# A prospective, double-blind, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of NT 201 doses in the treatment of platysma prominence

| | |
|---|---|
| **Development phase:** | Phase 2 |
| **Study identifier:**<br>**EudraCT Number:**<br>**IND Number:** | M602011078 / NCT05773053<br>Not applicable.<br>161381 |
| **Indication:** | Improvement in moderate to severe prominence of the platysmal bands associated with platysma muscle activity |
| **Planned study period:** | First Subject First Visit: Q1 2023<br>Last Primary Outcome Visit: Q4 2023<br>Last Subject Last Visit: Q1 2024 |
| **Investigational product(s):** | Clostridium botulinum neurotoxin type A (150 kD, free of complexing proteins) powder for solution for injection (NT 201) |
| **Sponsor:** | Merz Aesthetics GmbH<br>Eckenheimer Landstr. 100<br>60318 Frankfurt am Main Germany<br>CCI [redacted] |
| **Responsible for the clinical study protocol content at the sponsor:** | PPD [redacted] Senior Clinical Project Manager<br>PPD [redacted] Associate Director Clinical Development<br>PPD [redacted] Lead Biostatistician |

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# 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:

| | | |
|---|---|---|
| PPD | Date (dd-MMM-yyyy) | Signature |
| | Date (dd-MMM-yyyy) | Signature |
| | Date (dd-MMM-yyyy) | Signature |
| | Date (dd-MMM-yyyy) | Signature |


CCI [redacted]

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

| | | |
|---|---|---|
| PPD | Date (dd-MMM-yyyy) | Signature |

## 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 (IB). 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 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, IRB review, and regulatory inspections;
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, 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 department of the CRO, without undue delay but no later than within 24 hours, any adverse event (AE) that is serious and any event of special interest (AESI), whether considered treatment related or not; and
- Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest in accordance with 21 CFR Part 54 and a signed FDA 1572 form according to 21 CFR Part 312.


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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 IRB and regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to Merz.
- 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 |
|---|---|---|


CCI [redacted]

## List of abbreviations and definitions of terms

| | |
|---|---|
| **AE** | Adverse event |
| **AESI** | Adverse event of special interest |
| **ANCOVA** | Analysis of covariance |
| **ATC** | Anatomical Therapeutic Chemical classification system of the World Health Organization |
| **BDRM** | Blind data review meeting |
| **BoNT/A** | Botulinum neurotoxin A |
| **BMI** | Body mass index |
| **CI** | Confidence interval |
| **COVID-19** | Coronavirus disease-2019 |
| **CRO** | Contract research organization |
| **CSP** | Clinical study protocol |
| **DMC** | Data monitoring committee |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **EOS** | End of study |
| **FDA** | Food and Drug Administration, US |
| CCI [redacted] | |
| **GCP** | Good clinical practice |
| **IB** | Investigator's brochure |
| **ICH** | International Council for Harmonization |
| **IND number** | Investigational new drug number, issued by the FDA |
| **IP** | Investigational product |
| **IRB** | Institutional review board |
| **IRT** | Interactive response technology |
| **ISF** | Investigator's site file |
| **ITT** | Intention to treat set |
| CCI [redacted] | |
| **LS** | Least square |
| **MAPS-D** | Merz Aesthetic Platysma Scale – Dynamic |
| CCI [redacted] | |
| **MedDRA** | Medical Dictionary for Regulatory Activities |


CCI [redacted]

| | |
|---|---|
| **N** | Number of non-missing observations |
| **PI** | Principal investigator |
| CCI | [redacted] |
| **PT** | Preferred term |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SES** | Safety evaluation set |
| **SOC** | System organ class |
| **SOP** | Standard operating procedure |
| **TEAE** | Treatment emergent adverse event |
| **TEAESI** | Treatment emergent adverse event of special interest |
| **TESAE** | Treatment emergent serious adverse event |
| **V** | Visit |
| **U** | Unit |
| **US** | United States |


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# 1 SYNOPSIS

**Study title**

A prospective, double-blind, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of NT 201 doses in the treatment of platysma prominence.

**Study phase**

2

**Indication**

Improvement in moderate to severe prominence of the platysmal bands associated with platysma muscle activity

**Study objectives**

The primary objective is to assess the efficacy of different NT 201 doses for treatment of moderate to severe platysma prominence by demonstrating superiority of NT 201 versus placebo.

The secondary objective is to assess the safety of different NT 201 doses for treatment of moderate to severe platysma prominence.

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

A total of 68 male and female subjects CCI will be recruited.

*Key inclusion criteria*

- CCI
- Presence of four (medial and lateral, left and right) prominent platysmal bands; and
- A score of moderate to severe on the Merz Aesthetic Platysma Scale-Dynamic (MAPS-D) at maximum contraction, as assessed by the investigator and the subject.

*Key exclusion criteria*

- Any serious disease or disorder (medical or psychiatric) that could, CCI CCI, interfere with the safe completion of treatment CCI CCI or compromise subject safety CCI ;

- Botulinum toxin treatment in the face (below the lower orbital rim), neck, or chest within the last 12 months prior to study treatment;
- History of lower face surgery (i.e., below the level of the bottom of the nose; including rhytidectomy), neck or chest surgery, aesthetic procedures (e.g., ablative skin resurfacing, laser, chemical peel, micro-focused ultrasound, deoxycholic acid injections, micro- needling, non-surgical fat reduction procedure), and orthodontic procedures (e.g., braces) in the 12 months prior to study treatment;
- Previous use of any permanent (non-biodegradable) or semi-permanent (e.g., calcium hydroxylapatite, poly-L-lactic acid, polymethyl methacrylate, etc.) facial tissue augmentation therapy, lifting sutures, permanent implants or autologous fat to the lower face (i.e., below the level of the bottom of the nose), neck, or chest within 24 months prior to study treatment;
- Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy to the lower face (i.e., below the level of the bottom of the nose), neck, or chest within 12 months prior to study treatment;
- Any medical condition that may put the subject at increased risk with exposure to botulinum toxin of any serotype, including myasthenia gravis, Lambert-Eaton-Syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function; and
- Female of childbearing potential not using a highly effective method of birth control, planning to get pregnant, or pregnant or lactating.

**Study design**

The study will be a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter, 17-week, phase 2 clinical study with one treatment of different doses of NT 201 or placebo.

A total of 68 subjects will be randomized at approximately seven sites in the United States (US). An equal number of subjects will be randomly assigned with a balance ratio (1:1:1:1) to one of four groups, and all randomized subjects will receive a single treatment on the platysma at V2 (Day 1).

- Group 1 (N = 17): NT 201, CCI [redacted]
- Group 2 (N = 17): NT 201,
- Group 3 (N = 17): NT 201,
- Group 4 (N = 17): Placebo


CCI [redacted]

**Planned study period**

First Subject First Visit: Q1 2023

Last Primary Outcome Visit: Q4 2023

Last Subject Last Visit: Q1 2024

**Duration of treatment per subject**

Subjects will receive one injection treatment followed by an injection-free observation period of 17 weeks ± 7 days. Therefore, the overall study duration will be about 17 weeks (i.e., four months) plus the individual duration of screening (up to 14 days).

**Endpoints for analysis**

Efficacy endpoints

*Primary efficacy endpoint*

- Change from baseline on the MAPS-D score at maximum contraction, as assessed live by the investigator at V4 (Week 2).

  Note that the MAPS-D investigator's assessment conducted at the screening visit will be used as the baseline value for MAPS-D scores.

  The primary estimand is defined as follows:

  - Treatment condition of interest: Single study treatment with NT 201 or placebo according to randomization group; this includes protocol defined allowed concomitant treatments (i.e., medication and therapies);
  - Population: Randomized, adult subjects of CCI [redacted] with a moderate to severe MAPS-D score at maximum contraction, as assessed live by the investigator and subject at baseline, and as defined by the protocol inclusion/exclusion criteria;
  - Endpoint: Change from baseline on the MAPS-D score at maximum contraction, as assessed live by the investigator at V4 (Week 2);
  - Intercurrent events (ICEs): Discontinuation of study treatment at V2 (treatment) and prohibited concomitant treatments; and
  - Population-level summary: Treatment difference in least square (LS) means from an analysis of covariance (ANCOVA) model.

*Secondary efficacy endpoint*

- Change from baseline on the MAPS-D score at maximum contraction, as assessed by the subject at V4 (Week 2).


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Note that the MAPS-D subject's assessment conducted at the screening visit will be used as the baseline value for MAPS-D scores.

Safety endpoints

*Secondary safety endpoint*

- Incidence of related treatment emergent adverse events (related TEAEs).

**Total number of subjects and number of countries**

A total of 68 subjects will be recruited from one country, the US.

**Number of study sites**

It is planned to conduct the study in approximately seven sites in the US.

**Number of visits**

A total of eight on-site visits are planned.

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

NT 201 (active ingredient: NT 101, *Clostridium Botulinum* neurotoxin type A, free from complexing proteins) or matching placebo provided in 200 U vials.

The investigational product will be injected intramuscularly CCI CCI. Each subject will receive one intramuscular treatment of CCI of NT 201 or an equivalent volume of placebo. The same volume of reconstituted trial medication CCI will be administered in equal aliquots CCI to the CCI, irrespective of the treatment group.

**Statistical analysis methods**

Unless indicated otherwise, all efficacy analyses will be based on the intention to treat set (ITT) and will be performed per randomized treatment group.

The primary efficacy analyses will be based on the target population of main primary efficacy estimands. Metric descriptive statistics by randomized treatment group will be provided. A baseline-adjusted repeated measures ANCOVA ($\alpha = 5\%$, two-sided) with randomized treatment group and study site as fixed factors will be used for the analysis of the primary efficacy endpoint. The covariates will be MAPS-D at baseline and age at screening. LS means of the change from baseline to V4 (Week 2), calculated by the model described above, will provide an estimate for the average treatment effect of both body sides and it will be used to test the difference of each NT 201 group to placebo in a

hierarchical manner. The same analyses based on observed cases will be performed on the ITT for sensitivity purposes.

For the secondary efficacy endpoint, responder rates will be summarized as frequency tables with absolute and percent frequencies (N, %) and by two-sided 95% Wilson score confidence intervals. Responder rates of each NT 201 group will be compared with the placebo group using two-sided 95% Newcombe confidence intervals based on Wilson scores for the risk difference.

All safety analyses will be performed on the safety evaluation set (SES) per actual treatment group and for total active group. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed. Only TEAEs will be analyzed.


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# 2 STUDY ADMINISTRATIVE STRUCTURE

## 2.1 Internal responsibilities

| Name | Function | Address |
|---|---|---|
| Merz Aesthetics GmbH | Sponsor | Eckenheimer Landstrasse 100<br>60318 Frankfurt am Main<br>Germany |

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PPD



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## 2.2 External responsibilities

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

For multicenter studies, the sponsor will maintain a list of all principal investigators.

| Name | Function | Address |
|---|---|---|
| PPD | Overall coordinating investigator | PPD |
| CCI | Contract Research Organization (CRO) for medical writing | CCI |
| | CRO (Data management, eCRF, and statistical analysis) | |
| | Interactive response technology (IRT) services | |
| | IP Distribution / drug management | |


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| Name | Function | Address |
|---|---|---|
| CCI | CRO, Monitoring, serious adverse event (SAE) reporting, and Central Laboratory | CCI |
| | Photography Services | |


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## 2.3 Committees

If any of the conditions described in Section 10.3 of this protocol are met, a data monitoring committee (DMC) will be established to advise the sponsor regarding the safety of trial subjects. Procedures for the evaluation of safety data will be documented in a separate DMC charter.


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# 3 ETHICS

## 3.1 Independent Ethics Committee/Institutional Review Board

The following documents must be submitted to the responsible IRB and approval obtained:

- The clinical study protocol (CSP);
- Any amendment to the CSP that is not solely of an administrative nature;
- The investigator's brochure (IB) and all updates;
- Subject information and informed consent forms, as well as updates (if applicable);
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable); and
- Any other required documents, including subject questionnaires.

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 ICH-GCP (International Council for Harmonization - Good Clinical Practice) and applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the study.

All required approvals, favorable opinions, or additional requirements of the appropriate IRB, or other regulatory authority will be obtained prior to initiation of the trial.

In case of a pandemic disease outbreak, e.g., coronavirus disease-2019 (COVID-19) public health emergency, procedures that prioritize the reporting of protocol deviations that could impact subject safety to the IRB will be defined. In addition, changes in protocol conduct necessary to promptly assure subject safety, such as conducting telephone or video contact visits for safety monitoring rather than on-site visits, can be implemented immediately with subsequent review by the IRB and notification to regulatory authorities (e.g., Food and Drug Administration [FDA]).


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## 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 (effective as of 17-JAN-1997), 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.

### *3.3.2 Informed consent*

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

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 informed consent form as well as all consent form updates (if applicable). The investigation site is responsible to file the original and any amended signed and dated informed consent forms at the investigation site.

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 adverse events (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.

In case of a pandemic disease outbreak, e.g., COVID-19 public health emergency, if reconsenting of the subjects is deemed necessary due to significant changes made to the CSP and/or any essential document which reflects the investigation conduct that could impact them:

- Alternative ways of obtaining consent will be defined as subjects should not visit sites for the sole purpose of obtaining re-consent. Subjects will, e.g., be contacted


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via phone or video calls and their verbal consent will be supplemented with written (e.g., email) confirmation;

- Approved updated subject information sheet and consent form will be provided by email, mail, or courier to obtain a re-consent; and
- All instances of consent that is obtained this way will be documented.

The subjects' understanding will be re-confirmed by way of normal consent procedures at the earliest opportunity when/if the subjects are able to return to the sites, if applicable.

### 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:

- Each subject's number (handwritten by the site), randomization number (handwritten), and information that the subject is taking part in a study with botulinum toxin A in the indication prominence of the platysmal bands with a total dose of up to CCI and
- The name, address, and telephone number of the investigator or institution, as the main contact for product information and emergency unblinding.

### 3.3.4 Post-study treatment

No specific post-study arrangements are made and no specific post-study care will be provided after this study. After study discontinuation, subjects will be treated by their physician according to their medical condition and standard treatments in the United States (US).

### 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 coded 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-coded 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 IRBs) who have been bound to confidentiality. If the results of the study are published, the subject's identity will remain confidential. CCI


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## 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 informed consent form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the subject, if requested or if required by local law.

