at least one score of tremor amplitude at wrist level [injected UL] at the study baseline and at least at one post-baseline score was available. The analysis was performed by randomized treatment.

End point type	Secondary

End point timeframe:

Week 6

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: score on a scale				
arithmetic mean (standard deviation)	0.9 (± 1.27)	0.8 (± 1.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS ADL Functional Impact Score

End point title	Bilateral Treatment Period: Change From Cycle 2 Baseline to

	Week 6 in TETRAS ADL Functional Impact Score

End point description:

TETRAS ADL Functional Impact score was the sum of the following three ADL items: occupational impairment (item 10), overall disability (item 11), and social impact (item 12) of ET. The items are rated on a 5-point response scale each ranged from 0 (normal status/impact) to 4 (severe status/impact). The ADL Functional Impact score ranged from 0 to 12. Higher scores indicated greater tremor severity. The FAS-BP was the subset of subjects in SES-BP (all subjects who received NT 201 during the bilateral treatment period) for whom at least one score of tremor amplitude at wrist level at the Cycle 2 baseline visit and at least at one post-baseline score.

End point type	Secondary

End point timeframe:

Baseline of Cycle 2 up to Week 6 (Cycle length = 12 weeks)

End point values	Bilateral Treatment Period: NT 201			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: score on a scale				
arithmetic mean (standard deviation)	-1.4 (± 1.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Unilateral Treatment Period: Investigator's GICS Score of Motor-dominant UL at Week 6

End point title	Unilateral Treatment Period: Investigator's GICS Score of Motor-dominant UL at Week 6

End point description:

The GICS was used to evaluate the overall clinical impression of change after treatment by the investigator. The response option was a common 7-point Likert scale ranged from 4 to +4, with the following values: +4 (very much improved); +3 (much improved); +2 (improved); +1 (minimally improved); 0 (no change); -1 (minimally worse); -2 (worse); -3 (much worse); 4 (very much worse). The FAS-UP was the subset of subjects in the SES-UP (all subjects who received NT201 or placebo during the unilateral treatment period) for whom at least one score of tremor amplitude at wrist level (injected UL) at the study baseline and at least at one post-baseline score was available. The analysis was performed by randomized treatment.

End point type	Secondary

End point timeframe:

Week 6

End point values	Unilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	26		
Units: score on a scale				
arithmetic mean (standard deviation)	1.2 (± 1.36)	0.8 (± 1.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS Performance Dominant UL Score

End point title	Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS Performance Dominant UL Score

End point description:

TETRAS was a validated clinical scale for the assessment of essential tremor severity. The TETRAS performance subscale was utilized by the qualified investigators to assess the tremor severity. The TETRAS Performance dominant UL score included TETRAS Performance items 4 ((including subitems a, b, c for 3 manoeuvres), 6 to 8 of dominant UL. Each individual item score ranged from 0 to 4. The performance dominant UL score ranged from 0 to 24. Higher scores=more severe tremor. The full analysis set for the bilateral treatment period (FAS-BP) was the subset of subjects in the safety evaluation set for the bilateral treatment period (SES-BP that is, all subjects who received NT 201 during the bilateral treatment period) for whom at least one score of tremor amplitude at wrist level at the Cycle 2 baseline visit and at least at one post-baseline score.

End point type	Secondary

End point timeframe:

Baseline of Cycle 2 up to Week 6 (Cycle length = 12 weeks)

End point values	Bilateral Treatment Period: NT 201			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: score on a scale				
arithmetic mean (standard deviation)	-2.8 (± 2.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS Performance Subscale Score

End point title	Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS Performance Subscale Score

End point description:

The TETRAS was a validated clinical scale for the assessment of essential tremor severity. The TETRAS

performance subscale was utilized by the qualified investigators to assess the tremor severity. TETRAS performance subscale consisted of 9 items: head, face, and voice tremor (items 1-3), UL tremor of right and left UL (item 4) in three tasks (forward outstretched postural tremor, lateral "wing-beating" postural tremor, kinetic tremor), Archimedes spirals with both hands, handwriting with motor-dominant hand, and dot approximation task with both hands (items 6-8), and lower limb tremor and standing tremor (items 5 and 9). Each item was rated from 0 (no tremor) to 4 (severe tremor) with overall performance score of 0 to 64, calculated as the sum of subscale items. Higher scores = greater tremor severity. The FAS-BP was the subset of subjects in the safety evaluation set for the SES-BP (that is, all subjects who received NT 201 during bilateral treatment.

End point type	Secondary

End point timeframe:

Baseline of Cycle 2 up to Week 6 (Cycle length =12 weeks)

End point values	Bilateral Treatment Period: NT 201			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: score on a scale				
arithmetic mean (standard deviation)	-5.6 (± 5.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS ADL UL Score

End point title	Bilateral Treatment Period: Change From Cycle 2 Baseline to Week 6 in TETRAS ADL UL Score

End point description:

TETRAS ADL subscale was another component of TETRAS. ADL subscale of TETRAS was completed by study subjects through an interview procedure to assess impact of tremor on activities of daily living. TETRAS ADL UL score was the sum of eight ADL items on UL tremor (items 2-9). Items were rated on a 5-point response scale each ranged from 0 (normal status/impact) to 4 (severe status/impact). The ADL UL score ranged from 0 to 32. Higher scores = greater tremor severity. The FAS-BP was the subset of subjects in the SES-BP (all subjects who received NT 201 during the bilateral treatment period) for whom at least one score of tremor amplitude at wrist level at the Cycle 2 baseline visit and at least at one post-baseline score.

