



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 | v2 (current) |
| This version publication date | 26 March 2025 |
| First version publication date | 05 December 2024 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Corrections: <ul style="list-style-type: none">- Title of 3rd endpoint- Number of investigational sites |

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 14 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 | Incobotulinumtoxin A, 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 | Incobotulinumtoxin A, 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

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| 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

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| 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 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

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

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|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Unilateral Treatment Period: Change From Baseline to Week 6 in the TETRAS Performance Activities of Daily Living (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-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: 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 (\pm 1.87) | -1.3 (\pm 1.83) | | |

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

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| 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 (\pm 1.27) | 0.8 (\pm 1.14) | | |

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 |
|-----------------|-----------------------------------------------------------|

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

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|-----------------|----------------------------------------------------------------------------------------------------------|
| 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: 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

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| Dictionary name | MedDRA |
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| Dictionary version | 26.1 |
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Reporting groups

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| Reporting group title | Unilateral Treatment Period: NT 201 |
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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).

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| Reporting group title | Bilateral Treatment Period: NT 201 |
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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).

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| Reporting group title | Unilateral Treatment Period: Placebo |
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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 | | | |

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|------------------------------------------------------|----------------|----------------|----------------|
| 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 | | | |

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|-------------------------------------------------|----------------|----------------|----------------|
| 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 | | | |

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

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| 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 | | | |

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|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 72 (1.39%) 1 | 0 / 27 (0.00%) 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 | | | |

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|----------------------------------------|----------------|----------------|----------------|
| 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 | | | |

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|-------------------------------------------------|------------------|------------------|----------------|
| 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 | | | |

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

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|------------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|
| 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