Any medical or non-medical deviation from the CSP 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 CSP. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical study staff, and/or contract research organization (CRO), including failure to act according to ICH-GCP principles or to comply strictly with the CSP.

## 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.


CCI [redacted]

# 4 INTRODUCTION

## 4.1 Study background

Botulinum toxin A (BoNT/A) is synthesized by a wild-type strain of the anaerobic bacterium *Clostridium botulinum* as part of a high molecular weight complex, comprised of several hemagglutinins and other non-toxic non-hemagglutinin proteins. Acting selectively on peripheral cholinergic nerve endings, BoNT/A inhibits the release of the neurotransmitter acetylcholine and paralyzes muscle contraction.

The selective action of BoNT/A at its target requires a four-step sequential process [1-4]: a) docking to the binding site at the plasma membrane; b) internalization of the BoNT/A molecule; c) translocation of the zinc-dependent endopeptidase part of BoNT/A to the cytosol; and d) proteolysis of synaptosomal associated protein 25 (SNAP-25), a component of the vesicle fusion machinery, which prevents exocytosis of acetylcholine into the synaptic cleft and inhibits nerve-impulse transmission at the motor endplate.

NT 201 (Clostridium botulinum neurotoxin type A [150 kD, free of complexing proteins] powder for solution for injection) is the only marketed BoNT/A preparation that is free from complexing proteins. The highly purified nature of NT 201 is regarded as a clinical advantage compared with other BoNT/A preparations, with a reduced potential for development of neutralizing antibodies following repeat treatment. [5, 6] Currently, NT 201 is approved in over 50 countries for a variety of therapeutic indications (e.g., blepharospasm, cervical dystonia, upper limb spasticity, focal spasticity, strabismus, tremor, sialorrhea) and aesthetic indications (e.g., hyperkinetic facial lines, lateral periorbital lines, upper facial lines, glabellar frown lines).

The platysma is a broad flat muscle that covers the anterior and lateral aspects of the neck. It originates inferiorly from the pectoralis and deltoid fascia and ascends upward, partially inserting directly under the mandible (its only bony insertion) into the modiolus, the *depressor anguli oris*, the lower lip, the *depressor labii inferioris*, and finally continuing upward to blend into the Superficial Musculo-Aponeurotic System (SMAS) and the skin of the cheeks. During the natural aging process, the youthful appearance of the neck is lost and vertical neck bands, or platysmal bands, become increasingly more prominent as a result of hyperkinetic platysma activity and loss of muscle tone. Additionally, the platysma acts as a major depressor in the lower face. The increased tone associated with aging pulls down the lower face contour, and thus results in its loss of sharpness (i.e., blunting). As a result, subjects seek cosmetic treatments that can improve the appearance of the aging neck and jawline.


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## 4.2 Study rationale

The current study is a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter, phase 2 clinical study to assess the efficacy and safety of different NT 201 doses for treatment of moderate to severe platysma prominence.

The use of BoNT/A is a potentially safe and effective treatment of the platysma muscle, particularly its bands and jawline insertion. Several reports describe treatment of platysmal banding with BoNT/A injection, leading to decreased platysmal prominence and improvement of the lower face contour. [7-11] Specific to NT 201, Prager et al., [12] demonstrated an 87% responder rate (> 1-point change on a dynamic platysmal bands assessment scale) at 14 days following intramuscular injection of NT 201 (15 U per band; 60 U total). Using the same response definition, Gubanova et al., [13] demonstrated 100% responder rate at 14 days post-treatment with NT 201 (60 U total).

A variety of doses are described for this indication in the scientific literature. Published consensus recommendations on platysma treatment refer to BoNT/A (onabotulinumtoxin A or incobotulinumtoxin A) doses ranging from 1 U to 5 U in 3 to 6 injection points per band, for a total of 6 U to 40 U per platysma band [8-10, 14, 15]. Specific to incobotulinumtoxin A (NT 201), Yutskovskaya et al [9] recommend a maximum dose of 2 U to 5 U per injection point, and an initial dose of 15 U to 20 U per band. Sugrue and colleagues [16] performed a systematic literature search and identified three articles reporting botulinum toxin injections for platysma bands in neck rejuvenation. The included studies used a maximum 20 U of incobotulinumtoxin A per platysma band. Patient-reported metrics demonstrated an improvement in 91% of subjects.

The highly purified nature of NT 201 is regarded as a clinical advantage compared with other BoNT/A preparations, with a reduced potential for development of neutralizing antibodies following repeat treatment [5, 6] particularly when using doses that are reflective of the caliber of the muscle.

Initial descriptions of platysmal prominence treatment with BoNT/A [17] report the following post-treatment AEs: transient edema and ecchymoses; hematoma formation; muscle soreness or neck discomfort; and headaches. Further, several subjects reported mild neck weakness while performing sit-ups or lifting their head off the pillow, lasting for 1 to 2 weeks post-treatment. Rarely, transient instances of neck muscle weakness, hoarseness (i.e., dysphonia), or dysphagia may occur. [17] AEs appear independent of the dose selected and more associated with injection technique. [16]

Taking into consideration the literature, and considerable feedback from physicians well versed and experienced in injecting the platysma muscle with NT 201, Merz developed a treatment map (described in Section 8.1.1.2) for this study that addresses the intricate


CCI [redacted]

anatomy of this muscle group, including intramuscular injections along the length of each of four platysma bands in the neck and each side of the jawline.

In this trial, the efficacy and safety of NT 201 will be investigated and a clinical dose for the treatment of platysma prominence will be determined.

## 4.3 Risk-benefit assessment

Merz' goal is to ensure the protection of the safety and well-being of the participating subjects. Injection of BoNT/A for aesthetic indications represents the most common, minimally invasive cosmetic procedure in the US, with nearly 7.7 million procedures performed in 2019 alone. [18] In combination with this wealth of clinical experience, decades of clinical and scientific investigation demonstrate an excellent safety/tolerability profile for BoNT/A across a wide range of subject populations for multiple therapeutic and aesthetic indications. [15]

In general, the known safety profile for NT 201 on approved aesthetic indications shows good tolerability (see current investigator's brochure). Common undesirable effects after NT 201 injection include local, generalized, or procedural AEs such as injection site hematoma, injection site erythema, and ecchymosis. Local AEs are usually mild and temporary in nature for NT 201 approved aesthetic indications.