End point type	Secondary

End point timeframe:

Baseline of Cycle 2 up to Week 6 (Cycle length = 12 weeks)

End point values	Bilateral Treatment Period: NT 201			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: score on a scale				
arithmetic mean (standard deviation)	-4.4 (± 4.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With At-least One Treatment Related Treatment-emergent AEs (TEAEs)

End point title	Percentage of Subjects With At-least One Treatment Related Treatment-emergent AEs (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in subject administered pharmaceutical product. TEAEs of unilateral treatment period (Cycle 1) = AEs from first injection up to injection in the bilateral treatment period (Week 24). TEAEs of bilateral treatment period (Cycle 2) = AEs from injection in bilateral treatment period up to end of study (Week 36). The safety evaluation set for the SES-UP included all subjects who received NT 201 or placebo during the unilateral treatment period and for SES-BP included all subjects who received NT 201 during the bilateral treatment period. For the unilateral treatment period, the analysis performed according to actual treatment.

End point type	Secondary

End point timeframe:

Unilateral Treatment Period: From first injection in unilateral treatment period up to re-injection in Bilateral Treatment Period (Week 24); Bilateral Treatment Period: From re-injection in Bilateral Treatment Period at Week 24 up to end of study(Week 36)

End point values	Unilateral Treatment Period: NT 201	Bilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	72	27	
Units: percentage of subjects				
number (not applicable)	30.0	30.6	3.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unilateral Treatment Period: From first injection in unilateral treatment period up to re-injection in Bilateral Treatment Period (Week 24); Bilateral Treatment Period: From re-injection in Bilateral Treatment Period at Week 24 up to end of study(Week 36)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Unilateral Treatment Period: NT 201

Reporting group description:

Subjects received unilateral intramuscular injections of NT 201 into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).

Reporting group title	Bilateral Treatment Period: NT 201

Reporting group description:

Subjects received NT201 or placebo in the unilateral treatment period, transitioned to bilateral treatment period and who were eligible for re-injection, received bilateral intramuscular injections of NT 201 into the muscles of both upper limbs on Day 1 of Cycle 2 (Cycle length = 12 weeks).

Reporting group title	Unilateral Treatment Period: Placebo

Reporting group description:

Subjects received unilateral intramuscular injections of placebo into the muscles of the motor-dominant upper limb on Day 1 of Cycle 1 (Cycle length = 24 weeks).

Serious adverse events	Unilateral Treatment Period: NT 201	Bilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)	2 / 72 (2.78%)	2 / 27 (7.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
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			

Skull fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (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
Subdural haematoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (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			
Condition aggravated			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (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
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (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	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (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
Respiratory, thoracic and mediastinal disorders			

Aspiration			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Unilateral Treatment Period: NT 201	Bilateral Treatment Period: NT 201	Unilateral Treatment Period: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 50 (58.00%)	29 / 72 (40.28%)	5 / 27 (18.52%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Metastases to lung			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Rectal neoplasm			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 50 (6.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Essential hypertension			

subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Peripheral venous disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Injection site haemorrhage			
subjects affected / exposed	2 / 50 (4.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Inflammation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Injection site nodule			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 50 (0.00%)	2 / 72 (2.78%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gait disturbance			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Negative thoughts			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Investigations			

Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 50 (2.00%)	1 / 72 (1.39%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Fall			
subjects affected / exposed	1 / 50 (2.00%)	3 / 72 (4.17%)	2 / 27 (7.41%)
occurrences (all)	1	4	2
Craniofacial fracture			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Craniofacial injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Post-traumatic pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			

subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypertensive heart disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	2 / 72 (2.78%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Facial paralysis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 50 (2.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Fine motor skill dysfunction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Monoparesis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Paresis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Peritoneal adhesions			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Chronic gastritis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hydronephrosis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Arthritis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Intervertebral disc disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	12 / 50 (24.00%)	17 / 72 (23.61%)	0 / 27 (0.00%)
occurrences (all)	12	20	0
Pain in extremity			
subjects affected / exposed	2 / 50 (4.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Back pain			
subjects affected / exposed	3 / 50 (6.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	3	0	0
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 72 (2.78%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Muscle fatigue			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Joint swelling			

subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Coccydynia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	2 / 72 (2.78%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
COVID-19			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 72 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 72 (1.39%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 72 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Herpes zoster subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	0 / 72 (0.00%) 0	0 / 27 (0.00%) 0
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	1 / 72 (1.39%) 1	0 / 27 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2021	Protocol amendment version 3.0: The amendment was designed in order to add Poland in the list of countries where the study was performed and to eliminate some minor discrepancies in the content of the protocol.
26 May 2023	Protocol amendment version 1.0 to 3.0: The amendment was created in order to reduce the workload of the Independent Rater Panel (IRP). According to the amendment the IRP performed the TETRAS Performance subscale ratings based on videos from all subjects at Baseline (V2), and at Week 6 (V4).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported