Prospective, randomized, double-blind, placebo-controlled, parallel-group trial with an open-label period to investigate the efficacy and safety of NT 201 in the unilateral and bilateral treatment of essential tremor of the upper limb

Development phase:	Phase 2
Study identifier **EudraCT Number**	M602011069 2021-001988-24
IND Number	138433 Applies to all study sites in the US. IND requirements will not apply to Non-US sites; however, non-US sites will conduct the study according to GCP requirements and in compliance with 21 CFR 312.120
Date of original clinical study protocol:	Ver. 1.0 18-FEB-2020 (internal version) Ver. 2.0 23-SEP-2020 (first submitted version)
Indication:	Essential tremor
Planned study period:	First subject first visit: February 2021 Last primary outcome visit: July 2022 Last subject last visit: November 2022
Investigational product(s):	NT 201 (active substance NT 101, *Botulinum* neurotoxin type A free from complexing proteins. USAN: incobotulinumtoxinA) or matching placebo
Sponsor:	Merz Pharmaceuticals GmbH Eckenheimer Landstr. 100 60318 Frankfurt/Main Germany Telephone: +49 69 1503 0 Telefax: +49 69 1503 200
Responsible for the clinical study protocol content at the sponsor:	[redacted] (Clinical Project Manager) [redacted], MD (Medical Expert) [redacted] (Biostatistician)

SIGNATURE PAGE

The study will be conducted in compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

The following individuals are responsible for the content of the clinical study protocol:

[redacted] MD
Document owner

[redacted]
Date (dd-MMM-yyyy)

[redacted]
Sig

[redacted] PhD
Head of Global Clinical Development

[redacted]
Date (dd-MMM-yyyy)

[redacted]

The following individuals also significantly contributed to the development of the clinical study protocol:

[redacted] MD
Overall coordinating investigator

[redacted]
Date (dd-MMM-yyyy)

[redacted]

Statement of Compliance

Study site(s)

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the case report form, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

I have received the current investigator's brochure. Having been adequately informed about the IP development to date, I also agree to:

- Sign this clinical study protocol before the study formally starts;
- Wait until I have received approval from the appropriate IEC/IRB before enrolling any subject in this study;
- Obtain informed consent for all subjects prior to any study-related action performed;
- Start the study only after all legal requirements in my country have been fulfilled;
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections;
- Provide direct access to all study-related records, source documents, and subject file for the monitor, auditor, IEC/IRB, or regulatory authority upon request;
- Use the IP and all study materials only as specified in the clinical study protocol;
- Report to the responsible product safety officer, within 24 hours, any adverse event [AE] that is serious and any AE of special interest [AESI], whether considered treatment-related or not;
- Notify the appropriate IEC/IRB on SAEs according to local requirements;
- For U.S. sites: Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest in accordance with 21 Code of Federal Regulations [CFR] Part 54 and a signed US Food and Drug Administration [FDA] 1572 form according to 21 CFR Part 312; and
- For non-U.S. sites: Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest.

Furthermore, I understand that:

- Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Merz and – as applicable – of the appropriate IEC/IRB and regulatory authority;
- The content of the clinical study protocol is confidential and proprietary to Merz; and
- Any deviation from the clinical study protocol may lead to early termination of the study site.

Principal investigator (print name)	Date (dd-MMM-yyyy)	Signature

<Study site stamp:>

List of abbreviations and definitions of terms

ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
BoNT	*Botulinum* neurotoxin
***BoNT* A**	*Botulinum* neurotoxin type A
CFR	Code of Federal Regulations
COVID-19[1]	Coronavirus Disease 2019
CRO	Contract research organization
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Essential tremor
FAS-BP	Full analysis set, bilateral treatment period
FAS-UP	Full analysis set, unilateral treatment period
FDA	US Food and Drug Administration
GCP	Good clinical practice
GICS	Global Impression of Change Scales
β-HCG	Beta human chorionic gonadotropin
HHD	Handheld dynamometer
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IND number	Investigational New Drug number, issued by the FDA
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board

[1] All general measures and definitions described in this protocol as related to SARS-CoV-2 or COVID-19 outbreak also apply to any possible future coronavirus outbreaks or other public health emergencies that threaten the safety of subjects and investigators.

IRP	Independent rater panel
ISF	Investigator's site file
IWRS	Interactive web response system
LPOV	Last Primary Outcome Visit = Primary Completion Date: The date/visit that the final subject was examined or received an intervention for the purposes of final collection of data for the primary endpoint
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PI	Principal investigator
PPS	Per protocol set
QoL	Quality of life
QUEST	Quality of Life in Essential Tremor Scale
RMS	Root mean square
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2[2]	Severe acute respiratory syndrome-coronavirus-2 [2]
SES-BP	Safety evaluation set, bilateral treatment period
SES-UP	Safety evaluation set, unilateral treatment period
SmPC	Summary of product characteristics
SOP(s)	Standard operating procedure(s)
TEAE	Treatment emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
UL	Upper limb
USAN	US Adopted Name
VAS	Visual analog scale

[2] All general measures and definitions described in this protocol as related to the SARS-CoV-2 or COVID-19 outbreak also apply to any possible future coronavirus outbreaks or other public health emergencies that threaten the safety of subjects and investigators.

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1 SYNOPSIS

Study title

Prospective, randomized, double-blind, placebo-controlled, parallel-group trial with an open-label period to investigate the efficacy and safety of NT 201 in the unilateral and bilateral treatment of essential tremor of the upper limb

Study phase

Phase 2

Indication

Essential tremor

Study objectives

Primary objective(s)

The primary objective of this study is to assess the efficacy of unilateral intramuscular injections of NT 201, as compared with placebo, in subjects with essential tremor [ET] of the upper limb [UL].

Secondary objective(s)

A secondary objective of this study is to assess the safety of unilateral intramuscular injections of NT 201, as compared with placebo, in subjects with ET of the UL.

A further secondary objective of this study is to assess the efficacy and safety of bilateral intramuscular injections of NT 201 in subjects with ET of the UL.

Study population, diagnosis, and main criteria for in- and exclusion

A total of approximately 75 evaluable male and female adults will be recruited.

Key inclusion criteria

Male and female adults (≥ 18 years) suffering from ET.

Following TETRAS Performance subscale criteria as assessed by the investigator:

Score of ≥ 2 (at least 1 cm tremor amplitude) in at least two out of three maneuvers of test item 4 (upper limb tremor) confirmed by an independent TETRAS expert by means of video assessment.

Key exclusion criteria:

History or presence of day-to-day fluctuations in ET which would jeopardize meaningful tremor assessment over time, e.g. severe tremor on one day and minimal or no tremor on another day.

Other neurological signs, such as dystonia, ataxia, or parkinsonism, which in the judgment of the investigator could interfere with the ET diagnosis and/or assessment of ET in ULs.

Tremor types other than ET.

Study design

This will be a prospective, randomized, double-blind, placebo-controlled, parallel-group, phase 2 study, followed by an open-label treatment period.

The double-blind unilateral treatment period (Cycle 1) will start with the screening visit, which will be performed between 21 and 3 days prior to the study baseline visit. At the study baseline visit, on Day 1, eligible subjects will be randomized to one of two treatment groups, NT 201 or placebo, with a randomization ratio of 2:1. The unilateral intramuscular injection will be administered into the motor dominant UL. Subjects will be followed up during six subsequent visits until the end-of-Cycle 1 visit at Week 24 after injection.

At the end of the unilateral treatment period (end-of-Cycle 1 visit), subjects will be checked for eligibility to participate in the subsequent open-label bilateral treatment period (Cycle 2). If eligibility criteria for reinjection are met, the Cycle 2 baseline visit (Cycle 2, Day 1) will be performed on the same day, including bilateral UL treatment with NT 201. Subjects will be followed up during three subsequent visits until the end-of -study visit at Week 12 after reinjection.

Planned study period

First subject first visit: February 2021

Last primary outcome visit: July 2022

Last subject last visit: November 2022

Duration of treatment per subject

Overall, the duration of the study will be 36 weeks plus up to 3 weeks screening period.

Each subject will receive a single treatment on Day 1 of the unilateral treatment period (Cycle 1) (NT 201 or matching placebo in dominant arm) and Day 1 of the bilateral treatment period (Cycle 2) (NT 201 in both ULs).

Endpoints for analysis

Efficacy endpoints

Primary efficacy endpoint

Change from study baseline to Week 6 in maximum tremor amplitude measurement at wrist level during the unilateral treatment period.

Key secondary efficacy endpoints

Unilateral treatment period:

Change from study baseline to Week 6 in The Essential Tremor Rating Assessment scale [TETRAS] Performance dominant UL Score as assessed by the investigator.

Change from study baseline to Week 6 in TETRAS Activities of Daily Living [ADL] UL score.

Other secondary efficacy endpoints

Unilateral treatment period (Cycle 1):

Change from study baseline to Week 6 in TETRAS ADL Functional Impact score.

Subject´s Global Impression of Change Scale [GICS] score of motor dominant UL at Week 6.

Investigator´s GICS score of motor dominant UL at Week 6.

Bilateral treatment period (Cycle 2):

Change from Cycle 2 baseline to Week 6 in TETRAS Performance dominant UL score.

Change from Cycle 2 baseline to Week 6 in TETRAS Performance subscale score.

Change from Cycle 2 baseline to Week 6 in TETRAS ADL UL score.

Change from Cycle 2 baseline to Week 6 in TETRAS ADL Functional Impact score.

Total number of subjects and number of countries

This study will be performed in North America (USA and Canada) and Europe (Poland) and approximately 75 evaluable subjects are planned to be randomized.

Number of study sites

This study is planned to be performed at approximately 15 sites.

Number of visits

A total of 11 visits are planned.

Investigational product(s), dose, and route of administration

NT 201 (active ingredient: NT 101, *Botulinum* neurotoxin type A [*BoNT*-A], free from complexing proteins, US Adopted Name incobotulinumtoxinA) or matching placebo (human serum albumin plus sucrose) provided in 200 U vials.

In the unilateral treatment period (Cycle 1), NT 201 or placebo will be injected unilaterally into the muscles of the motor dominant UL under double blind conditions. In the open label bilateral treatment period (Cycle 2), NT 201 will be injected bilaterally into the muscles of both ULs. A total dose of 130 to 165 U of NT 201 per UL (or placebo in the unilateral treatment period) will be injected during each treatment period.

Statistical analysis methods

All efficacy analyses will be based primarily on the full analysis sets of the unilateral (Cycle 1) and bilateral (Cycle 2) treatment periods. The primary endpoint will be analyzed using least square means from a baseline adjusted analysis of covariance. This model will be used to test the difference between the treatment groups, NT 201 and placebo ($\alpha = 5\%$, 2-sided). The key secondary endpoints will be tested with ANCOVA models similar to that for the primary analysis of the primary endpoint.

Frequency tables based on the safety evaluation set for the unilateral treatment period and on the safety evaluation set for the bilateral treatment period will be provided for incidence of related TEAEs.

2 STUDY ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	Function	Address
Merz Pharmaceuticals GmbH	Sponsor	Eckenheimer Landstrasse 100 60318 Frankfurt/Main Germany Telephone: +49-69-1503-0
[redacted]	Clinical project manager	Telephone: +49-69-1503-[redacted] Email: [redacted]@merz.de
[redacted]	Medical expert	Telephone: +49-69-1503-[redacted] Email: [redacted]@merz.de
[redacted]	Biostatistician	Telephone: +49-69-1503[redacted] Email: [redacted]@merz.de
[redacted]	Product Safety Officer	Telephone: +49-69-1503-[redacted] Email: [redacted]@merz.de
[redacted]	Regulatory affairs manager (USA)	Telephone: +1-919-[redacted] Email: [redacted]@merz.com
[redacted]	Regulatory affairs manager (EU/RoW)	Telephone: +49-69-1503-[redacted] Email: [redacted]@merz.de

2.2 External responsibilities

The administrative structure for external responsibilities includes, but is not limited to, the following participants:

Name	Function	Address
[redacted], MD	Overall coordinating investigator	Icahn School of Medicine at Mount Sinai Dept. of Neurology, Box 1052 New York, NY 10029 United States of America Telephone: 212 [redacted] Telefax: 212 [redacted] Email: [redacted]
Metronomia Clinical Research GmbH	Data management/ Electronic case report form [eCRF]/ Biostatistics	Paul-Gerhardt-Allee 42 81245 München, Germany Telephone: +49 89 [redacted] Telefax: +49 89 [redacted] Email: info@metronomia.net
Pharmaceutical Research Associates GmbH (PRA Health Sciences)	Clinical Research Organization (CRO), Monitoring, Adverse Event (AE) reporting	Gottlieb-Daimler-Straße 10 68165 Mannheim, Germany Telephone: +49 621 87 [redacted] Telefax: +49 621 87 [redacted] For Safety only: FAX: USA and Canada: +1 888 [redacted] or +1 434 [redacted] Europe: +44 [redacted] Email (all countries): [redacted]@prahs.com
Tremor Research Group (TRG) Contacts: [redacted], prior President [redacted] President	Provision of TETRAS related services (license, training, independent expert, independent rater panel)	3627 Drummond Street Houston, Texas 77025 United States of America
MDDT Inc. Contact: [redacted] General Manager	Provision of TremorTek® related services (license, hardware, software, training, quality control)	488 Sunnyside Crescent London, Ontario, Canada N5X 3N7 Telephone: +1 519 [redacted] Email: [redacted]@mddtinc.ca
Almac Clinical Technologies LLC	Interactive web response system (IWRS) services	Almac Clinical Technologies LLC PA 18964 Souderton United States of America Telephone: +1 215 [redacted] Telefax: +1 215 [redacted] Email: info@almacgroup.com

Name	Function	Address
Almac Clinical Services Ltd.	Drug management	Almac Group, 9 Charlestown Road, Seagoe Industrial Estate Craigavon, BT63 5PW Northern Ireland, United Kingdom Telephone: +44 28 [redacted] Email: [redacted]@almacgroup.com
Infraserv GmbH & Co. Höchst KG Geschäftsfeld Umwelt/ Sicherheit/Gesundheit Arbeitsmedizinisches Zentrum	24 hours emergency unblinding service and hotline	Gebäude D 810 – Zimmer 122 Industriepark Hoechst 65926 Frankfurt am Main, Germany Telephone: +49 69 305 [redacted] Telefax: +49 69 305 [redacted]
Canfield Scientific, Inc.	Standardized Videography Services	4 Wood Hollow Road Parsippany, NJ, 07054 United States of America Telephone: +1-800-[redacted] Email: [redacted]@CanfieldSci.com
Medpace, Inc.	Central Laboratory	5375 Medpace Way Cincinnati, Ohio 45227 United States of America Telephone: +1 513 [redacted] Email: info@medpace.com

For a description of the independent TETRAS expert and independent TETRAS rater panel, see Section 12.4.7.4.

2.3 Committees

One independent The Essential Tremor Rating Assessment Scale [TETRAS] expert will, in addition to the investigator's assessment, assess a diagnosis of UL ET (see inclusion criterion no. 5). The independent assessment will be based on the review of standardized video recordings of the subjects completing the TETRAS Performance subscale at screening (V1).

In addition, an independent rater panel [IRP] will retrospectively score TETRAS based on standardized per-subject videos of assessment. Videos from the screening (V1), study baseline (V2), and Week 6 control (V4) visits of the unilateral treatment period will be recorded and assessed by the IRP accordingly.

A description of the scope of work and operating procedures for the IRP will be provided in a separate charter. See also Section 9.1.1.2.2 and Section 12.4.7.4.

3 ETHICS

3.1 Independent Ethics Committee/Institutional Review Board

The following documents must be submitted to the responsible independent ethics committee [IEC]/institutional review board [IRB] and approval obtained:

- The clinical study protocol;
- Any amendment to the clinical study protocol that is not solely of an administrative nature;
- The current investigator's brochure [IB] and all updates;
- Subject information and informed consent forms [ICFs], as well as updates (if applicable);
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable);
- Other documents given to the subject; and
- Information on site qualification.

If applicable, and in accordance with local legal requirements, the above documents also may be submitted to the respective regulatory authority(ies) for separate approval.

3.2 Ethical conduct of the study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation [ICH]-good clinical practice [GCP] and applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the study.

3.3 Subject information and informed consent

3.3.1 Subject information

Prior to study enrollment, the subject will be given full verbal and written information on the nature, objective, significance, expected benefits, potential risks, and expected consequences of the study. This verbal and written information will be provided by the investigator (or authorized designee) according to the provisions set forth in the Declaration of Helsinki. The obligations of the investigator are set forth in the clinical study protocol, the ICH-GCP principles (ICH E6 (R2), effective in US since 01-MAR-2018, in Canada since 03-APR-2019, and in the European Union since 14-JUN-2017), and the

respective national regulations governing medical research and experimentation on humans.

Each subject will have the opportunity to question the investigator (or authorized designee) about the study prior to giving consent.

For country-specific requirements, see Section 16.1

3.3.2 Informed consent

Informed consent will be obtained in writing directly from the subject.

A subject who can understand the content of the informed consent and agrees to participate has also to have the ability to write (as clinical study assessments also require handwriting abilities, e.g. Section 9.1.1.2.2). The procedure of signing and dating of the informed consent by an impartial witness is thus not allowed in the current study.

The consent must be confirmed by the investigator (or authorized designee in accordance with local requirements) who conducted the informed consent briefings. The informed consent process must be traceable from the available documentation. At a minimum, this documentation should include information about when the subject was first informed about the study and who supplied the information. The subject will be given a copy of the signed and dated written ICF as well as all consent form updates (if applicable).

During the course of the study, the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study. In case of AEs, or poor tolerability to the investigational product [IP], the subject should inform the investigator, who then will make a judgment whether continuing in the study serves the subject's best interests. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

3.3.3 Subject card

A subject card will be given to all subjects, who will be instructed to keep it in their possession at all times. The subject card will contain the following printed information:

- The name, address, and telephone number of the investigator or institution, as the main contact for product information and emergency unblinding;
- Information that the subject is taking part in a clinical study conducted with *Botulinum* toxin type A [*BoNT* A]; and
- A 24-hour hotline number for emergencies.

3.3.4 Post-study treatment

In accordance with the Declaration of Helsinki, every subject is entitled to the following post-study treatment:

No specific post-study arrangements will be made and no specific post-study care will be performed after this study. The subject may consult his/her physician for treatment options and receive medication to reduce the subject's ET at the investigator's discretion. This also applies to subjects who discontinue the study prematurely.

3.3.5 Subject privacy

The subject will be informed of procedures to protect subject privacy. Although recorded data will be passed on in a pseudonymized version only to authorized individuals, re-identification by the investigator (e.g. in case of emergencies) will be possible by the specific number assigned to the subject, see Section 8.2.1. Access to non-pseudonymized data will be allowed solely to check validity, and such access will be limited strictly to authorized individuals (e.g. the sponsor or individuals authorized by the sponsor, auditors, regulatory authorities, or members of IECs/IRBs) who have been bound to confidentiality. If the results of the study are published, the subject's identity will remain confidential.

The Sponsor will be responsible for all biological samples (e.g. blood samples) taken during the clinical study. The Sponsor may contract third parties to provide services for subject's biological samples, however it will oblige such service providers to keep all data confidential and to adhere to applicable data protection laws. The samples will be used for purposes of this study as described in this clinical study protocol only. Subject's blood samples will be labelled and stored in pseudonymized form (e.g. without subject's name or initials). Any remaining biological samples will be destroyed when the clinical study has finished.

Subjects will consent in the ICF to video recording of their TETRAS Performance. Further details will be described in a separate manual.

3.3.6 Contact point

All subjects will be provided in the subject informed consent form with a contact address where they may obtain further general information regarding this clinical study.

3.4 Insurance

From the beginning of the study until its termination, each subject is insured against any health impairment occurring as a result of participation in the study in accordance with the laws and regulations of the country in which the study is performed.

The subject will be informed by the investigator and through the subject's ICF about the existence of this insurance and the resulting obligations. The insurance documents will be handed out to the subject, if requested or if required by local law.

Any medical or non-medical deviation from the clinical study protocol that is deemed to have occurred through the subject's own fault may not be covered by this insurance.

The sponsor is usually not liable for injuries/cases of death that occur solely as a consequence of the subject's underlying disease or condition, or from diagnostic or therapeutic measures not specifically required by the clinical study protocol. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical study staff, and/or CRO, including failure to act according to ICH-GCP principles or to comply strictly with the clinical study protocol.

3.5 Financing

The financial aspects of the study will be documented in an agreement between the sponsor, the CRO, and each investigator or any other involved party, and must be confirmed in writing before the study commences.

4 INTRODUCTION

4.1 Study background

4.1.1 Disease background

Tremor is characterized by involuntary rhythmic oscillations of a part of the body around one or more joints. It can be attributed to various causes and many different types of tremor are known [Hess 2012].

While the tremor of Parkinson's Disease predominantly occurs at rest, ET is typically characterized by a slowly progressing symmetrical action tremor which is triggered or intensified by intentional use of the muscles of the affected body part including specific postures. While it may affect neck, vocal cord or lower limb muscles, the tremor of ET most typically affects the muscles of the upper limb. It is most prominent in the hands, with initially low amplitudes that can increase dramatically as the disease progresses, and with medium to high frequency (4 to 12 Hz) that decreases with increasing age [Hess 2012].

Recent classification by the International Parkinson and Movement Disorder Society [Bhatia 2018] defines tremor syndromes in distinct clinical entities based on the predominant presenting symptoms and additional signs. According to this classification ET is manifested as bilateral UL action tremor, with or without tremor in other locations such as the head, voice or lower limbs. It is typically not associated with additional neurological signs such as dystonia, ataxia, or parkinsonism and is characterized by a stable clinical appearance without sudden onset or stepwise deterioration. A definitive diagnosis of ET requires presence of its characteristic features for at least 3 years.

ET is the most common movement disorder. The severity of ET, and the disability and burden to the subject that it entails, varies greatly: Mild tremor brings about negligible disability, while a severe bilateral tremor can impede significantly, and even prevent completely, the pursuit of normal activities of daily life [Louis 2013, Rajput 2004].

As ET and Parkinson's Disease tremor occur mostly in the same age groups, and as both tremor types share clinical features, both disorders may be confounded; criteria for the distinction of these two have been published [Thenganatt 2012].

Existing therapies against tremor all have important shortcomings and do not sufficiently address the treatment needs of many patients. Standard drug treatments, used both on-label and off-label, are oral propranolol (approved for treatment of essential tremor e.g. in the US and Europe) and primidone (approved in the EU), alone or in combination. However, only approximately 50%–60% of subjects respond to these treatments [Deuschl 2012]. Furthermore, they are associated with a considerable rate of adverse events [AEs] leading to withdrawal of treatment (e.g. bradycardia, hypotension, sedation, nausea, ataxia, or confusion) [Ferreira 2019]. In a recent evidence-based review performed by the

International Parkinson and Movement Disorder Society [Ferreira 2019], propranolol and primidone, as well as topiramate at doses of more than 200 mg per day, were classified as clinically useful for the treatment of limb tremor in ET. Alprazolam and *BoNT* A, as well as unilateral ventralis intermedius thalamic deep brain stimulation, radiofrequency thalamotomy, and magnetic resonance imaging-guided focused ultrasound thalamotomy were considered possibly useful.

Furthermore, there are ongoing discussions that beta blockers like propranolol may play a causative role in Parkinson´s disease, which could limit their chronic use in ET in the future [Mittal 2017]. Deep brain stimulation is a powerful but invasive treatment option and can be associated with stimulation-induced and long-term side effects (ataxia, dysarthria, paresthesias, tonic muscle contractions, and impaired balance). Similarly, functional lesional (ablative) neurosurgery like magnetic resonance imaging-guided high frequency ultrasound thalamotomy is effective but induces permanent lesions in the brain with potentially serious adverse effects like postoperative paresthesia or numbness (in 38% of participants) and gait disturbance (in 36%) [Haubenberger 2018]. Both treatment modalities are only available at highly specialized neurosurgery centers to subjects whose tremor is severely incapacitating.

Botulinum neurotoxin [*BoNT*] has been reported as having good efficacy with some local side effects in UL tremor and the main advantage over above mentioned therapies being the lack of systemic side effects, see Section 4.1.2.

4.1.2 Botulinum toxin in essential tremor

Since the first observation of possible efficacy of *BoNT* A in the indication of ET [Jankovic 1991], little research has been conducted into this topic. A 2011 update of the American Academy of Neurology treatment guidelines for ET reported that, in the interval since the previous guidelines, new studies providing evidence above Class IV on the efficacy or safety of *BoNT* A for the treatment of ET had not been conducted [Zesiewicz 2011]. Consequently, the guidelines continued their assessment of *BoNT* A as a 'Level C, possibly effective' treatment for ET. The same conclusion was reached in another review [Deuschl 2011], which identified only two double-blind placebo-controlled parallel-design studies of *BoNT* A for the treatment of people with essential hand tremor: the afore mentioned Jankovic study [Jankovic 1996] comparing 50 U (plus an optional booster injection of 50 U after 4 weeks) of onabotulinumtoxinA with placebo, and another larger similarly designed confirmatory study [Brin 2001] in which subjects were randomized to either low-dose (50 U) or high-dose (100 U) onabotulinumtoxinA or placebo. Only the wrist flexors and extensors were injected in both these studies, with flexors receiving 60% of the dose and extensors 40%, and patients were followed up for 16 weeks.

In the second trial, the effect of treatment was assessed by clinical rating scales, measures of motor tasks and functional disability, and global assessment of treatment. Hand strength was evaluated by clinical rating and by a dynamometer. While both doses of botulinum toxin type A significantly reduced postural tremor on the clinical rating scales after 4, 6,

12 and 16 weeks, kinetic tremor was significantly reduced only at the 6-week examination. Measures of motor tasks and functional disability were not consistently improved with botulinum toxin type A treatment. Grip strength was reduced for the low- and high-dose botulinum toxin type A groups as compared with the placebo group. Adverse reactions consisted mainly of dose-dependent hand weakness. The authors concluded that *BoNT* A injections for ET of the hands resulted in significant improvement of postural, but not kinetic, hand tremors and resulted in limited functional efficacy. Hand weakness was found to be a dose-dependent significant side effect of treatment at the doses used in this study [Brin 2001]. The ET therapeutic indication development was consequently not further pursued by the sponsor company.

More recently, a study by Rahimi et al. described the use of *BoNT* A (incobotulinumtoxinA, NT 201) in the treatment of UL tremor in seven patients with Parkinson disease using kinematics-guided dosing and concluded that the treatment offered a viable management option [Rahimi 2013]. In a number of further smaller clinical trials conducted by the same group with kinematics-guided dosing of NT 201, improvement in clinical and kinematic assessments of ET as well as good tolerability were reported. These observations were made in patients with unilateral ET after two consecutive injections [Samotus 2016] and after four consecutive treatments and observation over 96 weeks [Samotus 2018], as well as in patients with bilateral ET [Samotus 2019].

Another recent study reviewing longitudinal experience with onabotulinumtoxin A injections for medically refractory hand tremor, including 53 of 91 subjects with ET, concluded that the injections were safe and led to clinically meaningful and sustained improvement of hand tremor in this mixed patient population [Niemann 2018]. Also, the above-mentioned International Parkinson and Movement Disorder Society review assessed *BoNT* A as possibly useful for UL ET therapy [Ferreira 2019].

Furthermore, the sponsor has previously conducted a small (n=30) placebo-controlled study (MRZ60201-2094-1) [Merz Pharmaceuticals GmbH 2017] to assess the feasibility of using customized doses of NT 201 to treat ET. The results of this study were generally positive combined with a favorable safety profile [Jog 2017] . The flexible dosing used in this trial informed the semi-flexible dose setting in the present study.

4.1.3 Investigational product

NT 201 (active ingredient: NT 101, *BoNT* A, free from complexing proteins, US Adopted Name [USAN] incobotulinumtoxinA) or matching placebo (human serum albumin plus sucrose, in the unilateral treatment period) provided in 200 U vials.

BoNT A is produced by fermentation of the anaerobic bacterium strain *Clostridium botulinum* as part of a high-molecular-weight protein heterocomplex. *BoNT* A acts selectively on peripheral cholinergic nerve endings, inhibiting the release of the neurotransmitter acetylcholine, and thus reduces muscle tone by local and slowly reversible paralysis. NT 201 (Xeomin®, USAN incobotulinumtoxinA, Merz), along with other *BoNT*

A preparations such as Botox® (USAN onabotulinumtoxinA, Allergan) and Dysport® (USAN abobotulinumtoxinA, Ipsen), as well as the *BoNT* B product Myobloc® (USAN rimabotulinumtoxinB; Solstice Neurosciences) /Neurobloc® (Eisai in Europe), have been granted approval in many countries for a number of indications including cervical dystonia, blepharospasm and upper-limb spasticity.

The study product, NT 201, is the only marketed *BoNT* A preparation that is free from complexing proteins. In animal models, NT 201 did not show any detectable immunogenicity [Jost 2007]. In repeated-dose studies performed in 564 adults with UL spasticity, no subject developed secondary clinical non-responses to NT 201 because of neutralizing antibodies [Merz Pharmaceuticals GmbH 2019].

4.2 Study rationale

As described in Section 4.1.1, existing therapies against tremor are unsatisfactory for many patients. Treatment with *BoNT* A may have advantages, especially due to its local effect, which specifically targets UL muscles affected by ET.

Earlier clinical studies using fixed doses of onabotulinumtoxinA had shown that the treatment effectively reduced the tremor, but efficacy was often compromised by significant muscle weakness at the wrist [Brin 2001, Jankovic 1991, Jankovic 1996]. A recent approach claimed satisfactory efficacy and improved tolerability by having administered onabotulinumtoxinA at customized dosages [Jankovic 2018, Niemann 2018] to the wrist flexor muscles only, based on landmark-guided injections and in an open-label study design. Other users of customized dosing emphasize the importance of injecting also the shoulder and elbow muscles and advocate the use of kinematics-guided dosing to optimize treatment of ET [Samotus 2018, Samotus 2019].

The sponsor has already performed a small (N = 30) exploratory, placebo-controlled Phase 2 study investigating the safety and efficacy of unilateral treatment with NT 201 for the treatment of essential upper limb tremor over a period of 24 weeks [Jog 2017, Merz Pharmaceuticals GmbH 2017]. Superiority of NT 201 over placebo was demonstrated for kinematically measured angular and accelerometric tremor amplitude at the wrist, on the FTM (Fahn-Tolosa-Marin) Part B motor performance tremor rating, and on the investigator's global impression of change (GICS), mostly at four and eight weeks after injection. The safety analysis revealed no new or unexpected safety concerns. Kinematic measurements conducted with TremorTek® were also used to select UL muscles for the treatment and to determine the dose.

The present study is based on the learnings from the previous study [Jog 2017, Merz Pharmaceuticals GmbH 2017] as well from other studies with *BoNT* A. It seeks to overcome limitations from previous studies and provide a more generalizable approach to dosing, without use of kinematic measurements for determination of muscles and dose. The prospective and placebo-controlled design is expected to generate high-quality data

that are expected to become the foundation of a more evidence-based approach to *BoNT* A treatment of ET.

The primary efficacy endpoint will again be measured kinematically with the TremorTek® device, a sensitive, specific, objective measure of tremor amplitude at multiple joints which provided reliable data in the previous study. Tremor kinematics will be complemented by the more ET-specific TETRAS scale, which otherwise builds on the FTM scale and includes ADL and performance subscales. Measures of investigator's and subject's global outcomes as well as HRQOL and general QOL scales will also be included. This study will be conducted according to current standards of clinical research and is expected to provide relevant efficacy and safety information to support an indication for NT 201 in male and female adults with UL tremor. [redacted]

4.3 Risk-benefit assessment

The existing data on the intramuscular administration of *BoNT* A in general, and of NT 201 in particular, suggest that the treatment to be administered in the current study will not represent a significant risk to the study subjects.

As of October 2019, 25 clinical studies investigating neurological indications have been completed, where a total of 3,987 subjects were exposed to NT 201 in doses up to 800 U per injection session [Wissel 2017]. The neurological and aesthetic study programs have demonstrated the efficacy and safety of NT 201 in various indications. In five clinical studies sponsored by the sponsor, more than 900 adult subjects with UL spasticity have been exposed to NT 201. The total body doses proposed in the current study (up to 165 U per UL, up to 330 U per subject for both ULs) will not exceed the already approved dose for UL spasticity (500 U in the European Union, 400 U in the United States).

The potential benefits of NT 201 in patients with ET have been clearly demonstrated in the placebo-controlled Study MRZ60201-2094-1 [Jog 2017, Merz Pharmaceuticals GmbH 2017], in which significant improvements in FTM Part B motor performance and wrist tremor amplitude were observed, in the absence of treatment-limiting side effects. Adverse drug reactions reported in the NT 201 group were muscular weakness (finger weakness) in two subjects (10.5%) and injection site bruising and injection site pain in one subject each, all of mild intensity. No subject in the NT 201 group had a serious adverse event or an adverse event leading to study discontinuation.

Placebo-treated subjects are expected to receive no objective additional benefit during the unilateral treatment period. However, comparison with a group of subjects treated with placebo allows the most scientifically reliable conclusions on the effect of the investigational drug. To reduce the required overall number of subjects exposed to placebo, a 2:1 randomization is foreseen. Furthermore, during the bilateral treatment period, all subjects, including those who previously received placebo, will receive NT 201. Thus, all subjects who continue into the bilateral treatment period are expected to receive therapeutic

benefit during the study. Subjects who are already on a stable concomitant anti-tremor medication are allowed to be included into the trial and are expected to continue with their medication throughout the study, providing continuing basic coverage. Additional risks that may arise in case of a public health emergency, e.g., due to a COVID-19[3] outbreak, may affect the clinical study conduct. In such a case it is the priority to ensure the safety and well-being of the participating subjects as described in the respective protocol sections (e.g. Section 6.1, 7.5.4, 9.1.1.1, 9.2 or 11.2). For example, the study might be halted, recruitment interrupted, and/or study processes and flow might be modified with impact to the study duration/visit schedule depending on the current study status. In conclusion, the sponsor believes that this study is designed in such a manner as to minimize risks and to maximize potential benefits for the subjects suffering from ET in the UL.

[3] All general measures and definitions described in this protocol as related to SARS-CoV-2 or a COVID-19 outbreak also apply to any possible future coronavirus outbreaks or other public health emergencies that threaten the safety of patients and investigators.

5 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of unilateral intramuscular injections of NT 201, as compared with placebo, in subjects with ET of the UL.

Secondary objectives are the following:

Safety of unilateral intramuscular injections of NT 201, as compared with placebo, in subjects with ET of the UL.

Efficacy and safety of bilateral intramuscular injections of NT 201 in subjects with ET of the UL.

6 INVESTIGATIONAL PLAN

6.1 Overall study design

Summary of study design

This multicenter study will be conducted according to a prospective, randomized, double-blind, placebo-controlled, parallel-group design followed by an open-label treatment period.

The study consists of a screening period, a double-blind unilateral treatment period (Cycle 1, V2 to V8), and a subsequent open label bilateral treatment period (Cycle 2, V8 to V11).

The study will start with the screening visit (V1) which will be performed between 21 and 3 days prior to the study baseline visit (V2) of the unilateral treatment period (Cycle 1). At V2, eligible subjects will be randomized to one of two treatment groups, NT 201 or placebo, with a randomization ratio of 2:1. An unilateral intramuscular injection of 130 to 165 U of NT 201 or placebo will be administered into the muscles of the motor dominant UL, according to a semi-flexible dosing scheme, see Section 8.2.2 and Section 8.2.3. Subjects will be followed up until the end-of-Cycle 1 visit V8 at Week 24 after injection.

At V8, subjects will be checked for eligibility to participate in the subsequent open-label bilateral treatment period (Cycle 2). If eligibility criteria for reinjection are met, subjects will receive total doses of 130 to 165 U NT 201 per UL, resulting in a total dose of 260 to 330 U for bilateral treatment. These subjects will be followed up until the end-of-study visit V11 at Week 12 after reinjection.

An overview of the study design is provided in Figure 1, for the visits schedule, see Section 9.2.

Tremor intensity will be assessed by angular tremor amplitude measurement at the shoulder (flexion/extension, adduction/abduction), elbow (flexion/extension), and wrist level (flexion/extension, radial deviation/ulnar deviation, pronation/ supination), using a standardized computerized kinematic tremor assessment, see Section 9.1.1.2.1.

This study is planned to be performed at approximately 15 sites in North America (USA and Canada) and in Europe (Poland).

In case of a public health emergency, e.g. due to a COVID-19 outbreak, the study might be halted, recruitment interrupted, and/or study processes and flow might be modified with impact to the study duration/visit schedule depending on the current study status (see also Section 7.5.4 and 9.2). This may further include, but is not limited to, extending visit windows, performing visits remotely by phone for efficacy and safety assessments (Section 9.1.1.1), or restart of study activities for subjects after halt (Section 7.4.1 and Section 9.2.).

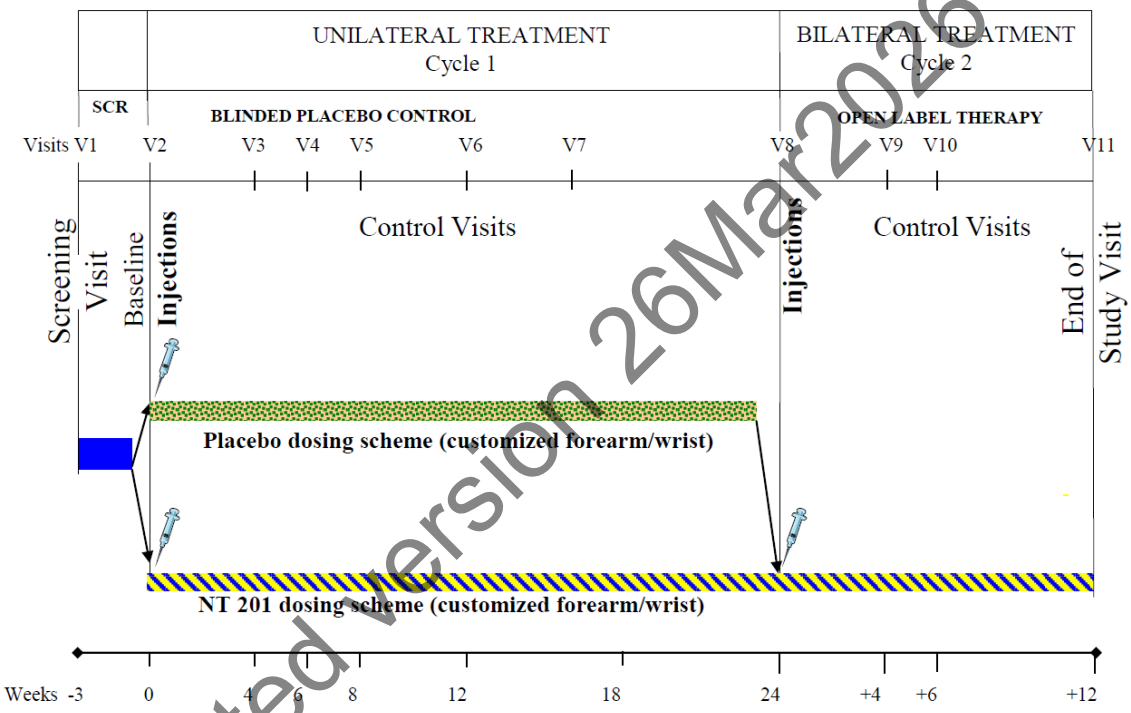
6.1.1 End of study

The end of study is defined as the last study visit of the last subject.

6.1.2 Study flow chart

The study flow chart is shown in Figure 1.

Figure 1: Study Flow Chart



V = Visit; SCR = Screening

6.2 Discussion of study design, including choice of control groups

Randomization, blinding, and placebo control

The double-blind, randomized, placebo-controlled design of the unilateral treatment period (Cycle 1) has been chosen to obtain scientifically robust efficacy and safety data on NT 201 in a representative sample of subjects with ET, while avoiding the risk of any bias by the subject or investigator. This study is designed to provide Class I evidence as defined by the American Academy of Neurology. A superiority study with a placebo control is valid for efficacy and safety and represents the state of the art.

Treatment allocation to NT 201 and placebo in the unilateral treatment period will be performed according to a 2:1 (NT 201: placebo) randomization scheme to limit the number of subjects treated with placebo. Placebo-treatment in a third of enrolled subjects is considered as justified because currently used oral medications are associated with various safety -related drawbacks and limited efficacy. Furthermore, subjects who wish to continue their existing oral anti-tremor medication will be allowed to do so provided that the dose will be kept stable during the study.

During the bilateral treatment period, all subjects will be administered active treatment, from which they are expected to benefit. Eligibility for reinjection will be assessed before subjects enter the bilateral treatment period.

Duration of treatment

NT 201 or matching placebo will be injected into each subject's motor dominant UL on Day 1 (V2) of the unilateral treatment period (Cycle 1). After a 24-week observation period, eligible subjects will receive another NT 201 injection into both ULs on Day 1 (V8) of the bilateral treatment period (Cycle 2), followed by a 12-week observation period.

The duration of observation following administration of NT 201 was chosen on the basis of the predecessor study [Jog 2017, Merz Pharmaceuticals GmbH 2017], in which wrist tremor amplitude reduction was observed until 24 weeks after injection with NT 201. The current study also aims to follow up subjects in the unilateral treatment period for 24 weeks. That period is deemed sufficiently long to allow for reinjection and to investigate individual differences in duration of response. An observation period of 12 weeks after reinjection (the typical injection interval with NT 201 in approved therapeutic indications) is considered sufficient for follow-up of safety and efficacy well beyond peak effects. No further reinjection is planned after completion of the study.

7 STUDY POPULATION

7.1 Selection of study population

The study population will consist of approximately 75 subjects, i.e. approximately 50 subjects in the NT 201 group, approximately 25 subjects in the placebo group. Study subjects (male and female adults) will be recruited according to criteria based on whether they have a relevant medical condition requiring study treatment, and whether they do not have a medical condition or other circumstance that might interfere with the conduct or result of the study or endanger the safety of the subject. NT 201 will either be added on to previous tremor treatment or will be given as standalone medication.

In this study the diagnosis of ET will be established considering key criteria of the Task Force on Tremor of the International Parkinson and Movement Disorder Society [Bhatia 2018]. The diagnosis must have been made or confirmed by a neurologist.

No stratification or selective recruitment by gender, age or race/ethnicity will be performed. Therefore, the distribution of these demographic characteristics in this study is expected to reflect their distribution in the general population.

7.2 Inclusion criteria

Only subjects meeting all of the following inclusion criteria at the screening (V1) and/or study baseline (V2) visit (as indicated below) will be considered for study enrollment:

Inclusion Criteria	Rationale	Screening	Baseline
1. Written informed consent obtained from the subject.	Administrative	X	
2. Understanding of study procedures and willingness to abide by all procedures during the course of the study.	Administrative	X	
3. Male and female adults (≥ 18 years) suffering from ET as follows: • Isolated tremor syndrome with bilateral UL action tremor, • At least three years duration before enrollment in the study, • With or without tremor in other locations (e.g. head, voice, or lower limbs), • Documentation of the diagnosis by a neurologist.	Efficacy	X	X
4. Following TETRAS Performance subscale criteria as assessed by the investigator: Score of ≥ 2 (at least 1 cm tremor amplitude) in at least two out of three maneuvers of test item 4 (forward outstretched postural tremor, lateral 'wing beating' postural tremor, kinetic tremor). To be confirmed for both ULs separately.	Efficacy	X	X

Inclusion Criteria	Rationale	Screening	Baseline
5. Confirmation of inclusion criterion no. 4 at screening visit V1 by an independent TETRAS expert via video assessment according to the following TETRAS Performance subscale criteria: Score of ≥ 2 (at least 1 cm tremor amplitude) in at least two out of three maneuvers of test item 4 (forward outstretched postural tremor, lateral 'wing beating' postural tremor, kinetic tremor). To be confirmed for both ULs separately.	Efficacy	X	
6. Fulfilment of all following TETRAS ADL subscale criteria: • A score of ≥ 1 (slight) in at least five of the items 2 to 9, • A score of ≥ 3 (moderate) in at least two of the items 2 to 9, • A sum score of ≥ 9 in items 2 to 9.	Efficacy	X	X
7. Ability to perform all four tasks during the kinematic tremor assessment and to complete all assessments of the TETRAS.	Efficacy	X	X
8. Visible tremor at wrist level in at least one of the four tasks used in the kinematic tremor assessment of the motor dominant UL.	Efficacy	X	X
9. Clinical need for study treatment of tremor (including mandatory injections in forearm/wrist, elbow, and shoulder muscles) of both ULs (deemed potentially beneficial to the subject by the investigator).	Efficacy, safety	X	X

Inclusion Criteria	Rationale	Screening	Baseline
10. Stable concomitant anti-tremor medication, if any, at least 4 weeks before screening and with no change expected until the end of the study (beta-adrenergic blockers, primidone, gabapentinoids, benzodiazepines, topiramate, all other antiepileptics, centrally acting muscle relaxants for the treatment of tremor).	Efficacy, safety	X	
11. Woman of childbearing potential[4] must be using a highly effective method of birth control[5] and must be willing to continue using this during the entire study period.	Safety	X	X
12. Negative result in a pregnancy test.	Safety	X	X

7.3 Exclusion criteria

Subjects meeting any of the following criteria at the screening (V1) and/or at the study baseline (V2) visits (as indicated below) will not be included in this study:

Exclusion Criteria	Rationale	Screening	Baseline
1. History or presence of day-to-day fluctuations in ET which would jeopardize meaningful tremor assessment over time, e.g. severe tremor on one day and minimal or no tremor on another day.	Efficacy	X	X

[4] Childbearing potential is defined as neither premenarche, nor permanently sterilized nor postmenopausal (i.e. 12 months with no menses without an alternative medical cause).

[5] Defined as a method that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.

Exclusion Criteria	Rationale	Screening	Baseline
2. Other neurological signs, such as dystonia, ataxia, or parkinsonism, which in the judgment of the investigator could interfere with the ET diagnosis and/or assessment of ET in ULs.	Efficacy	X	X
3. Tremor types other than ET (e.g. orthostatic tremor, task- and position specific tremors).	Efficacy	X	
4. Sudden onset and stepwise deterioration of tremor.	Efficacy, safety	X	X
5. Exposure to the following tremorgenic drugs: lithium, valproate, amiodarone, typical and atypical neuroleptics within six months prior to the screening visit (V1) or during the study. Exposure to other than the listed tremorgenic or potentially tremorgenic drugs is allowed only if, in the opinion of the investigator, this would not interfere with the study drug evaluation. In these cases, a stable medication has to be reached four weeks before the screening visit (V1) and intended to be maintained for the time during the study.	Efficacy	X	
6. Trauma to the central nervous system or the nerves of the ULs within the three months preceding the onset of tremor.	Efficacy, safety	X	
7. Body weight < 50 kg.	Safety	X	
8. Severe atrophy of the ULs.	Efficacy, safety	X	

Exclusion Criteria	Rationale	Screening	Baseline
9. Evidence of functional tremor (psychogenic origin of tremor) or other secondary causes of tremor, that in the judgment of the investigator may have an influence on the tremor symptoms (e.g., hyperthyroidism, hyperparathyroidism, hypocalcemia, hypoglycemia, renal insufficiency, vitamin B12 deficiency, multiple sclerosis, Parkinson's disease and other types of parkinsonism, anxiety, emotional stress, or exhaustion).	Efficacy	X	
10. Any evidence or reasonable suspicion of current alcohol or substance abuse, or addiction with, in the opinion of the investigator, impact on ET symptoms or impact on the subject´s participation in the study/with the assessment procedures.	Efficacy, safety	X	
11. Subject not fully stabilized after deciding to undergo withdrawal from any substance potentially interfering with the clinical presentation of tremor (e.g., nicotine, alcohol, other recreational drugs, performance-enhancing drugs, pain-killers, etc.).	Efficacy	X	
12. Any prior or planned surgery or invasive treatment to treat tremor (e.g., thalamotomy, deep brain stimulation surgery, magnetic resonance imaging-guided high frequency ultrasound therapy).	Efficacy, safety	X	
13. Treatment with any *BoNT* product for any reason less than 16 weeks preceding the study baseline visit (V2) in this study or planned for any time during the entire study period.	Efficacy, safety	X	

Exclusion Criteria	Rationale	Screening	Baseline
14. Previous surgery of the ULs within less than 12 months prior to the screening visit (V1) or any concomitant disease or condition or therapy in ULs that, in the investigator's opinion, might influence the study outcome.	Efficacy, safety	X	
15. Inability of the subject to abstain from tobacco use 1 hour prior to assessments.	Efficacy	X	
16. Previous treatment with phenol- or alcohol injections into the ULs or scheduled for any time during the study.	Efficacy, safety	X	
17. Concurrent use of antibiotics that interfere with neuromuscular transmission, such as aminoglycoside antibiotics (e.g., streptomycin sulphate, kanamycin sulphate, gentamicin sulphate, neomycin sulphate, spectinomycin hydrochloride), polypeptide antibiotics (e.g. polymixin B sulphate), lincomycin antibiotics (e.g. lincomycin hydrochloride, clindamycin), or enviomycin sulphate.	Efficacy, safety	X	
18. Treatment with parenterally administered drugs that interfere with neuromuscular transmission (e.g., intrathecal baclofen, tubocurarine-type muscle relaxants used in anesthesia), aminoquinolines, or local anesthetics in the treated region within 2 weeks before the screening visit (V1) or intended to be administered during the study.	Efficacy, safety	X	
19. Generalized disorders of muscle activity (e.g., myasthenia gravis, Lambert-Eaton-Syndrome, amyotrophic lateral sclerosis) or any other significant peripheral neuromuscular dysfunction which might interfere with the study.	Efficacy, safety	X	

Exclusion Criteria	Rationale	Screening	Baseline
20. Ongoing severe or uncontrolled disease, that, in the judgment of the investigator, may put the subject at significant risk, may interfere with the study, or may impede completion of the study including current malignancy (except basal cell carcinoma or squamous cell carcinoma).	Safety	X	
21. Clinically relevant pathological findings in laboratory parameters, indicating active disease of vital organs.	Safety	X	
22. Subject with an implanted electronic device that might interfere with or be influenced by the electromyography and/or electrical nerve stimulation.	Safety	X	
23. For subjects receiving anticoagulation therapy, the investigator confirms and documents that the subject has an: • aPTT time > 80 seconds (subjects on dabigatran, other direct thrombin inhibitors, factor Xa inhibitors, heparin and heparinoids) or • INR value of > 2.5 (subjects on coumarins or other anticoagulants monitored by INR).	Safety	X X	X
24. Pregnancy (as verified by a positive pregnancy test) or breast feeding.	Safety	X	X
25. Known hypersensitivity to human serum albumin, sucrose, or the active substance *BoNT* A.	Safety	X	X
26. Infection or inflammation in the area of the planned injection points.	Safety		X
27. Subject who is imprisoned or is lawfully kept in an institution.	Administrative	X	

Exclusion Criteria	Rationale	Screening	Baseline
28. Participation in any other clinical study within four weeks prior to the screening visit (V1).	Safety	X	
29. Previous participation in this study (i.e. study treatment received). Rescreening is allowed once.	Administrative	X	
30. Subject is an employee, relative, or spouse of the investigator, other staff of the investigational site, the sponsor, or the CRO.	Administrative	X	
31. Any factor that in the investigator's opinion is likely to compromise the subject's ability to participate in the study.	Safety	X	X
32. Evidence or suspicion that the subject might not comply with the requirements of the study and/or that he/she is not sufficiently reliable or trustworthy to be entrusted with participation.	Efficacy, safety	X	
33. Evidence or suspicion that the subject is unwilling or unable to understand the information that is given to him/her as part of the informed consent process, in particular regarding the risks and discomfort to which he/she would agree to be exposed.	Safety	X	
34. Subjects who, in the clinical judgment of the investigator, show suicidal ideations or behavior.	Safety	X	X
35. Acute COVID-19 or positive SARS-CoV-2 test[a] indicative of an acute infection at screening or within 14 days before screening or symptoms suspicious of COVID-19 (e.g. fever, tiredness, dry cough) at screening or during the past 14 days.	Safety	X	X

BoNT=Botulinum neurotoxin; CRO=Contract research organization.

a. SARS-CoV-2 test done by local healthcare provider. No SARS-CoV-2 tests will be conducted as part of the study procedures.

7.4 Eligibility criteria for reinjection

At the end-of-cycle 1 visit V8 at Week 24 (Day 168), subjects are evaluated for eligibility to continue in the bilateral treatment period (Cycle 2) of the study. Only subjects meeting all of the following criteria will be considered for reinjection in the bilateral treatment period. In this case, the Cycle 2 baseline visit V8 (Day 1) will be performed on the same day.

Subjects who do not meet these eligibility criteria will be discontinued from the study.

In case of a public health emergency, e.g. due to a COVID-19 outbreak in which the study or study visits for subjects in Cycle 1 were put on hold or in any way modified so that V8 could not be performed according to study plan (e.g. more than 25 weeks after Cycle 1 injection at baseline visit V2), subjects will not continue the study with Cycle 2 baseline visit V8 but will continue the study visit with V8a (Section 9.2). Then the eligibility criteria for study resumption of the bilateral treatment period (Cycle 2) in Section 7.4.1 for V8a apply and must be utilized.

Eligibility criteria for reinjection for Visit 8	Rationale
1. Combined agreement of subject and investigator on the subject's potential benefit from study treatment of both ULs.	Efficacy, safety
2. Visible tremor of both ULs as assessed by the investigator on TETRAS Performance subscale item 4 with a score of ≥ 1.5 in either the forward horizontal reach posture, and/or lateral 'wing beating' posture and/or finger-nose(chin)-finger movement.	Efficacy
3. Body weight ≥ 50 kg.	Safety
4. Negative pregnancy test (for females of childbearing potential).	Safety
5. Absence of any infection or inflammation in the areas of the planned injection sites.	Safety
6. Absence of medically relevant, severe, or any serious AEs that are judged to have a causal relationship to the study treatment.	Safety

Eligibility criteria for reinjection for Visit 8	Rationale
7. For subjects on coumarins or other anticoagulants monitored by INR, the investigator confirms and documents that the subject has an INR value of ≤ 2.5. Treatment with direct thrombin inhibitors, factor Xa inhibitors, heparin or heparinoids must have remained unchanged between the screening (V1) and reinjection (V8) visits.	Safety
8. No treatment with any BoNT other than study medication since baseline visit V2.	Efficacy, Safety
9. No acute COVID-19; no COVID-19 or positive SARS-CoV-2 test indicative of an acute infection in the past 14 days.	Safety
INR=International normalized ratio.	

7.4.1 Eligibility criteria for study resumption of the bilateral treatment period (Cycle 2) in case of a public health emergency, e.g., due to a COVID-19 outbreak

In case of a public health emergency, e.g., due to a COVID-19 outbreak in which the study or study visits for subjects in Cycle 1 were put on hold or in any way modified so that V8 could not be performed according to study plan (e.g., more than 25 weeks after Cycle 1 injection at baseline visit V2), subjects will not continue the study with Cycle 2 baseline visit V8, but will continue the study visit with V8a when possible (as outlined in Section 9.2). In this case, subjects need to fulfill the following eligibility criteria for study resumption below.

Subjects not meeting all of the eligibility criteria for study resumption due to an acute event (e.g. due to an inflammation of the planned injection site) can be re-assessed only once when the issue has been resolved.

Subjects who do not meet the eligibility criteria in the table below will be discontinued from the study.

Eligibility criteria for study resumption in case of a public health emergency	Rationale
1. Written re-consent obtained on current approved ICF version.[a]	Administrative
2. Subject does not meet any of the criteria that lead to discontinuation, as mentioned in chapter 7.5.1. This includes any	Efficacy, safety

condition which arose or treatment which was started (e.g. intrathecal baclofen) which in the opinion of the investigator no longer justifies or permits safe participation of the subject or significantly interferes with the study.	
3. At least 16 weeks passed since the last treatment with any *BoNT* product for any reason.	Efficacy, safety
4. No concurrent use of antibiotics that interfere with neuromuscular transmission, such as aminoglycoside antibiotics (e.g., streptomycin sulphate, kanamycin sulphate, gentamicin sulphate, neomycin sulphate, spectinomycin hydrochloride), polypeptide antibiotics (e.g. polymixin B sulphate), lincomycin antibiotics (e.g. lincomycin hydrochloride, clindamycin), or enviomycin sulphate.	Efficacy, safety
5. No treatment with parenterally administered drugs that interfere with neuromuscular transmission (e.g., intrathecal baclofen, tubocurarine-type muscle relaxants used in anesthesia), aminoquinolines, or local anesthetics in the treated region within two weeks before the study resumption or intended to be administered during the study.	Efficacy, safety
6. Women of childbearing potential [b] must be using a highly effective method of birth control [c] and must be willing to continue using this during the entire study period.	Safety
7. Understanding of study procedures and willingness to abide by all procedures during the course of the study.	Administrative
8. No acute COVID-19; no COVID-19 or positive SARS-CoV-2 test indicative of an acute infection or symptoms suspicious of COVID-19 (e.g. fever, tiredness, dry cough) in the past 14 days.	Safety
9. Combined agreement of subject and investigator on the subject's potential benefit from study treatment of both ULs.	Efficacy, safety
10. Visible tremor of both ULs as assessed by the investigator on TETRAS Performance subscale item 4 with a score of ≥ 1.5 in either the forward horizontal reach posture, and/or lateral 'wing beating' posture and/or finger-nose(chin)-finger movement.	Efficacy
11. Body weight ≥ 50 kg.	Safety
12. Negative pregnancy test (for females of childbearing potential).	Safety

13. Absence of any infection or inflammation in the areas of the planned injection sites.	Safety
14. Absence of medically relevant, severe, or any serious AEs that are judged to have a causal relationship to the study treatment.	Safety
15. For subjects on coumarins or other anticoagulants monitored by INR, the investigator confirms and documents that the subject has an INR value of ≤ 2.5. For subjects on direct thrombin inhibitors, factor Xa inhibitors, heparin or heparinoids, the investigator confirms and documents that the therapy has remained unchanged since screening (V1) or that the subject has an aPTT time ≤ 80 seconds.	Safety

INR=International normalized ratio.

a. *Written re-consent is necessary if new ICF version is available or if more than 2 months have passed between the end-of-cycle visit and the re-start assessment.*

b. *Childbearing potential is defined as neither premenarche, nor permanently sterilized nor postmenopausal (i.e. 12 months with no menses without an alternative medical cause).*

c. *Defined as a method that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or vasectomized partner.*

7.5 Removal of subjects from treatment or assessment

7.5.1 Discontinuation of subject's study participation

In accordance with the Declaration of Helsinki and the ICF, the subject may end his/her participation in the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled, see Section 7.5.3. Both the fact and the reason(s) why the subject's participation in the study was prematurely discontinued must be recorded in the source documentation (e.g. subject file) and the eCRF. Date and discontinuation circumstances should be stated.

The investigator **must** discontinue the subject's study participation at any time, if any of the following occurs:

- Withdrawal of informed consent.
- Treatment with any other IP in another clinical study.
- Treatment with any *BoNT* other than IP, except in case of a public health emergency, as specified below.

- In case the study was on hold or the study was not performed according to plan for a subject in case of a public health emergency, e.g. due to a COVID-19 outbreak, the treatment with any *BoNT* other than study medication to ensure subject's well-being does not lead to discontinuation (please refer also to Section 7.4.1). Injections of BoNT of any serotype (other than the IP) are permitted only if the subjects have completed their end-of-cycle 1 visit V8 (by phone). In this case subjects cannot resume the study until at least 16 weeks have passed since their last injection with any other BoNT than the study medication and this time-period must be considered for performance of V8a. Pregnancy (no further administration of IP(s), blood sampling, or any other interventional procedure will be performed).

- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.

- Any other condition arises which in the opinion of the investigator no longer justifies or permits safe participation of the subject or which significantly interferes with the study assessments so that participation is no longer justified.

- Any eligibility criterion not met for reinjection or resumption.

Deviations from this study protocol, or conditions comprising exclusion criteria established in Section 7.3 that arise after the subject has been included in the study may (but will not necessarily) lead to the discontinuation of subject's study participation. All such conditions must be properly documented. Any deviations related to a public health emergency, e.g., due to a COVID-19 outbreak (e.g., visit deviations, remote assessments, rater change due to staff being unavailable in case of a public health emergency) must be documented as such. Subjects who discontinue the study because of AEs will be treated according to standard clinical procedures. For any subject discontinuing the study, the end-of-study visit (V11) should be conducted. All pertinent information concerning the AE will be documented in the source documentation as well as in the eCRF report form until V11. No information will be collected in the eCRF thereafter.

The investigator is required to make every effort to contact subjects lost to follow-up, and all such efforts are to be documented in the source documentation (e.g. times and dates of telephone contact, copies of letters).

Subjects who discontinue the study will not be replaced.

7.5.2 Premature termination or suspension of the study or closure/suspension of a study site

The study or a study site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the study or closure of a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory;
- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits;
- The incidence of AEs constitutes a potential health hazard to the subjects;
- New scientific data on the IP(s) do not justify a continuation of the study;
- The investigator or study site exhibits serious and/or persistent non-adherence to the clinical study protocol, the Declaration of Helsinki, ICH-GCP, and/or applicable regulatory requirements; and
- The sponsor decides to terminate or suspend the study at any time for any other reason. The study may be prematurely ended if the regulatory authority or the IEC/IRB has decided to withdraw or suspend approval for the study, the study site, or the investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and ensure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, the IEC/IRB, and regulatory authorities of the termination or suspension of the study, as well as provide reasons for the action.

7.5.3 Provision of care for subjects after discontinuation of the study

After study discontinuation, the subjects will be treated by their physician according to their medical condition and standard treatments in the country concerned. For further information, see Section 3.3.4.

7.5.4 Study modifications in case of a public health emergency, e.g., due to a COVID-19 outbreak

In case of a public health emergency, e.g., due to a COVID-19 outbreak, the sponsor might put study recruitment and treatment overall, or for specific sites or countries, on hold. This may further include, but is not limited to, extending visit windows, performing visits remotely by phone for efficacy and safety assessments, or the restart of study activities for subjects after halt.

In order for a site to resume treatment and/or recruitment, the following conditions have to be fulfilled:

- The study site is not closed or put under quarantine;

- Relevant appropriately trained and qualified site staff members needed to conduct the study are available;
- Local restrictions, if in place, do not interfere with study conduct. Sites should follow local procedures regarding safety measures related to a public health emergency, e.g., due to a COVID-19 outbreak;
- All assessments can be performed as planned;
- Subjects are able to travel to the study site to conduct the visits on-site as planned;
- The study site does not know about any planned site closures or quarantine measures or any other issues that would interfere with study conduct; and
- The sponsor approves that the site resumes treatment and/or recruitment.

The sponsor will keep oversight of the global and local situation. In addition, the study sponsor will regularly re-assess the risk-benefit assessment. This assessment will evaluate if it is necessary to put recruitment and/or treatment on hold in order to protect the subjects' safety and well-being. If necessary, the sponsor will put recruitment and/or treatment on hold either on a global or on a local level.

The sponsor will inform sites about any restrictions pertaining to the site, as well as about when to resume treatment and/or recruitment.

8 TREATMENTS

8.1 Investigational product(s)

8.1.1 Description of investigational product(s)

NT 201, marketed as Xeomin (active ingredient: NT 101, *BoNT* A free from complexing proteins; USAN: incobotulinumtoxinA) will be provided in quantities of 200 U as a powder to be reconstituted for injection.

For subjects randomized to the placebo group the same procedure will be followed, but in this case the vials will contain human serum albumin and sucrose only. NT 201 and placebo vials will have the same appearance.

NT 201 and placebo are manufactured by Merz Pharma GmbH & Co. KGaA, Am Pharmapark, D-06861 Dessau-Rosslau, Germany, and released by Merz Pharmaceuticals GmbH, Alfred-Wegener-Straße 2, D-6048 Frankfurt am Main, Germany.

8.1.1.1 Instructions for preparation

In the unilateral treatment period (Cycle 1), one vial of the IP (200 U NT 201 or placebo) will be reconstituted with 2 mL sterile physiological preservative-free saline (0.9% NaCl), resulting in a concentration of 100 U/mL or placebo.

For bilateral treatment (Cycle 2) two vials (200 U NT 201 each) will be reconstituted with 2 mL sterile physiological preservative-free saline (0.9% NaCl) each, resulting in 4 mL in total resulting in a concentration of 100 U/mL.

No further dilution is required or allowed.

If during reconstitution, the vacuum does not draw the solvent into the vial, the vial must be discarded and replaced. Reconstituted NT 201 is a clear, colorless solution free of particulate matter. If the reconstituted solution has a cloudy appearance or contains flocculär or particulate matter the vial is to be discarded and replaced.

The IP should be reconstituted shortly before use. For storage of reconstituted IP, see Section 8.1.3.

8.1.1.2 Instructions for administration

The IP will be administered as intramuscular injections. Guided injection will be conducted throughout the study. Electromyography, electrical stimulation of the muscle, ultrasound imaging, or a combination of these techniques must be used to identify proper muscles and facilitate injection. Different techniques may be used to identify different muscles within a

subject. The chosen (set of) technique(s) should be applied at both injection visits for a subject. Likewise, the same injector should treat a subject at both injection visits. Anatomic landmark injection guidance may be used in a supplementary fashion only but must be confirmed with one of the above-mentioned techniques. All injectors need to provide evidence of their experience or training in eligible guided injection techniques for all muscles that are mandatory or eligible for injection in the study.

At the Cycle 1 baseline visit (V2) in the unilateral treatment period a total dose of 130 to 165 U NT 201 (or matching placebo) will be injected into selected elbow, shoulder, and forearm/wrist muscles of the motor dominant UL according to a semi-flexible dosing scheme (see Section 8.2.2 and Table 1). At the Cycle 2 baseline visit (V8) or at the Cycle 2 baseline visit (V8a) in the bilateral treatment period, a total dose of 130 to 165 U NT 201 will be injected into each UL, resulting in a total dose of 260 to 330 U.

The investigator will use the IP(s) and all study materials only within the framework of the clinical study and in accordance with this clinical study protocol.

8.1.2 Packaging and labeling

Boxes of IP(s), each containing one vial of NT 201 or placebo, will be sent to the study sites. If necessary during the course of the study, study sites will be replenished. The study site will administer IP(s) to each subject during the study baseline visit (V2) of the unilateral treatment period (Cycle 1) and visit (V8) of the bilateral treatment period (Cycle 2) or visit (V8a) of the bilateral treatment period (Cycle 2).

The IP will be labeled according to regulatory requirements in the participating countries. Parts of the IP may be subject to a reduced labeling according to the applicable regulations. For this double-blind study, the test product (IP) and reference product (placebo) will have the same printed label information on the outer/secondary packaging (box) or the inner/primary packing (vial) to ensure blinding. See Section 8.5 for details of the blinding procedures planned for this study.

8.1.3 Storage of investigational product(s)

Before reconstitution, NT 201 and placebo will be stored, according to the NT 201 storage requirements, at +2°C to +25°C (36°F to 77°F).

Storage temperature will be monitored at least once weekly, and the minimum/maximum temperature for each measurement will be recorded in a temperature log.

Reconstituted IP can be stored in the original vial for up to 24 hours at +2°C to +8°C (36°F to 46°F) if the injection needs to be postponed to the day following that on which the reconstitution was performed. Reconstituted IP is not to be stored in syringes.

8.1.4 Accountability for investigational product(s)

It is the responsibility of the investigator or pharmacist according to local law to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by the FDA or other regulatory authorities at any time. Each shipment of materials for the study will contain an 'IP supply and return form' to assist the investigator in maintaining up-to-date and accurate inventory records. This form includes the following information: study number, dates, quantities, batch number, expiration date, and the code number assigned to the IP.

Upon receipt of the IP(s), the investigator or pharmacist will visually inspect the shipment and verify the number and condition of the IP(s). Medication will be registered in an interactive web response system [IWRS].

For further details, see Section 8.2.5.

8.1.5 Destruction of investigational product(s)

All used vials and all vials with residual fluid content are to be inactivated according to local standard practice. Upon the completion or termination of the study, all unused and/or partially used IP(s) must be returned to the sponsor. The sponsor will destroy the IP(s) at the end of the study. Destruction of IP(s) at the study site may be allowed if written authorization is provided by the sponsor. If destruction at the study site is agreed upon, then a certificate of destruction must be given to the sponsor.

8.2 Treatments administered

8.2.1 Methods of assigning subjects to treatment groups

The study is planned as a multicenter study. At the study baseline visit (V2), subjects will be randomized to treatment groups stratified by site. Randomization in blocks of appropriate size and blockwise distribution of the IP to the study sites ensure an approximately correct ratio of 2:1 of enrolled subjects in the two treatment groups per site and overall. The block size will not be disclosed to investigators until the study is unblinded.

No other criteria for stratification of randomization will be applied.

Randomization will be done by using an IWRS.

At the Cycle 2 baseline visit (V8) of the bilateral treatment period, all eligible subjects will receive open-label NT 201.

8.2.2 Selection of doses in the study

In this study, a semi-flexible dosing scheme is going to be applied, with a fixed total dose of 100 U NT 201 (or placebo in Cycle 1) injected into selected shoulder and elbow muscles and an individualized dose between 30 U and 65 U NT 201 (or placebo in Cycle 1) into selected muscles of the forearm/wrist (Table 1).

Elbow and shoulder muscles are injected since it is assumed that they contribute significantly to the arm tremor and that they also amplify the tremor at wrist level. Flexible dosing at the forearm/wrist is planned because the tremor has three degrees of freedom at forearm/wrist level and interindividual differences in contribution of individual muscles to the forearm/wrist tremor are expected, as well as interindividual differences in susceptibility of individual muscles to unwelcome weakness. See Section 8.2.3 for details on the individual decision on muscles of the forearm/wrist per subject.

During the unilateral treatment period (Cycle 1), NT 201 or placebo will be injected into muscles of the motor dominant UL of subjects. The permissible dose range is 130 to 165 U per UL per subject.

During the bilateral treatment period (Cycle 2), the total permissible dose range is 260 to 330 U per subject, with 130 to 165 U per UL.

Table 1: Semi-flexible dosing scheme

Muscles	No. of injection points	Units of NT 201 per muscle	Injection volume per muscle
Forearm/wrist muscles	**Total forearm/wrist dose: 30.0 - 65.0 U**		
NB: At least 4 of the following 7 forearm/wrist muscles must be injected			
[redacted]			
Elbow muscles	**Elbow total dose: 40.0 U**		
[redacted]			
Shoulder muscles	**Shoulder total dose: 60.0 U**		
[redacted]			
Total dose per Upper Limb:		130.0 – 165.0 U	1.3 – 1.65 mL

M. = Musculus; U = Unit; NB = Nota bene

8.2.3 Selection and timing of doses for each subject

Doses injected into the predetermined shoulder and elbow muscles are fixed (total dose of 100 U NT 201 (or placebo in Cycle 1)), as described in Section 8.2.2. For each subject, the muscles for treatment in the forearm/wrist and respective dosing will be decided by the investigator. This decision will be based upon clinical assessment prior to each injection. This clinical assessment will include visual assessment of the following tremor characteristics: flexion/extension, radial/ulnar deviation patterns at wrist, and pronation/supination at forearm. The muscle selection decision might be supported by presence of rhythmic burst potentials during optional needle electromyogram recordings. At least four out of seven eligible forearm/wrist muscles must be injected with a dose between 30 and 65 U NT 201 (or placebo) in total. The investigator should consider tremor

severity, the tremor pattern, and the muscle mass of the forearm for dose selection of wrist and forearm muscles.

Injections will be administered on Day 1 of the unilateral treatment period (V2) and Day 1 of the bilateral treatment period (V8) or (V8a). Selection of forearm/wrist muscles for treatment as well as the respective dosing may vary between Cycle 1 and Cycle 2 for the dominant UL. Furthermore, selection of forearm/wrist muscles for treatment as well as the respective dosing may vary between the dominant and non-dominant UL in Cycle 2, the bilateral treatment period.

No other dose levels and no further injections will be permitted.

8.2.4 Duration of treatment per subject

Overall, the duration of the study will be 36 weeks plus up to 3 weeks screening period.

Each subject will receive injection of NT 201 or matching placebo into the motor dominant UL on Day 1 of the unilateral treatment period (Cycle 1), followed by a 24-week observation period, and injection of NT 201 into both arms on Day 1 of the bilateral treatment period (Cycle 2), followed by a 12-week observation period.

In case of public health emergency measures, e.g., due to a COVID-19 outbreak the treatment may be halted or postponed (see Section 6.1 and 7.5.4). If a subject is affected by the treatment halt due to a COVID-19 outbreak, the study duration will be extended by the duration of the hold (see Section 7.4.1).

8.2.5 Treatment compliance

The investigator will inject the IP during the subject's visit at the investigation site. IP will not be handed over to subjects. Thus, treatment compliance is assured for each individual subject. Details on IP handling will be documented on a Drug Accountability log and in the subject file, as well as in the eCRF.

8.2.6 Treatment of overdose

An overdose is defined as treatment with IP exceeding the total dose per UL specified in the protocol. Any overdose must be recorded in the relevant sections of the eCRF. Any case of overdose leading to serious AE(s) [SAE(s)] or adverse event(s) of special interest [AESI(s)] must be reported to the CRO in an expedited manner using the appropriate reporting form, see Section 10.1.

As study treatment will be administered exclusively in a clinical setting by skilled study-site medical personnel with previous *BoNT* A injection experience, the risk of overdose in

this study is considered to be low. The investigator is advised to use best clinical judgment in the unlikely event of an overdose with the randomized IP.

In the event of overdose the subject should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Respiratory support may be required if paralysis of the respiratory muscles occurs.

There is very limited experience with specific antidotes to *BoNT* A in the clinical management of overdose. Marchini [Marchini 1997] published a case report of a patient with torticollis treated with *BoNT* A, describing the successful treatment of toxic symptoms (oropharyngeal weakness, dysphagia) by means of intranasal neostigmine.

8.3 Previous and concomitant therapies

Before enrollment, the subject's medical history taking should include a detailed list of all medications that the subject was taking during the 3 months preceding the screening visit (V1). In particular, any anti-tremor medication documented since tremor diagnosis should be reported. *BoNT* treatments, administered to any body region, regardless of the time of administration before the screening visit (V1), should be documented. Records of previous and concomitant medications (including vaccination) should include the drug name (preferably the trade name), route of administration (e.g. intravenous, oral), total daily dose/unit (expressed in mg, mL, or international units), indication, the start and, if applicable, stop date (day, month, and year) for each medication.

Therapy changes (including changes of regimen) during the study are to be documented in the subject file and in the eCRF.

Any tests for COVID-19 / SARS-CoV-2 and their outcome should be documented as non-drug treatments in the eCRF.

At the end of the study an additional statement will be entered to indicate whether the administration of the concomitant medication is ongoing at the end of the study.

Similar information should be collected and assessed for any non-drug therapies that may have an effect on study results.

The following concomitant medications are permitted during the study:

Tremorgenic or potentially tremorgenic drugs other than lithium, valproate, amiodarone, typical, and atypical neuroleptics if, in the opinion of the investigator, this would not interfere with the study drug evaluation. In these cases, a stable medication has to be reached 4 weeks before the screening visit (V1). Any change in dosage level for the time during the study should be avoided (exclusion criterion no. 5).

Anticoagulation therapy if the investigator confirms and documents that the subject has an:

- aPTT time ≤ 80 seconds (subjects on dabigatran, other direct thrombin inhibitors, factor Xa inhibitors, heparin and heparinoids) at the screening visit (V1), or

- INR value of ≤ 2.5 (subjects on coumarins or other anticoagulants monitored by INR) prior to injection on the day of injection.

The following medications are forbidden, or their administration is restricted, before and/or during the study, according to the exclusion criteria listed in Section 7.3:

- Exposure to defined tremorgenic drugs (lithium, valproate, amiodarone, typical and atypical neuroleptics; exclusion criterion no 5);

- *BoNT* of any serotype (other than the study treatment) during the 16 weeks before the study baseline visit (V2) or at any time during the study (exclusion criterion no 13).
  If a subject experiences a treatment halt between Cycle 1 and Cycle 2 in case of a public health emergency, e.g., due to a COVID-19 outbreak, injections of *BoNT* of any serotype (other than the IP) are permitted only after they have completed their end-of-cycle 1 visit V8. The subject will need to fulfill the criteria for study-resumption to resume the study after the study was put on hold (see Section 7.4.1 and 7.5.4);

- Previous or planned treatment with phenol- or alcohol-injection into the ULs at any time during the study (exclusion criterion no. 16);

- Concurrent use of antibiotics that interfere with neuromuscular transmission such as aminoglycoside antibiotics, polypeptide antibiotics, lincomycin antibiotics, or enviomycin sulphate (exclusion criterion no. 17). Strictly topical use of such antibiotics is permitted; and

- Parenterally administered drugs that interfere with neuromuscular transmission, aminoquinolines, or local anesthetics in the treated region within two weeks before the screening visit (V1) or intended to be administered during the study (exclusion criterion no. 18).

If administration of forbidden medication becomes necessary during the study, the subject will only be discontinued if this represents a safety risk. Exception: Administration of another IP will always entail study termination except the case described in Section 7.5.1.

The following non-drug therapies are forbidden:

- Prior or concomitant surgery or invasive treatment to treat tremor before and during the study (exclusion criterion no. 12), and

- Previous surgery of the ULs within less than 12 months or any concomitant therapy in the ULs that, in the investigator's opinion, might influence the study drug outcome (exclusion criterion no. 14).

8.4 Restrictions during the study

Not applicable.

8.5 Blinding

The unilateral treatment period (Cycle 1) of this study is double-blind. Placebo vials will have the same appearance as NT 201 vials. The identity of individual study materials will remain unknown to the sponsor's and the CRO's study team, site staff, all subjects, the independent TETRAS expert, and the IRP.

8.5.1 Emergency unblinding

All site staff will remain blinded throughout the study. If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the treatment assignment, the study blind may be broken by an authorized investigator. Unless the medical emergency is deemed to be life-threatening, the medical monitor of the sponsor/CRO should be consulted prior to unblinding. The principal investigator or authorized staff of each study site will receive a password for the IWRS enabling him/her to break the blind of subjects through this system in case of an emergency. Upon breaking the blinding code the investigator will indicate in the subject file the date and reason.

Merz Global Product Safety will receive IWRS access for unblinding of individual cases, only when this is necessary to ensure subject safety or fulfill regulatory reporting requirements.

Furthermore, the CRO will also receive IWRS access and a password for regulatory unblinding for reporting suspected unexpected serious adverse reactions to regulatory authorities and IEC(s)/IRB(s). Personnel involved in unblinding procedures at the CRO will not take any action to jeopardize the blinding of all the members of the operational team at the sponsor and at the CRO.

8.5.2 Unblinding procedures

The blind will not be broken until the blind data review meeting has convened, the statistical analysis plan has been finalized, and the database has been closed. After the blind is broken, the statistical analysis of results will proceed. These steps will be documented according to GCP.

9 STUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 Assessments

An overall description of the study plan is provided in Section 6.1 and is summarized in the flow chart in Section 6.1.2. Schedules of assessments are detailed in Section 9.2, where tabular overviews of the study assessments are given for the unilateral, Cycle 1 (Table 5), and bilateral treatment period Cycle 2 (Table 6).

9.1.1 Clinical assessments

9.1.1.1 General assessments

At the screening visit (V1), the subject's tremor history, medical history, prior and all current treatments and medications, including tremor-specific medications, will be recorded, see Section 8.3. Concomitant medication and treatments will be assessed at each clinical visit during the study.

Other data will be collected as required, including information obtained from the following (see Table 5 and Table 6):

Physical and neurological examination: The physical and neurological examination will cover standard examinations, including the auscultation of heart, lungs and abdomen Any abnormal findings will be documented in the subject file.

Body weight and height.

Standard clinical chemistry and hematology.

Vital signs (blood pressure, pulse rate) will be recorded with the subject in a sitting position after the subject has rested for at least five minutes at each visit.

A standard 12-lead ECG is to be performed at the screening visit for all subjects with previous history of any cardiac disease in order to exclude subjects with severe, uncontrolled or acute phase cardiac diseases. Full standard 12-lead electrocardiogram [ECG] (I, II, III, aVR, aVL, aVF, V1-V6, ≥ 3 beats per lead, rhythm recorded by 1-minute single-lead ECG) will be recorded by a physician or other qualified person after the subject has rested in a supine position for at least 10 minutes. The ECG print-outs will be interpreted by a qualified investigator of the site or delegate.

For subjects without a history of any cardiac disease the interpreted copy of an ECG print-out not more than three months old prior to the screening visit and without any clinically significant findings is acceptable. The interpreted copy of the ECG print-out should be kept as part of the source documentation in the subject's file.

If no interpreted copy of an ECG is available, a standard 12-lead ECG has to be performed at the screening visit.

Demographic data.

Pregnancy testing.

In case of a public health emergency, e.g. due to a COVID-19 outbreak, it might be required to replace an on-site visit V3-V8 of Cycle 1 or V9-V11 of Cycle 2 with a remote phone visit (reasons for this include but are not limited to the site being closed due to an outbreak, travel restrictions being in place or investigator and/or subject considering it not safe to travel to the site, see also Section 6.1 and Section 7.5.4). Any modifications/deviations to usual study procedures need to be documented accordingly (see Section 11.2). On a remote phone visit the following safety and efficacy assessments shall be performed by the investigator (see also Section 9.2):

- Occurrence of adverse events;
- Occurrence of adverse events of special interest (investigators should refer to the list of AESIs, as they would during a regular study visit);
- Suicidality assessment;
- Concomitant medication, i.e. change in medication and non-drug treatments;
- Occurrence of pregnancy (questioning subject about possible pregnancy);
- TETRAS ADL subscale;
- Subject's GICS;
- [redacted] and
- Quality of Life in Essential Tremor [QUEST] Scale.

For all adverse events that are collected during a remote visit (e.g., by phone call), it is up to the medical judgement of the investigator to refer a subject to a specialist if deemed necessary, thus ensuring the safety of the subject and the validity of the data.

9.1.1.2 Efficacy assessments

Clinical outcome assessments for efficacy include the following:

- Standardized computerized kinematic tremor assessment;
- TETRAS;

- Global Impression of Change Scales [GICS];
- Quality of Life in Essential Tremor [QUEST] Scale; and
- [redacted].

Generally, self-assessments for the subject (TETRAS ADL subscale, subject's GICS, [redacted], and QUEST) will be performed as an interview procedure by the investigator or site staff. Attention should be given that subject assessments are answered independently from the opinion of the interviewer and in an undisturbed environment. The interviewer can provide general guidance for assessments and their procedures to support best practices. Best practice procedures for the performance of the clinical outcome assessments and the sequence of assessments at a site visit will be described in the outcome assessment manual of this study.

Self-assessments for the subject will be provided in local language.

Efficacy endpoints assessed in this study are listed in Section 12.3.1.

9.1.1.2.1 Standardized computerized kinematic tremor analysis

For evaluation of the primary efficacy endpoint and some other efficacy endpoints, the status of UL tremor in dependency of different tasks will be assessed by measuring the angular tremor amplitude with standardized computerized kinematic analysis using the TremorTek® device. The measurement also includes a standardized notebook with study-specific software for assessment and for electronic data transfer. This will be performed for the injected UL(s), i.e., the motor dominant UL in the unilateral and both ULs in the bilateral treatment period. Tremor intensity will be assessed by measurement of angular tremor amplitude at the shoulder (flexion/extension, adduction/abduction), elbow (flexion/extension), and wrist (flexion/extension, radial deviation/ulnar deviation, pronation/supination) levels. Measurements will be performed while the subject is performing the following four tasks:

- Task I: Shoulders flexed at 90° with forearms extended anteriorly and pronated;
- Task II: Shoulders flexed at 90° with forearms extended anteriorly in neutral position;
- Task III: Holding an empty cup; and
- Task IV: Holding the same cup filled with 1 pound in weight (453.6 g).

Assessments of all four tasks will always be performed in a sitting position and with standardized task assessment positions, as described in a separate manual.

There will be three consecutive measurement rounds per subject in which Tasks I to IV will be repeated in the exact same order. The duration of the entire TremorTek® assessment with four tasks and three measurement rounds will be about 10 to 15 minutes per UL per subject. This time includes setup and initial calibration as well as short breaks between tasks, the duration of which is up to the investigator's decision. Usually a break of 5 to 10 seconds between tasks is necessary for the majority of subjects. For some elderly subjects a longer break is needed, however it is recommended not to exceed 30 seconds.

The kinematic tremor analysis will be performed as described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment periods (Table 6). In the bilateral period, the dominant arm will be assessed before the non-dominant arm.

Detailed instructions for the standardized computerized kinematic analysis with TremorTek® device, including software use, performance, recording of the four tasks, and data transfer will be made available in a separate manual. Specific training related to TremorTek® will be provided prior to study start.

9.1.1.2.2 The Essential Tremor Rating Assessment Scale (TETRAS)

The validated TETRAS assessment consists of an ADL subscale with 12 items (to be completed by subjects) and a Performance subscale with 9 items (to be assessed by qualified investigators) [Elble 2016, Ondo 2018]. The TETRAS will be assessed in a standardized fashion at each study visit in both study periods. The TETRAS version of reference is Version 3.3.

TETRAS ADL subscale

The TETRAS ADL subscale completed by the subjects, through an interview, addresses speech (item 1), UL tremor (items 2-9), 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 ranging from 0 to 4, representing a normal status/impact for the lowest score and most severe status/impact for the highest.

At the screening (V1) and study baseline (V2) visits, a pre-defined level of severity in items 2 to 9 of the TETRAS ADL subscale will have to be present for the subject to be eligible to receive IP (see inclusion criterion no.6 for further details).

TETRAS scores used for statistical analysis in this study to investigate NT 201 ET UL treatment are listed in Table 2.

TETRAS Performance subscale

The TETRAS Performance subscale will be assessed for both ULs. Generally, investigators will perform the TETRAS Performance subscale assessment at each study visit. Furthermore, the execution of the TETRAS Performance subscale assessment will be video recorded by the site according to standardized instructions for each subject at the screening (V1), study baseline (V2), and Week 6 visits (V4) of the unilateral treatment period (Cycle 1).

At the screening visit (V1), TETRAS Performance subscale will be assessed by the investigator in a first step (live assessment, see inclusion criterion no. 4). If the inclusion criterion no. 4 is fulfilled in the opinion of the investigator, the video recording of the TETRAS Performance assessment will be provided to an independent TETRAS expert in a second step for confirmation, which should preferably be performed within 72 hours (see inclusion criterion no. 5). If the quality of the recording does not allow for proper assessment, the TETRAS Performance subscale assessment will need to be completely repeated during the screening period. This will include TETRAS Performance subscale assessment by the investigator, video recording, and independent TETRAS expert assessment.

At the study baseline visit (V2), the inclusion criterion no. 4 based on the TETRAS Performance subscale assessment by the investigator will still need to be fulfilled for the subject to be eligible to receive IP.

Furthermore, an IRP consisting of three qualified experts otherwise not involved in study activities will retrospectively evaluate the TETRAS Performance subscale videos from the screening (V1), study baseline (V2), and Week 6 (V4) visit of the unilateral treatment period (Cycle 1) for each subject. This evaluation will be performed prior to unblinding. The IRP ratings will complement the investigator ratings [redacted] as well as for assessment of efficacy of the study treatment. A prospectively defined IRP charter will define in detail the procedures for TETRAS Performance subscale rating and blinding of subjects for the IRP.

The TETRAS Performance subscale utilized by qualified investigators includes the following assessments with specific performance maneuvers to be completed by the subjects:

- Head, face, and voice tremor (items 1-3);
- UL tremor of the right and left UL (item 4) in three tasks (i.e., the assessment of six tasks overall):

  1) Forward outstretched postural tremor,

  2) Lateral "wing-beating" postural tremor,

  3) 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).

All TETRAS Performance subscale items share a response scale ranging from 0 to 4, representing no tremor signs for the lowest score and severe tremor for the highest. All have defined 5-point response scales, except items 4 and 8 in which in-between 0.5-step options are additionally defined between scores 1 and 4. Generally, 0.5 increments may be used also for the other items if the rating is between the whole score definitions. Only trained and qualified investigators may use the TETRAS Performance subscale in the study.

TETRAS scores used for statistical analysis in this study to investigate NT 201 ET UL treatment are listed in Table 2.

Table 2: TETRAS scores and variables used in this study

TETRAS scores *Number and name*	**TETRAS score items**	**[Range]**
[redacted]	[redacted]	[0-48]
2. TETRAS ADL UL score	Sum of eight ADL items 2-9	[0-32]
3. TETRAS ADL Functional Impact score	Sum of three ADL items 10-12	[0-12]
4. TETRAS Performance subscale score[b]	Sum of all Performance items 1-9	[0-64]
5. TETRAS Performance dominant UL score	Sum of Performance items 4, 6-8 of dominant UL	[0-24]
[redacted]	[redacted]	[0-20]
[redacted]		

b. Representing the validated TETRAS Performance subscale score with all test items, including tests for both ULs.

TETRAS = The Essential Tremor Rating Assessment Scale; ADL = Activities of Daily Living; UL = Upper Limb

[redacted]

TETRAS assessments will be performed as described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment period (Table 6).

See Section 12.4.7.7 for details on the [redacted]

9.1.1.2.3 Global Impression of Change Scales (GICS)

The GICS represent commonly used global outcome assessment scales to evaluate overall clinical impression of change after treatment. GICS are to be independently completed by the subject and the investigator at the Week 6 control visits of the unilateral (Cycle 1) and bilateral (Cycle 2) treatment period (V4 and V10, Table 5 and Table 6). Across both treatment periods, the GICS will be asked for the motor dominant UL only.

The investigator will be asked for the motor dominant UL: 'Based on your clinical experience, what is your overall impression of change of the subject's tremor in the motor dominant arm due to treatment, compared to the condition before the last injection?'

Likewise, the subject will be asked: 'What is your overall impression of change of your tremor in the dominant arm due to treatment, compared to the condition before the last injection?'

A balanced 9–point symmetrical Likert response scale ranging from –4 ('Very much worse') to +4 ('Very much improved') is used for these questions:

+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

9.1.1.2.4 Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a validated health-related quality of life [QoL] questionnaire for ET, developed by the International Parkinson and Movement Disorder Society [Troester 2005]. This patient-reported outcome questionnaire has 30 items that inform on interference and impact of ET on five dimensions of QoL: Physical (9 items), Psychosocial (9 items), Communication (3 items), Hobbies/Leisure (3 items), and Work/Finance (6 items). Most items have 5-point frequency response scale ranging from 0 ('Never') to 4 ('Always'). For the items 6, 7, 11, and 12 a 'No' or 'Yes' response is asked for (scored as 0 or 4, respectively).

The QUEST scores on the five dimensions/domains are each expressed as a percentage of the total score possible, ranging from 0 to 100. A total score (summary index) is calculated as the mean of the five domain scores, also ranging from 0 to 100. A higher score represents higher dissatisfaction with health-related QoL and disability.

Subject self-assessments with the QUEST will be performed through an interview at the timepoints described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment periods (Table 6).

9.1.1.2.5 [redacted]

[redacted]

9.1.1.3 Safety assessments

Safety endpoints assessed in this study are detailed in Section 12.3.5.

9.1.1.3.1 Adverse events

AEs will be recorded in source documents after the ICF has been signed and will be recorded in the eCRF at all successive visits.

Subjects are requested to report all AEs to the investigator or site staff. It is the obligation of the investigator to detect AEs by questioning the subject at each visit. At the injection visits, AE questioning will be done twice; first before injection and the second assessment will be performed about 30 minutes after injection. All AEs observed throughout the course of the study are to be documented in the subject file and in the eCRF. This equally applies to AEs during the period of a potential COVID-19 related temporary halt. For definitions and details regarding documentation and reporting of AEs, see Sections 10.1 to 10.3.

Subjects will be actively questioned and closely monitored for signs of potential toxin spread as indicated by specific AESIs, defined by the European Medicines Agency and FDA, see Section 10.3 and Table 7. The investigator or delegate must actively question each subject for AESIs, see Section 10.3 and Table 7, at each visit, beginning at the study baseline visit (V2) before injection and approximately 30 minutes after injection. Questioning at baseline before injection is done to identify possible concomitant diseases which have not been recorded as medical history. The questioning and documentation of answers will be standardized.

If any contact with the subject identifies an (S)AE/AESI that needs confirmation or treatment, (e.g. respiratory disorder, dyspnea, aspiration, dysphagia, speech disorder, dysphonia, other signs of bulbar palsy, or botulism) the investigator must schedule an extra visit as soon as possible after the contact. If such an extra visit is not possible in case of a public health emergency, e.g. due to a COVID-19 outbreak, it is up to the medical

judgement of the investigator to decide whether referral to a specialist or emergency care is necessary for further treatment and confirmation.

9.1.1.3.2 Other safety assessments

Other assessments include the following, see Table 5 and Table 6, and are described in detail below:

- Global assessment of tolerability;
- Handheld Dynamometer [HHD] maximum grip strength in both hands;
- [redacted]
- Suicidality assessment.

Investigator's global assessment of tolerability

The global assessment of tolerability is performed by the investigator after injection as described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment periods (Table 6).

The investigator will perform a global assessment of tolerability on a 4-point response scale with the following options:

1 = very good

2 = good

3 = moderate

4 = poor

Grip strength testing (of both hands)

Handheld Dynamometer [HHD] grip strength testing will be performed as described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment periods (Table 6).

Maximum grip strength is measured with an HHD for each hand during both treatment periods.

[redacted]

Suicidal assessment

At each visit, the investigator will clinically assess whether the subject has suicidal ideations or shows suicidal behavior with a simple yes/no question. The assessment is based on the investigator's clinical judgment and the investigator is free to follow standardized assessment guides. Subjects may be referred to a mental health specialist or to emergency management depending on the investigator's risk assessment. In case of a high risk assessment, this will lead to individual study termination of the subject.

9.1.2 Laboratory evaluations

Standard safety laboratory assessments will include the parameters described in Table 3 and will be performed as described in the schedules of assessments for the unilateral (Table 5) and bilateral treatment periods (Table 6).

For standardization of laboratory test results, a central laboratory will analyze blood samples in this multicenter study, unless the central laboratory contingency plan is in place and specifies otherwise. In case the central laboratory becomes unavailable due to a COVID-19 outbreak, e.g. due to the lab being closed or courier services being unavailable, sponsor and investigators will act according to the central laboratory contingency plan. Contingency measures might include analyzing blood samples at local authorized/ certified laboratories.

The number and kind of tubes, sample processing at the site (if any) as well as storage conditions will be specified in a separate instruction manual. The amount of blood required is given in Table 4.

If laboratory evaluations are missing or are unreliable (e.g., due to failed analysis) a retest of these parameters has to be performed at the central laboratory, unless the central lab contingency plan is in place and specifies otherwise. Reliable laboratory results for all required parameters have to be available prior to the subject's study baseline visit (V2). The results of the retest will be entered in the database.

Any laboratory results outside the normal range must be graded by the investigator or delegate as 'abnormal, not clinically relevant' or 'abnormal, clinically relevant'. After the first injection of IP, a laboratory abnormality should be regarded as an AE if the investigator judges the value to be significantly worse than prior to treatment and should then be recorded in the subject file and in the AE report section of the eCRF.

For subjects receiving anticoagulation therapy, coagulation citrate blood tests will be performed at the screening visit (V1), and analyzed by the central laboratory, according to the exclusion criteria in Section 7.3. Before each injection, additional testing of INR will be performed locally for subjects on coumarins or other anticoagulants monitored by INR, see eligibility criteria for reinjection in Section 7.4. To ensure availability of results before the injection, a finger prick on-site test is acceptable.

An additional safety laboratory assessment can be performed in the course of an AE if deemed necessary by the investigator and can be evaluated either in a local or the central laboratory. Results of these additional assessments will not be entered in the study data base but can be added to the safety database optionally if values are part of safety reporting.

If the investigator suspects that a subject presents with the symptoms associated to a public health emergency, e.g., due to a COVID-19 they should, if possible, refer the subject for further testing. This includes testing for the virus itself as well as testing for antibodies, depending on the medical judgement of the investigator and local health care providers. All such tests and their outcome, whether positive or negative, have to be documented in the subject file and in the eCRF.

Table 3: Standard safety laboratory parameters

Clinical chemistry:	Alanine aminotransferase	Creatine kinase
	Alkaline phosphatase	Creatinine
	Aspartate aminotransferase	Glucose[b]
		γ-Glutamyltransferase
	Bilirubin, total[a]	HbA1c[c]
	Calcium	Potassium
	Chloride	Sodium
	Cholesterol, total	Urea/blood urea nitrogen
Hematology	Hematocrit, hemoglobin, red blood cell count	
	White blood cell count	
	Differential count (automated count, absolute)	
	Platelet count	
Coagulation (for subjects receiving anticoagulation therapy):[d]	aPTT and/or INR	
Pregnancy test (females only)	β-HCG in urine or serum[e]	

β-HCG = Beta human chorionic gonadotrophin; HbA1c = Hemoglobin A1c.

a. If total bilirubin is increased, then conjugated and free bilirubin will also be measured.

b. Standardized blood collection (preferably identical time since last nutritional intake per subject throughout the study).

c. Only at the screening visit (V1).

d. aPTT and INR to be tested at the screening visit (V1) and analyzed in central laboratory. Before each injection, additional INR testing is performed and analyzed locally for subjects on coumarins or other anticoagulants monitored by INR.

e. For women of childbearing potential (serum test at the screening (V1) and end-of-study (V11) visits, urine test at the study baseline (V2) and end-of-cycle 1 Visit 8 or Visit 8a before injections.

9.1.3 Pharmacodynamics

Not applicable.

9.1.4 Pharmacokinetics

Not applicable.

9.1.5 Pharmacogenetics

Not applicable.

9.1.6 Table of blood volume

Blood samples will be taken for general safety testing (hematological and clinical chemistry assessments), for pregnancy testing in female subjects of childbearing potential, and also for assessment of some coagulation parameters in subjects on oral anticoagulants.

Table 4 shows the maximum amounts of blood that will be required and the calculated maximum total amount of blood to be drawn during the study (30 mL over 39 weeks).

Additional blood sampling may be necessary in case of missing values (e.g., due to a failed analysis).

Table 4: Blood volumes required per subject

Study period/Visit		Blood volume withdrawn (mL)			
		Clinical chemistry, β-HCG, HbA1c	Hematology	Coagulation[a]	Total
Unilateral treatment period	V1	6	3	3	12
	V8	6	3	–	9
Bilateral treatment period	V11	6	3	–	9
Maximum total blood volume per subject		18	9	3	30

a. Coagulation parameters in subjects on anticoagulants only. aPTT and/or INR at the screening visit V1 will be analyzed in central laboratory (citrate blood samples). INR testing (for subjects who take coumarins and other anticoagulants monitored by INR) should be done before each injection and will be analyzed locally; the amount of blood drawn with point-of-care methods is considered to be negligible in this context.

9.1.7 Specimen preparation, handling, storage, and shipping

Blood samples for hematology, clinical chemistry (including serum pregnancy testing at selected visits) and coagulation testing (at the screening visit (V1) for subjects receiving anticoagulation therapy) will be analyzed by a central laboratory. If in case of a public health emergency, e.g. due to a COVID-19 outbreak, this is not possible, they will be handled according to the central lab contingency plans.

Additional blood samples for INR tests before each injection will be processed at the point of care according to local standards.

This study does not involve the retention of any biological samples. The only samples taken will be blood for safety testing and urine (for on-site pregnancy testing only).

9.2 Visit schedule

The screening visit (V1), will be performed between 21 and 3 days prior to the study baseline visit (V2). The purpose of the screening visit is to determine subject eligibility for study participation, including TETRAS Performance subscale assessment by the investigator (see inclusion criterion no. 4) and an independent TETRAS expert (see inclusion criterion no. 5), as described in Section 9.1.1.2. Rescreening of a subject deemed ineligible (screening failure) is allowed once independent from the cause of initial failure. This includes patients who were screened but could not be randomized due to the COVID-19 outbreak.

Study baseline is defined as Day 1 (V2), which is the day of randomization and first administration of the IP. At the study baseline visit, eligible subjects will receive unilateral treatment with NT 201 or matching placebo, followed by a 24-week observation period, including six subsequent visits.

At the end-of-Cycle 1 visit (V8) of the unilateral treatment period, subjects will be checked for eligibility to participate in the subsequent bilateral treatment period (Cycle 2). If eligibility criteria for reinjection are met, the Cycle 2 baseline assessments of the bilateral treatment period will be performed at the same visit. In subjects who are not eligible for reinjection at V8, the end-of-study examination will be performed. At the Cycle 2 baseline visit (V8) of the bilateral treatment period, eligible subjects will receive treatment with NT 201 into each UL, followed by a 12-week observation period, including three subsequent visits.

The study activities and the visit schedule are shown in Table 5 for the unilateral and Table 6 for the bilateral treatment period.

The clinical study protocol allows a window of ±3 days in scheduling study visits for Cycle 1 control visits V3 to V5 and Cycle 2 control visits V9 and V10, and ±7 days for Cycle 1 control visits V6 to V7, end-of-Cycle 1 visit (V8)/Cycle 2 baseline visit V8, and end of study visit V11.

The last primary outcome visit will occur at Week 6 (V4) conducted for the last subject included in the unilateral treatment period.

During the entire study attempts should be made to arrange visits at the same time of day for an individual subject, in order to limit the effects of any circadian variability of tremor severity.

In case of premature discontinuation from the study, the procedures of the end-of-study visit (V11) will be conducted at the subject's last visit, if possible. If additional safety follow-up is necessary after this assessment, i.e., for SAEs ongoing at the time of V11, subjects may be contacted by telephone or assessed in the clinic, depending on the nature of the follow-up required.

In case of a public health emergency, e.g. due to a COVID-19 outbreak the study might be put on hold, recruitment interrupted, and/or study processes and flow might be modified with impact to the study duration/visit schedule depending on the current study status (see Section 7.4.1 and Section 9.1.1). In case of such a public health emergency the study procedures foresee the following implications for visit performance by subjects:

- Any modifications to visits and visit activities need to be documented accordingly (see Section 11.2). For example, visits performed outside the visit window because of such events must to be documented as such.

- Subjects having completed screening visit V1 and not received study medication due to any of such an event must perform a rescreening if a delay in planned activities occurred and study activities at site are possible again (see allowance of one rescreening for a subject described above in this Section 9.2).

- Investigators and subjects can decide to replace on-site visits V3-V8 of Cycle 1 or V9 – V11 of Cycle 2 with a remote visit (e.g. by phone call) (see Section 9.1.1 and Table 5 and Table 6 below).

- If in case the end-of-Cycle 1 visit (V8) had to be conducted as a remote visit (e.g. by phone call), the Cycle 2 open-label bilateral treatment period will be postponed until on-site activities are possible again (see also Section 7.4.1)

- In case study visits for subjects in Cycle 1 were put on hold or in any way modified so that V8 of Cycle 2 could not be performed according to study plan (e.g. more than 25 weeks after Cycle 1 injection at baseline visit V2), subjects will not perform V8 of Cycle 2 but will continue the study with V8a of Cycle 2 on site when this is possible again (see Section 7.4.1, Table 5, and Table 6 below).

Table 5: Visit schedule during the double-blind unilateral treatment period

M602011069	Screen-ing	Cycle 1: Double-blind unilateral treatment period						
	Screening visit	Study baseline visit	Control visits					End-of-Cycle 1 visit
Timepoint		Day 1	WEEK 4	WEEK 6	WEEK 8	WEEK 12	WEEK 18	WEEK 24
Study day	-21 to -3	1	28	42	56	84	126	168
Visit window (days)	19		±3	±3	±3	±7	±7	±7
Visit no.	V1	V2	V3	V4	V5	V6	V7	V8
Informed consent	X							
In- & exclusion criteria	X	X						
Demographics	X							
Medical history/ concomitant diseases	X							
Tremor history	X							
Previous & concomitant medication & treatments *	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse rate)	X	X	X	X	X	X	X	X
12-lead ECG [a] and Auscultation	X							
Body weight	X							X
Body height	X							
Physical and neurological examination	X							X
TETRAS ADL subscale by subject *	X	X	X	X	X	X	X	X
TETRAS Performance subscale by investigator	X [b]	X [b]	X	X [b]	X	X	X	X
TETRAS independent video rating [c]	X							
Kinematic tremor assessment with TremorTek (dominant arm)	X	X	X	X	X	X	X	X
QUEST by subject*		X		X				X
[redacted]								
Subject´s GICS *				X				
Investigator´s GICS				X				

M602011069	Screen-ing	Cycle 1: Double-blind unilateral treatment period						
	Screening visit	Study baseline visit	Control visits					End-of-Cycle 1 visit
Timepoint		Day 1	WEEK 4	WEEK 6	WEEK 8	WEEK 12	WEEK 18	WEEK 24
Study day	-21 to -3	1	28	42	56	84	126	168
Visit window (days)	19		±3	±3	±3	±7	±7	±7
Visit no.	V1	V2	V3	V4	V5	V6	V7	V8
HHD(grip strength) in both hands		X	X	X	X	X		X
[redacted]								
AE *	X	X [d]	X	X	X	X	X	X
AESI questioning *		X [e]	X	X	X	X	X	X
Suicidality assessment *	X	X	X	X	X	X	X	X
Global assessment of tolerability								X
Pregnancy test [f]	X	X						X
Coagulation test (INR or aPTT)[g]	X							
Pre-injection coagulation test(INR)[h]		X						
Blood sampling for safety	X							X
Randomization and injections of IP		X						
Eligibility criteria for reinjection [i]								X

* If site visits V3-V8 are to be replaced by remote visits (e.g. by phone calls) in case of a public health emergency, e.g. due to a COVID-19 outbreak, assessments with an asterisk should be performed during those visits. Active questioning about possible pregnancy is required for all remote visits (e.g. phone calls).

a. For subjects without a history of any cardiac disease the interpreted copy of an ECG print out without any clinically significant findings, not more than 3 months prior to the screening visit V1, is acceptable.

b. TETRAS Performance assessment will be video recorded at V1, V2 and V4.

c. TETRAS Performance assessment video recording will be provided to independent TETRAS expert for confirmation of inclusion criterion no. 5, which should be performed preferably within 72 hours. In case of non-conformity of video quality, the complete TETRAS Performance assessment, recording, and expert assessment need to be repeated within the screening period.

d. Prior to injections and 30 min after injections of IP.

e. Active questioning for AESI terms (prior to injections and 30 minutes after injections at cycle baseline visits).

f. For women of childbearing potential (serum test at V1, urine test at V2 and end-of-cycle 1 Visit V8).

g. For subjects treated with anticoagulants.

h. For subjects who take coumarins and other anticoagulants monitored by INR.

i. Eligible subjects continue with V8 assessments specific for bilateral treatment phase.

Table 6: Visit schedule during the open-label bilateral treatment period

MRZ M602011069	Cycle 2: Open-label bilateral treatment period				
	Cycle 2 baseline visit [a]		Control visits		End-of-study visit
Timepoint	DAY 1		WEEK 4	WEEK 6	WEEK 12
Visit window (Days)	168 ±7 days after V2	Only after health emergency situation [b]	±3	±3	±7
Visit no.	V8	V8a	V9	V10	V11
Eligibility criteria for study resumption		X			
Concomitant medication & treatments*	(X)	X	X	X	X
Vital signs (blood pressure,pulse rate)	(X)	X	X	X	X
Body weight	(X)	X			X
Physical and neurological examination	(X)	X			X
TETRAS ADL subscale by subject*	(X)	X	X	X	X
TETRAS Performance subscale by Investigator	(X)	X	X	X	X
Kinematic tremor assessment with TremorTek (both arms)	(X)	X	X	X	X
QUEST by subject*	(X)	X		X	X
[redacted]					
Subject´s GICS*				X [c]	
Investigator´s GICS				X [c]	
HHD(grip strength)	(X)	X	X	X	X
[redacted]					
AE *	(X)[d]	X [d]	X	X	X
AESI questioning *	(X)[e]	X [e]	X	X	X
Suicidality assessment *	(X)	X	X	X	X
Global assessment of tolerability		X			X
Pregnancy test [f]	(X)	X			X

MRZ M602011069	Cycle 2: Open-label bilateral treatment period				
	Cycle 2 baseline visit [a]		Control visits		End-of-study visit
Timepoint	DAY 1		WEEK 4	WEEK 6	WEEK 12
Visit window (Days)	168 ±7 days after V2	Only after health emergency situation [b]	±3	±3	±7
Visit no.	V8	V8a	V9	V10	V11
Pre-injection coagulation test (INR)[g]	X	X			
Blood sampling for safety	(X)	X			X
Injections of IP	X	X			

Note: All crosses with parentheses (X) mean that those tests are performed as part of Cycle 1 and do not need to be repeated for V8 of Cycle 2.

* If visits V9-V11 are replaced with a remote visits (e.g. by phone calls) in case of a public health emergency, e.g. due to a COVID-19 outbreak, assessments with an asterisk should be performed during those visits. Active questioning about possible pregnancy is required for all remote visits (e.g. phone calls).

a. No need to repeat V8 assessments to subjects who are not eligible for Cycle 2.

b. In case of a public health emergency, e.g. due to a COVID-19 outbreak in which the study or study visits for subjects in Cycle 1 were put on hold or in any way modified so that V8 could not performed according to study plan (e.g. more than 25 weeks after Cycle 1 injection at baseline visit V2), subjects will not perform V8 of Cycle 2 but continue the study with visit 8a of Cycle 2.

c. Assessment for motor dominant arm only.

d. Prior to injections and 30 min after injections.

e. Active questioning for AESI terms (prior to injections and 30 minutes after injections at cycle baseline visits).

f. For women of childbearing potential (urine test at Cycle 2 baseline Visit 8a before injection, serum test at end-of-study Visit 11).

g. For subjects who take coumarins and other anticoagulants monitored by INR.

10 SAFETY ASSESSMENTS

10.1 Definition of an adverse event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign, symptom, or disease (including intercurrent illness); deterioration of a pre-existing illness; accident; any suspected drug reaction; or a clinically relevant change of laboratory values whether or not considered related to the IP(s) or study procedure.

Changes in efficacy endpoints, e.g., subject-reported outcome endpoints (questionnaires and scales) during the course of the study, do not need to be documented as AEs, because these changes will be recorded as efficacy endpoints.

Elective treatments planned before the screening period and which are documented in the subject's source data are not regarded as AEs.

Pre-existing conditions noted in the medical history should not be reported as an AE, unless the condition worsens, or the disease reoccurs during the reporting period. To determine whether a condition has worsened, it is compared to the condition of the subject at the screening visit (V1). Abnormal laboratory values obtained during the subject's screening period will only meet AE criteria if newly detected and if considered clinically significant.

The period of observation for an AE extends from the time when the ICF was signed until the end of the subject's study participation. In case of premature termination, the end-of-study visit (V11) is to be conducted, if possible. Non-serious AEs will not be followed up after the subject's end-of-study visit.

Any untoward medical occurrence during the observation period is an AE and has to be documented in the subject's file. For screening failures, AEs are not to be documented in the eCRF. For randomized subjects that experienced AEs during the screening period these have to be entered into the eCRF.

Data pertaining to AEs will be collected during each study visit on the basis of the subject's spontaneous report, through investigator inquiry, or discovered in the course of examinations performed during the visit. The investigator will assess and record any AE in detail in the source documentation and on the eCRF AE report form. The following information must be recorded:

- AE diagnosis or main symptom;
- Date and time of onset;
- Date and time of worsening;
- Intensity (maximum observed; see Section 10.1.1);

- Causal relationship (not related, related);
- Causal relationship to COVID-19 (not related, related);
- Serious ('yes' or 'no'), 'serious since' date and reason for seriousness;
- Outcome (see Section 10.1.4);
- AE leading to discontinuation of the study ('yes' or 'no');
- Stop date and time; and
- Comment if applicable.

After completion of all scheduled visit assessments the investigator must document any AEs arising from these assessments.

In case of an SAE, or AESI (alert term, as defined in Section 10.3), the investigator must also complete an SAE report form or AESI form and report the event according to safety reporting process, as described in Section 10.2 and Section 10.3.

Treatment of overdose with IP(s) is described in Section 8.2.6.

10.1.1 Definition of intensity

The clinical intensity of an AE will be classified on the basis of its associated signs and symptoms, as follows:

Mild: Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.

Moderate: Signs and symptoms that cause discomfort and interfere with normal functioning, but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.

Severe: Signs and symptoms that affect usual daily activity and incapacitate the subject, thereby interrupting his/her daily activities.

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the eCRF AE form). In such situations, the investigator should make a judgment based on clinical experience.

10.1.2 Definition of causal relationship with investigational product(s)

An AE is considered to be 'related' to IP(s) if a causal relationship between the IP(s) and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

The expression 'reasonable causal relationship' is meant to imply that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline). Otherwise, the AE should be considered as 'not related.'

10.1.3 Definition of causal relationship with COVID-19 or infection with SARS-CoV-2

An AE is defined as having a causal relationship to COVID-19, if there is, by medical judgement of the investigator, a reasonable possibility that the AE is secondary to an infection with SARS-CoV-2 or that an infection with SARS-CoV-2 caused the worsening of an AE or a pre-existing illness. Reasonable possibility means there is medical evidence to suggest a causal relationship. For formal reason, in addition a confirmed COVID-19 infection itself should also be recorded in the eCRF as an AE having a causal relationship to COVID-19.

10.1.4 Categories of outcome

The reportable outcomes and/or sequelae of an AE are as follows:

- Recovered/resolved;
- Recovering/resolving;
- Not recovered/not resolved;
- Recovered/resolved with sequelae;
- Fatal; and
- Unknown.

If there is more than one AE, only the AE leading to death will be recorded as having had a 'fatal' outcome.

10.2 Definition of a serious adverse event

An SAE is any untoward medical occurrence, at any dose, that:

- Results in death;

- Is life-threatening[6];
- Requires inpatient hospitalization, or prolongation of existing hospitalization[7];
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; and
- Consists of any other medically important condition[8].

In case of death, an autopsy report should be submitted (if available). The date and cause of death should be recorded.

Hospitalizations for elective treatments that were planned before the screening visit (V1) and which are documented in the subject's source data are usually not regarded as SAEs.

All SAEs that occur during the study period whether considered to be related to IP(s) or not, must be reported in writing on an SAE form, either by telefax or as a scanned attachment to an E-mail, within 24 hours of the investigator's becoming aware of the event. Plain E-mails without an attached scanned SAE form, or telephone calls, are not sufficient for the reporting of SAE information. SAE report forms are provided in the investigator site file [ISF].

Although all information required for completion of an SAE report form may not be available within the specified time period, an initial report should be submitted if the following minimum information is available:

- An identifiable subject (number);
- A suspect product;

[6] The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

[7] An overnight admission is considered as hospitalization and serious. An admission and discharge on the same day is no hospitalization but may be considered as medically important if the event was treated.

[8] According to ICH E2A, CPMP/ICH/377/95: 'Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.'

- An identifiable reporting source (investigator/study site identification); and
- An event or outcome that can be identified as serious.

The report must be addressed and delivered to the following contact address of the responsible CRO:

PRA Health Sciences – Pharmacovigilance and Patient Safety

Email: [redacted]@prahs.com

PRA Safety Fax Line:

Europe, Asia, Pacific & Africa (EAPA):	North America:
Fax +44 [redacted]	Fax +1 888 [redacted] or 1 434 [redacted]

Telephone to contact the CRO safety helpline for questions or issues:

Note: This number is not for reporting of cases

Phone **North America: +1 800** [redacted]

EAPA: +49 621 [redacted]

The investigator must supply further supporting information within three days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information. Follow-up reports are to be sent without delay to the CRO as an SAE report form (marked as a 'follow-up' report) and accompanied by appropriate supporting documentation (e.g., hospital reports). The SAE is to be followed up until the SAE is resolved/recovered or a plausible explanation is available. These SAEs will be followed-up only in the Global Product Safety database of the sponsor after final SAE reconciliation is completed.

SAEs occurring after the end of the observational period need only be reported if the investigator considers the event to be related to IP(s). These reports will generally not be entered into the database.

10.3 Adverse events of special interest (alert terms)

AESIs are considered to have a special meaning or importance for a particular drug or class of drugs. They may be non-serious and precursors (prodromes) of more serious medical conditions. Therefore, they should be closely monitored and promptly reported to the CRO. Subjects will be actively asked at each visit (beginning at V2) by the investigator or his/her authorized delegate if any AESI terms occurred since the last contact. The questioning and documentation will be standardized. For confirmation of certain AESI terms, the investigator may require a physical and/or neurological examination to assess the event.

AESIs for this study are listed in Table 7.

The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, by telefax, or email to the responsible CRO within 24 hours of knowledge of the event. The CRO will transmit these AESIs to the sponsor. Each AESI must be reported by the site on the AESI reporting form. Moreover, AESIs should be documented on the general pages of the AE eCRF as well as in the subject file.

The AE form in the eCRF as well as the eCRF forms for medical history/concomitant diseases and for previous/concomitant medication and non-drug treatment are to be faxed/sent along with the AESI reporting form. For contact details, see Section 2.2.

Serious AESIs will be followed up until recovered/resolved or a plausible explanation is available. Non-serious AESIs will not be followed up after the subject's end-of-study visit.

Table 7: List of adverse events of special interest

MedDRA Preferred Term (MedDRA version 23.0)		
Accommodation disorder	Eyelid function disorder	Peripheral nerve palsy
Areflexia	Eyelid ptosis	Peripheral paralysis
Aspiration	Facial paralysis	Pelvic floor muscle weakness
Botulism	Facial paresis	Pneumonia aspiration
Bradycardia	Hemiparesis	Pupillary reflex impaired
Bulbar palsy	Hypoglossal nerve paresis	Quadriparesis
Constipation	Hyporeflexia	Respiratory arrest
Cranial nerve palsies, multiple	Hypotonia	Respiratory depression
Cranial nerve paralysis	IIIrd nerve paresis	Respiratory failure
Diaphragmatic paralysis	Ileus paralytic	Speech disorder
Diplopia	IVth nerve paresis	Trigeminal nerve paresis
Dry mouth	Monoparesis	Urinary retention
Dysarthria	Muscular weakness	Vision blurred
Dysphagia	Paralysis	Vocal cord paralysis
Dysphonia	Paraparesis	Vocal cord paresis
Dyspnoea	Paresis	
Extraocular muscle paresis	Paresis cranial nerve	

10.4 Expected adverse events

Tremor is a new explorative indication; however, the sponsor expects a similar AE profile as for the treatment of upper limb spasticity.

Furthermore, expected AEs are those listed in the current IB in Chapter 7.1, in the respective Section “Adverse reactions independent from indication”.

10.5 Unexpected adverse events

An unexpected AE is an event not previously reported in nature, severity, or incidence in the RSI of the current IB.

10.6 Pregnancy

Each pregnancy that starts during the study must be reported by the investigator to the product safety department of the CRO within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on a pregnancy monitoring form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the IP(s). Each normal pregnancy is to be reported as a non-serious AE (drug exposure before or during pregnancy). Any abnormal pregnancy or pregnancy outcome is to be reported as SAE (on an SAE form).

In case of pregnancy prior to injection, the subject must not receive any IP and the end-of-study visit will be conducted right away without any invasive procedures (such as blood drawing) performed.

If a pregnancy occurs after a subject has received injection, the subject must not receive any further IP and the end-of-study visit (V11) will be conducted right away without any invasive procedures (such as blood drawing) performed.

10.7 Other safety assessments

All other safety endpoints assessed in this study are detailed in Section 9.1.1.3.2 and Section 12.3.5.3.

11 DATA QUALITY ASSURANCE

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or regulatory authorities and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

11.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, [redacted] If necessary, e.g., due to long periods of study inactivity, an increase in protocol deviations or any other factors that make additional training necessary, investigators will be re-trained. A need for re-training will be decided on a case-by-case basis.

This study will be monitored regularly by a qualified monitor from the CRO according to ICH-GCP and the respective standard operating procedures [SOPs], see Section 11.4.

11.2 Source documentation requirements

All data collected from a subject during the course of this clinical study should be retained in the respective source documentation (e.g. subject file). This includes a copy of the letter sent to the subject's primary physician about the subject's participation in the study (provided the subject has a primary physician and has agreed to the general practitioner being informed). The source documentation must also contain a descriptive statement on the informed consent procedure, see Section 3.3.2. The investigator must also confirm by written statement in the source documentation that all inclusion criteria and all exclusion criteria were checked prior to inclusion of the subject. In addition to this statement, the subject's meeting or non-meeting of the in- and exclusion criteria and eligibility criteria have to be traceable on the basis of the documentation in the subjects file. The childbearing potential of female subjects must be noted in the source documentation. The site will keep a source data location list which will outline for the different data categories including electronic data (e.g., demographics, medical history, and AEs etc.) which document serves as source for these data (e.g., subject file, laboratory report).

If the subject has no medical history on file at the study site, every attempt (e.g., by letter, e-mail, telephone) should be made to obtain medical history data by means of a doctor's letter, in order to verify inclusion and exclusion criteria. These attempts must be documented in the subject file.

In case of a public health emergency, e.g. due to a COVID-19 outbreak during the study period, the subjects might get tested for e.g., SARS-CoV-2. However, such a testing is not a general procedure foreseen in this study. Nevertheless, according to national and international guidance documents (e.g., issued by the FDA or EMA), collection of specific information which might explain the basis for missing data, is important. Therefore, any relevant circumstances related to the public health emergency should be documented in the source data, e.g. reason for visit not performed / visit performed via phone, date of a performed test on SARS-CoV-2 including test method and outcome. Corresponding documentation in the eCRF should be done as follows:

- A test on e.g., SARS-CoV-2 should be documented in the eCRF in the non-drug treatment section, providing as much information as possible (see above).
- Any positive infection, e.g., for SARS-CoV-2, has to be documented in the AE Section 10.3 (see also Section 10.1.3).
- All changes to visits or premature terminations in case of a public health emergency, e.g., due to a COVID-19 outbreak, should be documented in the source data as well as in the eCRF.
- Visits not done regularly on site in case of a public health emergency, e.g., due to a COVID-19 outbreak will be marked in eCRF as visit not done or done as a remote visit (e.g., by phone call) (see Section 9.1.1.1 and 9.2).

If a study site is using an electronic system for documenting source data, a member of the site staff must print out the source data after each visit. The paper print-outs must overlap, if possible (i.e. must contain at least the last row of data from the subject's previous visit). If it is not possible to obtain overlapping paper print-outs, the completeness of source data must be ensured by other suitable means. The print-out must be signed and dated by a member of the site staff who can confirm the accuracy and completeness of data in the paper print-out. The monitor will also sign and date after verifying the source data. The paper print-out should be stored in the ISF. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initialed and dated. The same applies to any corrections of initial data.

If the site is using a validated computer system including audit trail with a separate access for the monitor (i.e., the monitor can only access the data of the study subjects), then no such paper print-outs are required.

11.3 Data management

Data required according to this protocol is to be recorded in the web-based eCRFs (electronic data capture system) provided by the CRO. All users who will enter data into the eCRF will be previously trained. All participants will be trained, which will be a

prerequisite for the access to the eCRF. The access to the eCRF is password-controlled and conforms with CFR part 11.

Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data capture system; answers to queries or changes to the data will also be documented in this system directly by an authorized member of the investigator's site staff. The audit trail in the electronic data capture system documents all changes. Edit checks generate automatic queries during data entry when a field is not populated according to specifications defined in the data validation plan. Manual queries (to be answered by site staff) can be raised during source data verification, medical or safety review and data management review.

Central laboratory data and TremorTek® assessment data, see Section 9.1.1.2.1, will be received electronically and merged with the eCRF data (but not uploaded into the electronic data capture system). Plausibility checks will be performed to ensure correctness and completeness of these data. The sponsor's data management function will be responsible for data processing, in accordance with the sponsor's data management procedures as far as possible.

After all data are entered and all queries are solved, the database will be closed. After database closure, unblinding will take place. In case of any changes to the data after database closure, these changes will be documented according to relevant SOP.

11.4 Monitoring

This study will be monitored by a qualified monitor from the CRO according to GCP guidelines and the respective SOPs. During these corresponding activities, the monitor will prepare the study site for the conduct of the study, check for subject eligibility, for completion of the entries in the source data and on the eCRFs; for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements. Monitoring will also be aimed at detecting any misconduct or fraud.

In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits. In addition, the investigator is required to:

- Have all data properly recorded in the source documentation and the eCRF prior to each monitoring visit;
- Have the source documentation available at the monitoring visits; and

- Record all IP(s) dispensed in the eCRF and the drug inventory records.

All subjects who are screened, including those who are not randomized, will be listed on the subject screening/enrollment log.

Monitoring will be systematic, prioritized and risk-based. Further details of monitoring activities will be provided in the monitoring manual, which describes the procedures to identify, evaluate, control and report risks to critical processes and data on an ongoing basis throughout all stages of the trial's life-cycle.

11.5 Auditing

Audits will be performed according to the corresponding audit program, which will include the possibility that a member of the sponsor's quality assurance function may arrange to visit the investigator in order to audit the performance of the study at the study site, and all study documents originating there. Auditors will conduct their work independently of the clinical study and its performance.

Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). For audits at the study site, the monitor will usually accompany the auditor(s).

12 STATISTICAL METHODS

This section describes the statistical analyses intended at the time of study planning. Further details on the statistical and analytical aspects will be presented in the SAP.

Any deviations from planned analyses, the reason(s) for such deviation(s), and all alternative or additional statistical analyses that may be performed before database close or unblinding, respectively, will be described in amendments to the clinical study protocol or the SAP. All deviations and/or alterations will be summarized in the clinical study report. The clinical study report will cover corresponding requirements related to a COVID-19 outbreak as applicable and stipulated in the relevant national and international guidance documents.

If in case of a public health emergency, e.g. due to a COVID-19 outbreak, on-site visits are not possible due to site closures, travel limitations, or other considerations, if site personnel or trial subjects become infected, the following mitigations will be considered and assessed in an updated statistical analysis plan:

- Changes to planned and additional analyses due to a public health emergency will be described. Drop-out patterns and sources of bias such as missing values and virtual instead of live assessments (if applicable); will be assessed thoroughly and
- Systematic identification of protocol deviations due to a public health emergency will be included.

12.1 Determination of sample size

The results of the previous study [Jog 2017, Merz Pharmaceuticals GmbH 2017] suggest that a treatment effect of about one standard deviation might be expected. Assuming a 5% type I error and a randomization ratio of 2:1 a total sample size of 51 analyzable subjects is required to achieve 90% power. In order to account for uncertainty in parameter estimates and drop-outs it has been decided to randomize approximately 75 subjects.

12.2 Analysis sets

The following analysis sets will be defined for the statistical analysis of this study:

Safety evaluation sets

The Safety evaluation set for the unilateral treatment period (SES-UP) includes all subjects who received NT 201 or placebo during the unilateral treatment period.

The Safety evaluation set for the bilateral treatment period (SES-BP) includes all subjects who received NT 201 during the bilateral treatment period.

Full analysis sets

The Full analysis set for the unilateral treatment period (FAS-UP) is the subset of subjects in the SES-UP for whom at least one score of tremor amplitude at wrist level (injected UL) at the study baseline (V2) and at least at one post-baseline score (V3 to V8) during the unilateral treatment period are available.

The Full analysis set for the bilateral treatment period (FAS BP) is the subset of subjects in the SES-BP for whom at least one score of tremor amplitude at wrist level at the Cycle 2 baseline visit (V8) and at least at one post-baseline score (V9 to V11) of both arms during the bilateral treatment period are available.

Per protocol set

The Per protocol set (PPS) is the subset of subjects in the FAS-UP without major protocol deviations. Major protocol deviations will be defined during the blinded data review meeting.

12.3 Endpoints for analysis

12.3.1 Efficacy endpoints

12.3.1.1 Primary efficacy endpoint

Change from study baseline to Week 6 in maximum tremor amplitude measurement at wrist level during the unilateral treatment period.

The maximum angular tremor amplitude at wrist level will be computed in the following three steps:

Step 1: For each of the four tasks and each of the three measurement rounds, described in Section 9.1.1.2, individual 20-second recordings from a kinematic sensor will yield three angular tremor amplitude values for flexion/extension, radial deviation/ulnar deviation and for pronation/supination levels and a single combined Root Mean Square (RMS) angular tremor amplitude value.

Step 2: Calculation of the arithmetic mean from the three measurement rounds of the combined RMS, separately for each task.

Step 3: Among Tasks I to IV selection of the task with the maximum arithmetic mean calculated during Step 2. The amplitudes of this task will be considered as the primary endpoint.

For details on the statistical analysis of the primary efficacy endpoint methods, see Section 12.4.1.1.

12.3.1.2 Secondary efficacy endpoints

12.3.1.2.1 Key Secondary efficacy endpoints

Change from study baseline to Week 6 in TETRAS Performance dominant UL Score (Score no. 5 of Table 2) in the unilateral treatment period as assessed by the investigator.

Change from study baseline to Week 6 in TETRAS ADL UL score (Score no. 2 of Table 2) in the unilateral treatment period.

For details on the statistical analysis of the key secondary efficacy endpoints methods, see Section 12.4.1.1.

12.3.1.2.2 Other secondary efficacy endpoints

Unilateral treatment period:

Change from study baseline to Week 6 in TETRAS ADL Functional Impact score (Score no. 3 of Table 2).

Subject´s GICS score of motor dominant UL at Week 6.

Investigator´s GICS score of motor dominant UL at Week 6.

Bilateral treatment period:

Change from Cycle 2 baseline to Week 6 in TETRAS Performance dominant UL score (Score no. 5 of Table 2).

Change from Cycle 2 baseline to Week 6 in TETRAS Performance subscale score (Score no. 4 of Table 2).

Change from Cycle 2 baseline to Week 6 in TETRAS ADL UL score (Score no. 2 of Table 2).

Change from Cycle 2 baseline to Week 6 in TETRAS ADL Functional Impact score (Score no. 3 of Table 2).

12.3.1.3 Other efficacy endpoints

Unilateral treatment period (comparisons NT 201 versus placebo):

[redacted]

Time course of absolute values and change from study baseline to Week 6 of QUEST total score and dimension scores.

[redacted]

Bilateral treatment period

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

Subject´s GICS score of motor dominant UL at Week 6 of Cycle 2.

Investigator´s GICS score of motor dominant UL at Week 6 of Cycle 2.

Time course of absolute values and change from study baseline and Cycle 2 baseline to Week 6 of QUEST total score and dimension scores.

[redacted]

12.3.2 Pharmacodynamic endpoints

Not applicable.

12.3.3 Pharmacokinetic endpoints

Not applicable.

12.3.4 Pharmacogenetic endpoints

Not applicable.

12.3.5 Safety endpoints

12.3.5.1 Primary safety endpoint

No primary safety endpoint has been defined.

12.3.5.2 Secondary safety endpoints

The secondary safety endpoint for both the unilateral and bilateral treatment period will be the following:

Incidence of treatment-emergent AEs [TEAEs] related to treatment as assessed by the investigator.

12.3.5.3 Other safety endpoints

Exposure to study treatment by muscle and treated UL for both study periods.

Incidence of TEAEs, TEAEs of special interest [TEAESIs], serious TEAEs, TEAEs leading to discontinuation, and COVID-19 related TEAEs for both study periods.

Time course (i.e., absolute values and changes form respective baseline) during the unilateral treatment period (Cycle 1) in HHD maximum grip strength (in hand of injected UL) and in maximum grip strength difference between both hands.

Time course (i.e., absolute values and changes from respective baseline) during the bilateral treatment period (Cycle 2) in HHD grip strength in both hands.

[redacted]

Global assessment of tolerability scale as assessed at Week 24 of unilateral treatment period and at Week 12 of bilateral treatment period.

Time course of vital signs (blood pressure, pulse rate) measurement during both study periods.

Time course of body weight measurement during both study periods.

Time course of standard clinical chemistry and hematology parameter measurements during both study periods.

Time course of suicidality assessment during both study periods.

12.3.6 Other endpoints

Other endpoints include subject disposition, demographic data, baseline characteristics, medical history and concomitant diseases, prior and concomitant medication, prior and concomitant non-drug therapies, and [redacted]

[redacted]

12.4 Statistical analysis methods

12.4.1 Efficacy endpoints

If not otherwise specified, efficacy analyses of the unilateral treatment period will be based on the observed cases of the FAS-UP. Efficacy analyses of the bilateral treatment period will be based on the observed cases of the FAS-BP.

Adequate descriptive statistics will be provided for all endpoints. Continuous variables (values and changes from baseline) will be summarized by number of non-missing observations, mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (number of non-missing observations, %) and, if applicable, shift tables will be displayed. Confidence limits and descriptive p-values will be given, where appropriate.

In the bilateral treatment period it will be distinguished between:

- Category A: endpoints that are general (e.g. TETRAS ADL scores) or applicable to one UL only (e.g. TETRAS Performance subscale dominant UL, TETRAS Performance subscale non-dominant UL); and

- Category B: endpoints that are determined for both ULs (dominant and non-dominant) separately (e.g. TremorTek® maximum amplitude).

If not otherwise specified, endpoints in Category B will be summarized by UL (dominant/non-dominant).

12.4.1.1 Primary efficacy endpoint

The primary endpoint (see Section 12.3.1.1) will be analyzed based on the FAS-UP using least square means from a baseline-adjusted analysis of covariance (ANCOVA) as implemented in SAS PROC MIXED. Fixed factors will be the treatment group (NT 201 versus placebo) and study site. Study baseline angular tremor amplitude at wrist level for the task with the maximum amplitude will be the continuous covariate. Variances will be allowed to differ between treatment groups. This model will be used to test the difference between the treatment groups, NT 201 and placebo ($\alpha = 5\%$, 2-sided). Missing values will not be replaced for the primary analysis.

Sensitivity analyses will comprise:

- Similar model for the PPS;

- Model with treatment-by-site interaction to estimate treatment effects by site;
- Model with additional effects for gender and age; and
- In case, more than 10% missingness occurs in either treatment group, multiple imputation will be conducted as implemented in the FCS statement of SAS PROC MI. Variables considered will comprise maximum tremor amplitude from previous visits including study baseline, treatment, study site, gender, and age.

Study sites might be pooled for statistical analysis. The necessity and details of pooling will be determined under double-blind conditions.

12.4.1.2 Secondary efficacy endpoints

All statistical analyses to be performed on the secondary efficacy endpoints will be based on the FAS of the respective period.

12.4.1.2.1 Key secondary efficacy endpoints

The key secondary endpoints (see Section 12.3.1.2.1) will be tested with ANCOVA models similar to that for the primary analysis of the primary endpoint (see Section 12.4.1.1). However, the study baseline of the analyzed TETRAS subscale will be used for baseline adjustment. Missing data handling, sensitivity analyses and pooling of study sites will also be handled analogously to the primary endpoint analysis.

Multiplicity adjustments are addressed in Section 12.4.7.5.

12.4.1.2.2 Other secondary efficacy endpoints

Other secondary endpoints (see Section 12.3.1.2.2) will be analyzed for observed cases.

Unilateral treatment period:

Other secondary endpoints of the unilateral treatment period will be analyzed by applying ANCOVA models similar to that for the primary analysis of the primary endpoint (see Section 12.4.1.1). However, for TETRAS subscales, the study baseline of the analyzed TETRAS subscale will be used for baseline adjustment. For GICS by investigator and subject, the study baseline of the TETRAS ADL total score will be used for baseline adjustment.

Bilateral treatment period:

Endpoints of Category A (see Section 12.4.1) will be analyzed by applying ANCOVA models similar to that for the primary analysis of the primary endpoint (see Section 12.4.1.1). However, the Cycle 2 baseline of the analyzed variable will be used for

baseline adjustment. If no such baseline exists (e.g., GICS), the Cycle 2 baseline of the TETRAS ADL total score will be used for baseline adjustment.

Endpoints of Category B (see Section 12.4.1) will be analyzed by a repeated measures model. For that purpose the UL (dominant/non-dominant) will be added as repeated effect to the ANCOVA model. The covariance structure will be unspecified and allow to differ for the treatment groups.

The above mentioned ANCOVA models will be used to estimate the average changes from baseline by least-square means and respective 95% confidence intervals by UL and overall.

12.4.1.3 Other efficacy endpoints

Other efficacy endpoints will be analyzed by descriptive statistics only.

12.4.2 Pharmacodynamic endpoints

Not applicable.

12.4.3 Pharmacokinetic endpoints

Not applicable.

12.4.4 Pharmacogenetic endpoints

Not applicable.

12.4.5 Safety endpoints

If not otherwise specified, safety endpoints will be evaluated by treatment group (e.g. for AEs). All safety endpoints will be analyzed separately for the unilateral (SES-UP) and bilateral (SES-BP) treatment period, and by UL, where appropriate. Analyses for the unilateral phase and the total study duration will be based on the SES-UP while analyses for the bilateral phase will be based on the SES-BP.

AEs will be coded according to the Medical Dictionary for Regulatory Activities [MedDRA] version that is in effect at the time the database is closed. Only TEAEs will be analyzed, which are defined as AEs with onset or worsening after the first administration of the IP.

If in case of a public health emergency, e.g. due to a COVID-19 outbreak, the second injection visit V8a of Cycle 2 is performed later than 25 weeks after the first injection visit V2 the AEs starting or worsening later than 25 weeks after baseline visit V2 of Cycle 1 and before injection at V8a of Cycle 2 are treated as non-TEAEs.

12.4.5.1 Primary safety endpoint

No primary safety endpoint has been defined.

12.4.5.2 Secondary safety endpoints

See Section 12.3.5.2 for definition of the secondary safety endpoint. Frequency tables will be provided for incidences:

- by MedDRA system organ class (SOC) and preferred term (PT) level;
- by treatment group and, in addition for the bilateral phase, overall; and
- by treatment cycle and total study duration.

12.4.5.3 Other safety endpoints

See Section 12.3.5.3 for definition of the other safety endpoints.

- Exposure to study drug will be summarized descriptively by muscle and overall. This will be provided by treated UL (unilateral phase: dominant arm; bilateral phase: dominant and non-dominant arm). Moreover, the total exposure by subject will be summarized;
- Incidences of TEAEs, TEAEs of special interest [TEAESIs], serious TEAEs, and TEAEs leading to discontinuation, and COVID-19 related TEAEs will be presented by MedDRA SOC and PT and by treatment group and, in addition for the bilateral phase, overall;
- Global assessment of tolerability scale as assessed at Week 24 of unilateral treatment period will be summarized descriptively by treatment group. Week 12 of bilateral treatment period will be summarized descriptively by treatment group and overall. This includes frequency tables and statistics for continuous variables;
- Absolute values of HHD grip strength testing and changes from applicable cycle baseline to all applicable post-baseline visits will be summarized descriptively by treated UL. In addition, for the unilateral phase the intra-individual difference of changes from baseline between body sides will be summarized;
- [redacted]

- Time courses of vital signs (blood pressure, pulse rate) and body weight measurement at selected visits and changes from applicable cycle baseline will be summarized descriptively; and

- Time courses of standard clinical chemistry and hematology parameters measurement at selected visits and changes from applicable cycle baseline will be summarized descriptively.

12.4.6 Other endpoints

Subject disposition, demographic data and baseline characteristics will be presented by using standard descriptive statistics.

Frequencies of concomitant treatments will be given by Anatomical Therapeutic Chemical classification system of the World Health Organization code level. Indications for concomitant therapies will not be coded and will only be listed. Medical history and concomitant diseases will be described on the basis of MedDRA system organ classes and preferred terms levels.

12.4.7 Special statistical/analytical issues

12.4.7.1 Discontinuations and missing data

Reasons for premature discontinuation of a subject's study participation will be summarized descriptively. If the premature discontinuation is related to a public health emergency, e.g. due to a COVID-19 outbreak, this information will be documented and listed (see also Section 11.2).

Details of handling of missing data for primary and key secondary endpoints are specified in Section 12.4.1.1 and Section 12.4.1.2.1. Other analyses will be based on observed case.

In general, discontinued subjects will not be replaced. In case of unforeseen higher number of missing data of important efficacy data (like Change from study baseline to Week 6 in maximum tremor amplitude measurement at wrist level, in TETRAS Performance dominant UL Score, or in TETRAS ADL UL score), 10% or higher in case of a public health emergency, e.g. due to a COVID-19 outbreak, additional subjects can be enrolled for this study in order to have up to 75 evaluable subjects for efficacy analysis. It is not expected that the total number of randomized subjects will be increased to more than 100. General circumstances potentially related to a public health emergency which are independent of study treatment will result in missing values at completely random (e.g. site closed for study subjects, site decided to perform virtual visit due unfavorable epidemiological situation, subject refused to come to site due unfavorable epidemiological situation, curfew or restricted travel). Only for these missing values completely at random due circumstances of a public health emergency additional subjects will be randomized. For missing values which are potentially also related to study treatment or which are not

related to a public health emergency, no additional subjects will be randomized. In this approach of randomization of additional subjects only in case of missing values completely at random the type one error is not affected. The decision about recruitment of additional subjects will be made by Merz study team under double blind conditions.

12.4.7.2 Sensitivity analyses

Sensitivity analyses for primary and key secondary endpoints are specified in Sections 12.4.1.1 and 12.4.1.2.1.

12.4.7.3 Interim analyses

No interim analysis will be performed in this study.

12.4.7.4 Committees

Independent TETRAS expert

A video recording of the TETRAS Performance subscale assessment at the screening visit (V1) will be sent to an independent expert in order to assess inclusion criterion no. 5. See Section 9.1.1.2.2 for further details.

Independent TETRAS rater panel

The IRP will consist of three qualified experts who are otherwise not involved in any study activities. They will retrospectively evaluate the TETRAS Performance subscale videos that are recorded at the screening (V1), study baseline (V2), and Week 6 (V4) visit of the unilateral treatment period for each subject. This evaluation will be performed prior to unblinding of the study. The IRP ratings will complement the investigator ratings [redacted] as well as for assessment of efficacy of the study treatment.

A prospectively defined IRP charter will define in detail the procedures for TETRAS Performance subscale rating and blinding of subjects for the IRP. See Section 9.1.1.2.2 for further details.

12.4.7.5 Multiple comparisons/multiplicity

[redacted]

[redacted]

[redacted]

[redacted]

12.4.7.6 Examination of subgroups

Subgroup analyses are not planned for this study.

12.4.7.7 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

- [redacted]

13 DATA HANDLING AND RECORDKEEPING

By signing and dating the eCRF, the investigator will confirm that all investigations have been completed and conducted in compliance with this clinical study protocol, and that reliable and complete data have been entered into the eCRF.

13.1 Corrections to data

All data required by this clinical study protocol are to be recorded in the eCRF as soon as possible. However, unless otherwise specified in Section 11.2, direct entries are not allowed; data must be transcribed from the source documentation (e.g., subject file) to the eCRF.

If corrections are necessary, an authorized member of the investigator's site staff will enter the correct data into the web-based eCRF. The audit trail in the electronic data capture system documents all changes.

If corrections in the subject scales are necessary, the subject will be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject is to date the correction but not initial it. The investigator and site staff are not allowed to make any changes to these documents.

The CRO will be responsible for data processing, in accordance with the sponsor's data management procedures. Database close will occur only after quality assurance procedures have been completed.

13.2 Recordkeeping

Essential documents should be retained until at least two years after the last approval of a marketing application (whether pending or contemplated) in an ICH region, or at least two years have elapsed since the formal discontinuation of IP clinical development. These documents are to be retained for a longer period, if required by applicable regulatory requirements or by agreement with the sponsor.

Essential documents at the study site include (among other documents):

- Source documentation (e.g., subject file);
- Subject identification code list (respective template provided to the investigator along with the ISF, at the beginning of the study), which identifies the subject by number, name, and date of birth;
- A signed copy of the final clinical study protocol and any amendment;
- CD/DVD with eCRF data;
- Signed ICFs;

- Copies of site investigators' and co-workers' curricula vitae;
- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies);
- Copies of laboratory normal ranges and description of laboratory methods;
- Copies of study supply receipt forms and drug inventory forms;
- Copies of all correspondence between the investigator and the monitor, and between the investigator and the sponsor; and
- Copies of safety information reported during the study and submitted by the sponsor.

13.3 Destruction of study documents

Study documents may not be destroyed by study site personnel before end of the retention period specified above without the prior written consent of the sponsor. The principal investigator must inform the sponsor in due time if the PI leaves the institution during the retention period. This rule also applies if the institution closes within the retention period.

14 PUBLICATION POLICY

The study results will be published in the public domain, and publishing details will be given in the clinical study agreement. Publications concerning study results must be approved in advance by the sponsor in writing.

The results of this study and any discoveries related to this study, regardless of whether they have technical or medical character, are the property of the sponsor.

The study will be registered and study results are disclosed by the sponsor (or delegate) in at least one public clinical study registry, in accordance with national/international regulations and other requirements. Study registration may include a list of the study sites, as applicable.

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