Merz conducted a review of the medical literature to identify reports of AEs after platysmal prominence treatment with BoNT/A. Brand and Bellman [17] described the use of BoNT/A for the treatment of platysmal prominence in their clinical practice and reported the following AEs: transient edema and ecchymoses; hematoma formation; muscle soreness or neck discomfort; and headaches. The authors also described that several subjects reported mild neck weakness while performing sit-ups or lifting their head off the pillow, lasting for 1 to 2 weeks post-treatment. In rare instances, transient instances of laryngeal muscle weakness, hoarseness (i.e., dysphonia), or dysphagia may occur. [17]

Prager et al., [12] reported three treatment-related AEs across 23 subjects when treating platysmal bands with NT 201, all of which resolved including: two cases of hematoma and one case of minor neck muscle weakness noticed during yoga. Levy et al., reported four subjects experiencing AEs in a cohort of 130 subjects treated with onabotulinumtoxin A: two subjects with mild dysphagia and excess lifting effect, resolving within four weeks; and two subjects with "very slight" unilateral smile incontinence due to partial chemodenervation of the *depressor labii inferioris*. [19] Jabbour et al., reported five subjects with injection-site ecchymosis across 30 subjects treatment with abobotulinumtoxin A, resolving within two days. One subject reported mild dysphagia and minor neck muscle weakness, persisting for two weeks after injection. [20] Additionally, no treatment-related serious adverse events (SAEs) were reported in a phase 2 study of onabotulinumtoxin A for the treatment of platysma prominence in 171 subjects, most


CCI [redacted]

treatment-related AEs were procedure related, mild in severity, and the most common treatment-related AE was neck muscle weakness (n = 5). [21] Sundaram et al. [15] published consensus guidelines for treatment of the lower face/neck with BoNT/A identifying the following as potential AEs and/or post-treatment complications: asymmetry; oral motor insufficiency (e.g., impaired ability to raise or lower the lip); impairment of dental show in animation (smiling); impaired muscular support of lower face; dysphagia; neck weakness; and dry mouth.

Informed by these findings, the following key AEs of special interest were identified for this study: dysphagia, neck muscle weakness, hoarseness (i.e., dysphonia) and dry mouth. Dysphonia and dysphagia typically occur 12 to 72 hours after exposure [7, 17, 22] and have been reported to resolve within 2 to 4 weeks. Neck muscle weakness has been reported for 1 to 2 weeks post-treatment [12, 17, 20]. Given the early onset and transient nature of these key TEAEs of special interest, the proposed overall phase 2 study duration of 17 weeks (i.e., four months), is deemed sufficient to evaluate the safety of enrolled subjects.

With regard to treatment effect and safety, there should be a balance between a dose that allows for the desired effect in the targeted muscle and minimizes the risk of potential side effects. Treatment in an unintended area or partial correction of the platysma muscle may cause unintended effects. CCI [redacted]

To mitigate the risks of complications, NT 201 must be administered at the site where it exerts the desired pharmacological effect. In rare cases, the neurotoxin may diffuse to muscles near the injection site and exert effects on those muscles. Therefore, the choice of anatomical sites for injections, as well as the precision of the injections is important. The position of injection sites and the injection technique to be used in this study are described in detail in this protocol.

Considering all potential benefits and risks, the sponsor believes that the proposed study is carefully designed and special caution has been given to safeguard subjects against potential risks.

Additional risks that may arise such as a pandemic disease outbreak, e.g., COVID-19 or other public health emergency, may affect the clinical study conduct. It is our primary goal to ensure the protection of the safety and well-being of the participating subjects. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected. These challenges may lead to difficulties in meeting protocol-specified procedures, and thus, might lead to protocol modifications (please refer to Section 9.2.1).


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# 5 STUDY OBJECTIVES

The primary objective is to assess the efficacy of different NT 201 doses for treatment of moderate to severe platysma prominence by demonstrating superiority of NT 201 versus placebo.

The secondary objective is to assess the safety of different NT 201 doses for treatment of moderate to severe platysma prominence.


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[redacted]

# 6 INVESTIGATIONAL PLAN

## 6.1 Overall study design

The study will be a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter, phase 2 clinical study. A total of 68 subjects will be randomized at approximately seven sites in the US. Information on the sample size is presented in Section 12.1. Subjects enrolled will be adults, CCI at the time of screening, with a score from moderate (score 3) to severe (score 4) on the validated five-point Merz Aesthetic Platysma Scale-Dynamic (at maximum contraction; MAPS-D, see CCI), as assessed live by the investigator and the subject.

An equal number of study subjects will be randomly assigned with a balance ratio (1:1:1:1) to one of four groups, and all randomized subjects will receive a single treatment cycle on the platysma (CCI). Each subject will receive one intramuscular treatment with CCI CCI of NT 201 per injection point (given as injections of equal amount C CCI or an equivalent volume of placebo (given as injections of equal amount CCI) (more information is provided in Section 8.1.1).

CCI

Study subjects will have eight on-site study visits, including screening (V1), treatment (V2), and post-treatment visits at Week 1 (V3), Week 2 (V4), Week 4 (V5), Week 9 (V6), Week 13 (V7), and Week 17 (V8, end of study [EOS] visit). Subjects will receive one post-treatment phone call at 24 to 72 hours after treatment to evaluate safety. If a subject reports a safety concern during a phone call, an unscheduled visit will be scheduled if necessary to address safety concerns.


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The planned duration of participation for individual subjects will be 17 weeks plus the individual duration of screening (up to 14 days) for each subject. CCI provides an overview of the study design.

### 6.1.1 End of study

The EOS will be defined as the last study visit of the last subject.

### 6.1.2 Study flow chart

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## 6.2 Discussion of study design, including choice of control groups

The design of this phase 2 clinical study was chosen to investigate the efficacy and safety of NT 201 in the treatment of moderate to severe prominence of the platysmal bands associated with platysma muscle activity. No approved, marketed products are currently available in the US for treatment of platysmal prominence.

An equal number of study subjects will be randomly assigned with a balance ratio (1:1:1:1) to one of four groups: CCI NT 201 per injection point CCI total dose), CCI NT 201 per injection point CCI total dose), CCI NT 201 per injection point CCI total dose), and


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placebo. This multicenter design approach will increase the representativeness of the study results and decrease site-related biases. The risk of bias is minimized by including a placebo control. Randomization will eliminate selection bias in treatment assignment.

As detailed in Section 4.2, a variety of doses are described for this indication in the scientific literature. The proposed injection technique is informed by the different injection patterns published in the available literature [redacted]: NT 201 is to be injected intramuscularly across multiple injection points [redacted].

The proposed timeframe to evaluate efficacy is based in published studies specific to NT 201 [12, 13] which have reported efficacy at 14 days following intramuscular injection of NT 201 when assessing a > 1 point change on a dynamic platysmal bands assessment scale [25]. Prager and colleagues also showed a peak effect at 14 days when measuring the mean change from baseline in the platysmal bands scale scores. The overall study duration of 17 weeks (i.e., four months) will allow for early identification of potential AEs (as described in Section 4.3, above) as well as for a thorough evaluation of the efficacy results for all three NT 201 doses, including potential dose-dependent trends over time.


[redacted]

# 7 STUDY POPULATION

Subjects with a score of moderate (score 3) to severe (score 4) on MAPS-D at maximum contraction, as assessed by the investigator and the subject will be enrolled in this study. The ratings of the investigator and subject do not have to coincide.

Eligible subjects are those who meet all of the inclusion criteria and who do not present any of the exclusion criteria prior to randomization to treatment groups. Subjects are to be recruited regardless of gender and ethnic background. This study population will therefore be expected to be a representative sample of the target population for the treatment of moderate to severe prominence of platysmal bands.

## 7.1 Selection of study population

A total of 68 subjects CCI [redacted] are planned to be enrolled. Please refer to Section 12.1 for sample size calculation.

No stratification regarding gender is planned. According to experience from former studies, more females are expected to be interested to take part in this study. It is therefore expected that around 80% to 90% of subjects will be female; this represents the usual gender distribution in the daily practice among people seeking cosmetic procedures.

## 7.2 Inclusion criteria

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

| Inclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| CCI [redacted] | | | |


CCI [redacted]

| Inclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| 4. Presence of four (medial and lateral, left and right) prominent platysmal bands. | Efficacy | X | |
| 5. A score of moderate to severe on the Merz Aesthetic Platysma Scale-Dynamic (MAPS-D) at maximum contraction, as assessed by the investigator. | Efficacy | X | |
| 6. A score of moderate to severe on MAPS-D at maximum contraction, as assessed by the subject. The ratings of the investigator and subject do not have to coincide. | Efficacy | X | |
| CCI [redacted] | | | |

## 7.3 Exclusion criteria

Subjects meeting any of the following criteria at the screening (V1) and/or at the treatment visit examination (V2; as indicated below) will not be included as subjects in this study:

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| CCI [redacted] | | | |

CCI [redacted]



CCI [redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| 2. Botulinum toxin treatment in the face (below the lower orbital rim), neck, or chest within the last 12 months prior to study treatment. | Efficacy | X | X |
| 3. History of lower face surgery (i.e., below the level of the bottom of the nose; including rhytidectomy), neck or chest surgery, aesthetic procedures (e.g., ablative skin resurfacing, laser, chemical peel, micro-focused ultrasound, deoxycholic acid injections, micro-needling, non-surgical fat reduction procedure), and orthodontic procedures (e.g., braces) in the 12 months prior to study treatment, [redacted] | Efficacy | X | X |
| 4. Previous use of any permanent (non-biodegradable) or semi-permanent (e.g., calcium hydroxylapatite, poly-L-lactic acid, polymethyl methacrylate, etc.) facial tissue augmentation therapy, lifting sutures, permanent implants or autologous fat to the lower face (i.e., below the level of the bottom of the nose), neck, or chest within 24 months prior to study treatment. | Efficacy | X | X |


[redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| 5. Previous use of any hyaluronic acid based or collagen based biodegradable facial tissue augmentation therapy to the lower face (i.e., below the level of the bottom of the nose), neck, or chest within 12 months prior to study treatment. | Efficacy | X | X |

CCI [redacted]


CCI [redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| CCI [redacted] | | | |


CCI [redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| CCI [redacted] | | | |



CCI [redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| 17. Any medical condition that may put the subject at increased risk with exposure to botulinum toxin of any serotype, including myasthenia gravis, Lambert-Eaton-Syndrome, amyotrophic lateral sclerosis, or any other disorders that might interfere with neuromuscular function. | Safety concern | X | X |
| CCI [redacted] | | | |
| 19. Any serious disease or disorder (medical or psychiatric) that could, CCI [redacted] interfere with the safe completion of treatment CCI [redacted] CCI [redacted] CCI [redacted] or compromise subject safety CCI [redacted] CCI [redacted] | Efficacy and safety concern | X | X |
| CCI [redacted] | | | |


CCI [redacted]

| Exclusion Criteria | Rationale | V1 Screening | V2 Treatment |
|---|---|---|---|
| CCI [redacted] | | | |
| 23. Female of childbearing potential[2] and is not using a highly effective method of birth control[3], plans to get pregnant, or is pregnant or lactating. | Safety concern | X | X |
| CCI [redacted] | | | |

CCI [redacted]



CCI [redacted]

## 7.4 Removal of subjects from treatment or assessment

### *7.4.1 Discontinuation of subject's study participation*

In accordance with the Declaration of Helsinki and the informed consent form, 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 7.4.3). 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 electronic case report form (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;
- Pregnancy prior to study treatment. If a subject becomes pregnant during the study, the subject must not receive further treatments (i.e., additional injections), or any other invasive procedures (e.g., blood draw); however, the subject will remain in the study;
- Any AE occurring before V2 (treatment) for which study treatment would constitute an unacceptably high risk for the subject; or
- 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.

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. If a DMC is conveyed (see Section 10.3) it may recommend further criteria for subject's discontinuation.

Subjects who discontinue the study because of AEs will be treated according to standard clinical procedures and will be followed up until the EOS visit as described in Section 10.1. All pertinent information concerning the AE will be documented in the source documentation as well as in the eCRF AE report form.

In the event of a public health emergency the sponsor will inform the principal investigator (PI), the IRB, and the relevant regulatory authorities promptly of any planned mitigations to protect the safety and well-being of subjects. This can include but is not limited to: putting the study recruitment on hold, stopping or postponing further treatments, or changing on-site visits to visits by phone.


CCI [redacted]

Following discontinuation, the EOS visit is to be performed. 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).

### *7.4.2 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 re-assessed, and the risks outweigh any potential benefits;
- The incidence of AEs constitutes a potential health hazard to the subjects;
- Recommendation of the DMC (if applicable);
- 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 CSP, the Declaration of Helsinki, ICH–GCP, and/or applicable regulatory requirements; or
- The sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the 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, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as well as provide reasons for the action.

In case of a pandemic disease outbreak, e.g., COVID-19 public health emergency, it might not be feasible for the site to continue study participation. In this case, consideration should be made as to whether the trial site closure would affect the safety and well-being of participating subjects. Additionally, consideration should be made around impact and maintenance of data validity.


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### *7.4.3 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 US.


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[redacted]

# 8 TREATMENTS

## 8.1 Investigational product(s)

### *8.1.1 Description of investigational product(s)*

NT 201, marketed as Xeomin in the US (active ingredient: NT 101, *Clostridium Botulinum* neurotoxin type A [150 kDa], free from complexing proteins) will be provided in quantities of 200 U in glass vials containing sterile and lyophilized powder to be reconstituted for injection. Excipients are sucrose, human serum albumin. No international non-proprietary name for the drug substance has been assigned. The assigned US Adopted Name (USAN) for the active ingredient is incobotulinumtoxin A.

The placebo vials consist of powder for reconstitution with excipients only (sucrose, human serum albumin) and do not contain the active ingredient NT 101. Placebo vials and NT 201 vials have identical appearance and the solution properties of the powder with and without NT 201 are identical.

NT 201 and Placebo are manufactured by Merz Pharma GmbH & Co. KGaA, Am Pharmapark, 06861 Dessau-Rosslau, Germany. NT 201 and placebo are released by Merz Pharmaceuticals GmbH or Merz Therapeutics GmbH, Eckenheimer Landstr. 100, 60318 Frankfurt am Main, Germany. IP Distribution / drug management is conducted by CCI [redacted] supervised by Merz Therapeutics GmbH.

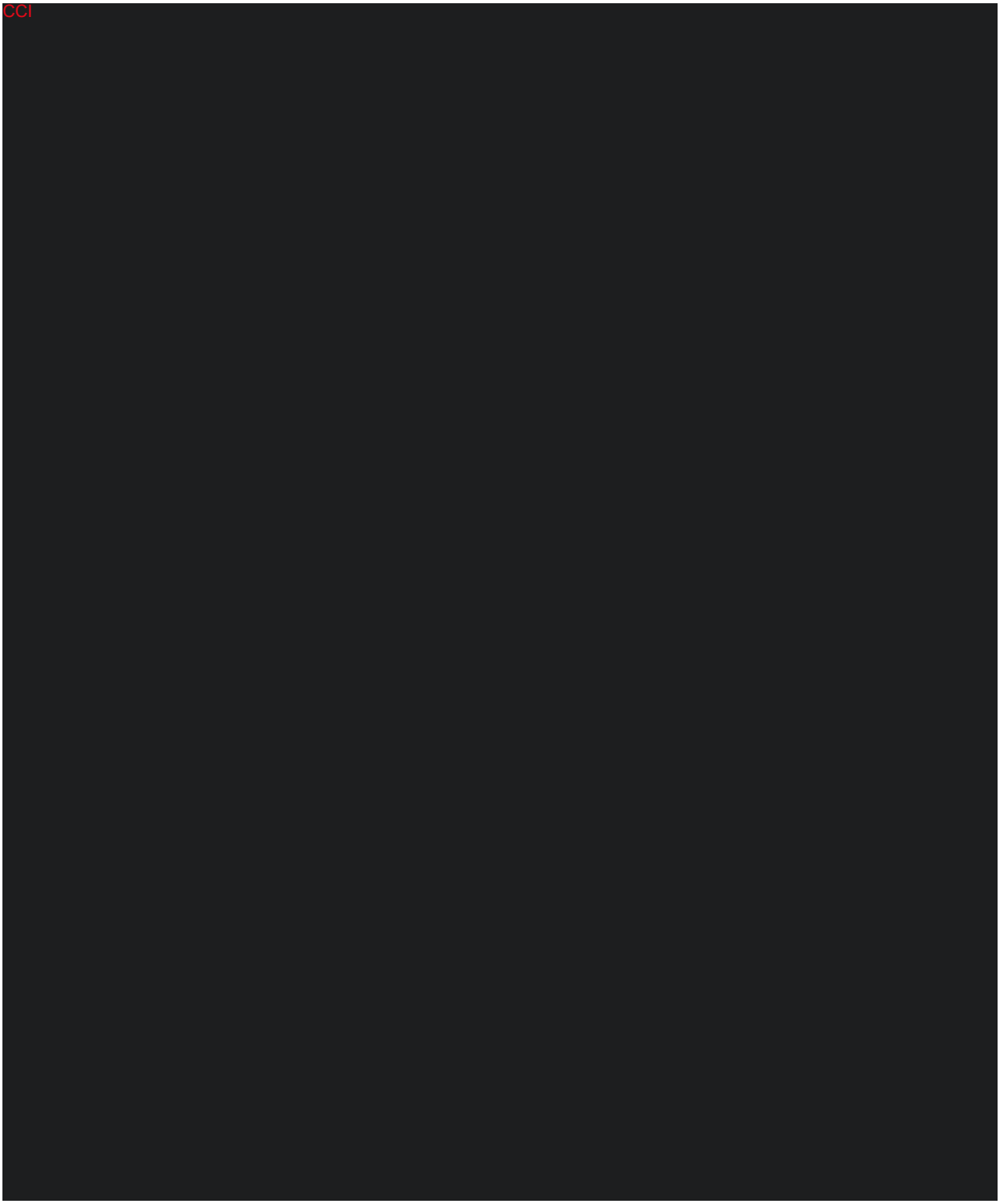
#### *8.1.1.1 Instructions for preparation*

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#### 8.1.1.2 Instructions for administration

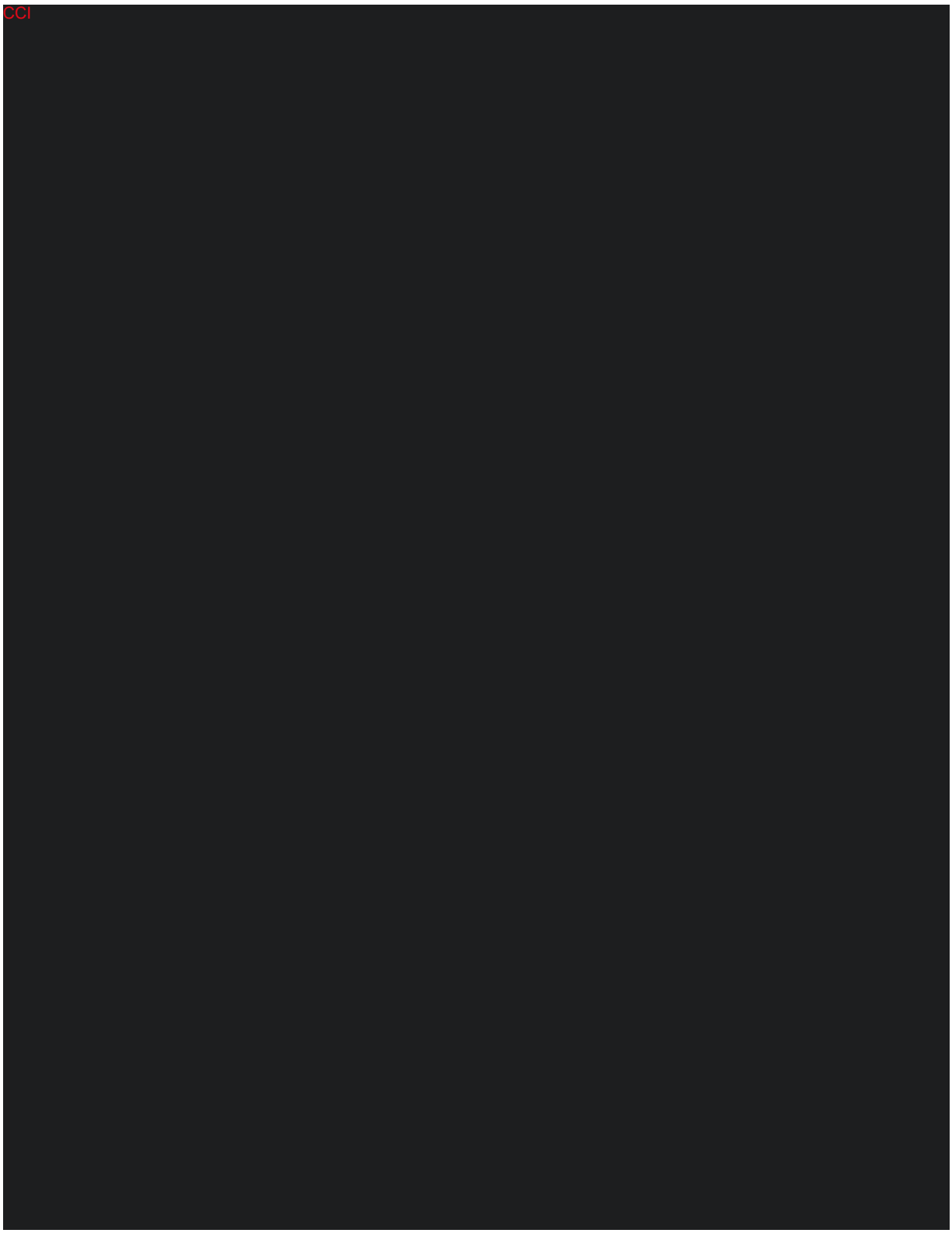
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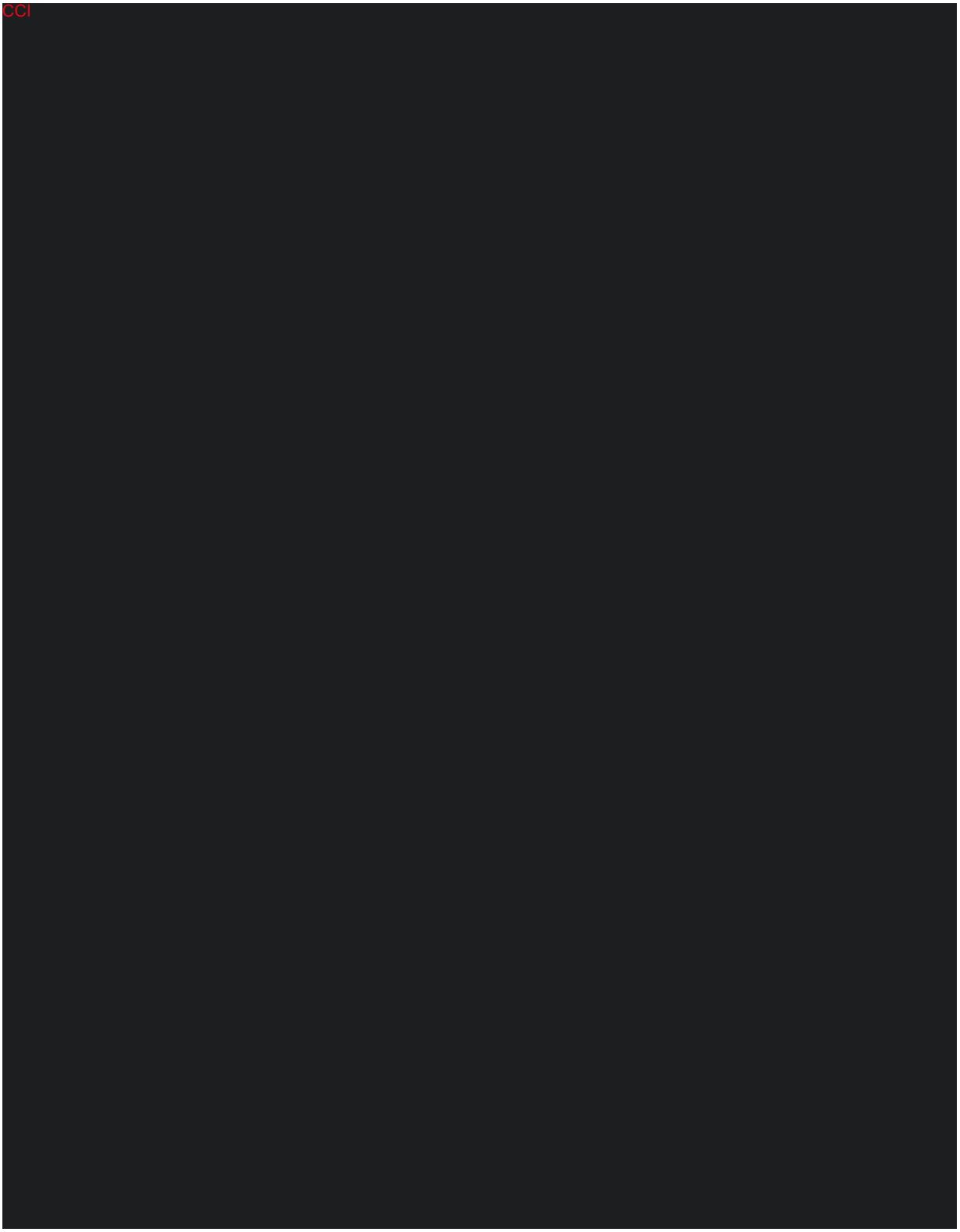



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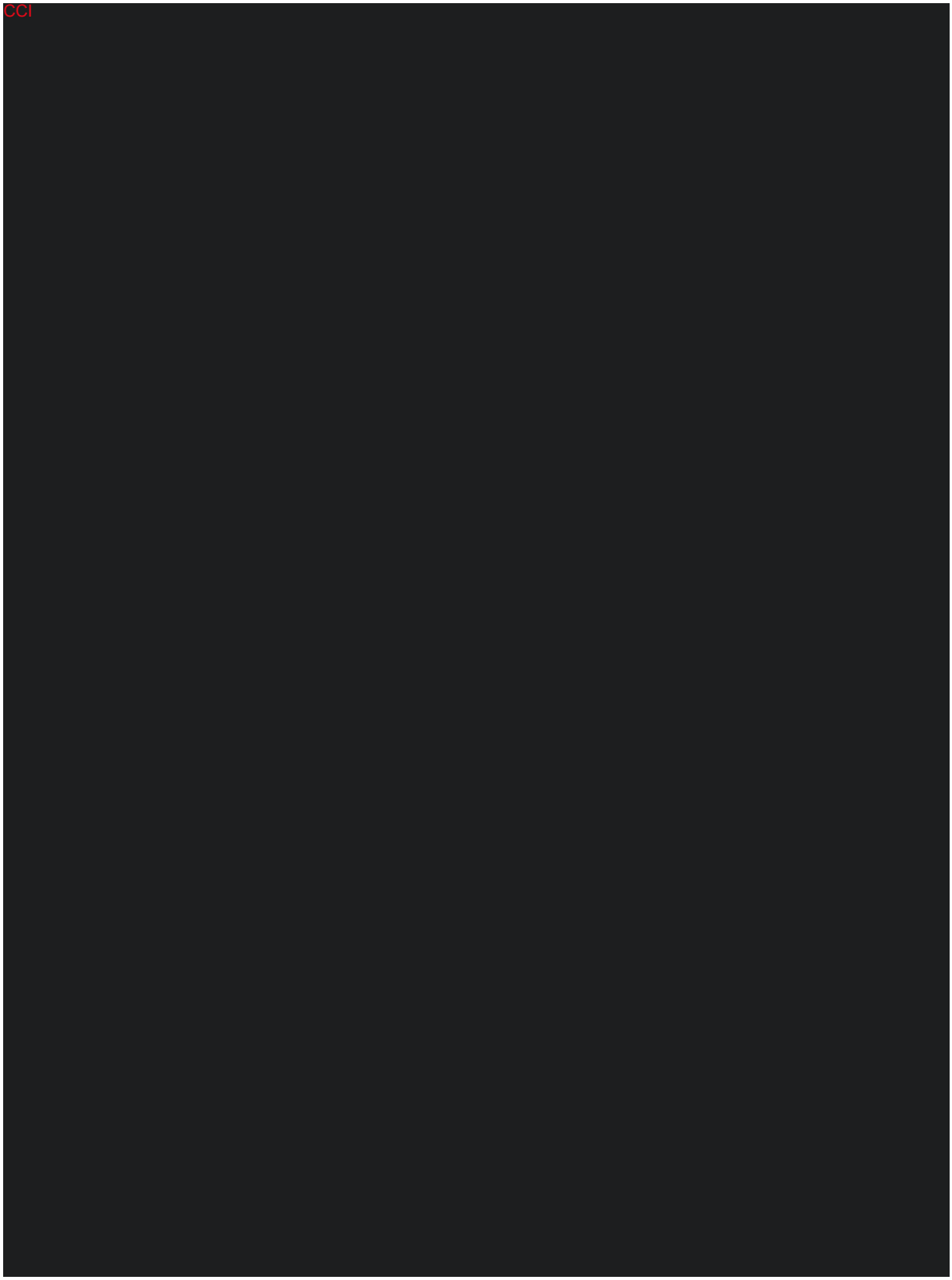

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## 8.2 Treatments administered

Subjects will be randomized into one of the following groups:

- Group 1: NT 201, CCI [redacted]
- Group 2: NT 201, [redacted]
- Group 3: NT 201, [redacted] or
- Group 4: Placebo.

### *8.2.1 Methods of assigning subjects to treatment groups*

The study is planned as a multicenter study. Subjects will be randomized to one of the four treatment groups in a 1:1.1:1 ratio using an IRT system. Balanced randomization in blocks of appropriate size and blockwise distribution of the IP to the study sites will ensure an approximately equal number of enrolled subjects in every treatment group per site. The block size will not be disclosed to investigators until the study is unblinded. The investigator, the subject, and the sponsor will be blinded. Subjects will receive a subject/screening number through the IRT, as well as a randomization number, if randomized.

The investigator will enter the subject in the IRT and confirm successful screening. The IRT will then assign to each subject a randomization number and the unique medication number of the IP kit to be used for injection. The screening, randomization, and medication numbers as well as the treatment will be recorded in the subject file and in the eCRF.

The unblinded study nurse or pharmacist responsible for preparation of the IP will add a sticker with the medication number (provided in the IP kit) on the ready for use syringe to ensure correct assignment to the subject by the investigator or a printed note accompanying the syringe stating subject/screening number and medication number.

Randomization will be performed at V2 (treatment) before administration of the investigational product.

Subjects who are withdrawn prematurely will retain their screening and randomization numbers, if applicable.

Discontinued subjects will not be replaced.


CCI [redacted]

### 8.2.2 Selection of doses in the study

The choice of the doses per treatment area used in this study are justified by published results from clinical studies with NT 201 and other BoNT-A preparations as described in Section 4.2 and Section 6.2.

### 8.2.3 Selection and timing of doses for each subject

Subjects will be randomized to one of the four treatment groups as presented in CCI Treatment (NT 201 or placebo) will be administered at V2 (treatment) according to the instructions detailed in Section 8.1.1.2 and the injection scheme shown in CCI

### 8.2.4 Duration of treatment per subject

The screening evaluation must be completed between 14 days and 3 days prior to V2 (treatment). Subjects will receive one injection treatment at V2 followed by an injection-free observation period of 17 weeks ± 7 days. Therefore, the total study duration for a single subject is 116 days to 141 days from V1 (screening visit) to the end of the observation period (V8, EOS visit).

In case of a public health emergency, 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. This might include, but is not limited to, extending study visit windows, performing study visits by phone or video, and/or performing efficacy assessments remotely.

### 8.2.5 Treatment compliance

At the beginning of the study, the site will receive drug accountability forms to document how and when IP is dispensed to subjects, or whether it is returned unused. These forms will be made available to the authorized individuals (e.g., monitor, auditor) and will include the following information: study number, dates, quantities, and the medication number assigned to the IP and study subjects. IRT print-outs can also be used for documentation.

The IP(s) will be administered to the lower face contour areas and neck by intramuscular injection performed by the investigator during the subject's visit at the site at V2 (treatment). Thus, full treatment compliance is assured for each individual subject.

### 8.2.6 Treatment of overdose

An overdose is defined as treatment with IP exceeding the total dose specified in the protocol. Any overdose must be recorded in the IP section of the eCRF and the source


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documents. Any case of overdose leading to SAEs or adverse event(s) of special interest (AESI) must be reported to the CRO in an expedited manner using the appropriate reporting form (see Section 10.1).

As treatment with IP is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this study is considered to be low. For the IP used in this study, no antidote has been identified to date, and there is no known therapy recommended for an overdose. The investigator is advised to use best clinical judgment in the unlikely event of an overdose with the IP.

The lethal amounts of crystalline BoNT/A for a 70 kg human is calculated to be approximately 0.09 to 0.15 µg applied intravenously or intramuscularly and 70 µg orally. It has been estimated that for a 70 kg adult the human lethal dose 50 (LD50) by injection is equivalent to approximately 2,800 mouse units, depending on the specific potency of the toxin. This is equivalent to 28 vials containing 100 U. [22]

In the event of an overdose, the investigator or treating physician is advised to use best clinical judgment and should closely monitor the subject for any AE and SAE and document the quantity of the excess dose. Excessive doses of NT 201 may be expected to produce neuromuscular weakness with a variety of symptoms.

Signs of an overdose include acute symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysphonia, and dysphagia, which would typically occur 12 to 72 hours after exposure. [22] Furthermore, signs and symptoms of overdose can result in ptosis, generalized muscle weakness, and paralysis of respiratory muscle leading to aspiration pneumonia. Clinical cases of iatrogenic botulism after BoNT injection were reported for four adult subjects whose clinical signs were consistent with those of naturally occurring botulism. [26]

Symptoms of overdose are not immediately apparent following injection. By the time symptoms of intoxication are observed, treatment with antitoxin will no longer be effective because the neurotoxin has already irreversibly blocked the transmitter release. Compounds releasing acetylcholine (e.g., physostigmine, guanidine, 3,4-diaminopyridine) might be helpful. However, there is no experience with a specific antidote to BoNT including NT 201 in the clinical management of overdose. A published case report describes the successful treatment of dysphagia with intranasal neostigmine. [27]

Subjects should be advised to seek immediate medical care and notify the study physician immediately if symptoms such as swallowing difficulties, speech or breathing problems occur. Subjects will receive a subject card with contact information in case of emergency (Section 3.3.3) if additional information on the scope of the study should be required.

Should accidental injection or oral ingestion occur, the subject should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or


CCI [redacted]

paralysis. Symptomatic treatment may be necessary. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. Antitoxin would not reverse any BoNT-induced effects already apparent by the time of antitoxin administration.

## 8.3 Previous and concomitant therapies

Before enrollment, the subject's medical history should include a detailed list of all medications (including rescue medication) that the subject was taking for a period of at least 30 days and for a period of 12 months for non-drug therapies (24 months for permanent or semi-permanent non-drug therapies) previous to screening. The record should include the drug name (trade or generic), route of administration (e.g., intravenous, oral), total daily dose/unit (expressed in mg, mL, or IU), indication, the start and stop date (day, month, and year) for each medication. At the end of the study an additional statement will be entered to indicate whether the intake of the 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 procedures, concomitant medications, and non-drug therapies are forbidden during the study (please see also exclusion criteria in Section 7.3):

- Any surgery or aesthetic procedures in the lower face, neck, and chest that may violate exclusion criteria number 1, 2, 3, 4, or 8;
- Any other investigational drug;
- Anticoagulants (e.g., heparin, cumarines, non-vitamin K antagonists, oral anticoagulants like Apixaban, Dabigatran, Edoxaban, Rivaroxaban) for prophylactic or therapeutic reasons within ten days prior to treatment to four days after treatment (however, aspirin and other platelet-aggregation inhibitors like Ticlopidine, Clopidogrel, Prasugrel, Abciximab, Eptifibatid and Tirofiban are allowed); and
- Any forbidden concomitant medications (e.g., drugs listed in World Health Organization Anatomical Therapeutic Chemical [WHO-ATC] class M03 Agents) or medications that affect neuromuscular transmission such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases, and aminoglycoside antibiotics within 14 days prior to treatment and during the entire course of the study.

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


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Women of childbearing potential[4] must be using a highly effective method of birth control[5] for the whole duration of the study.

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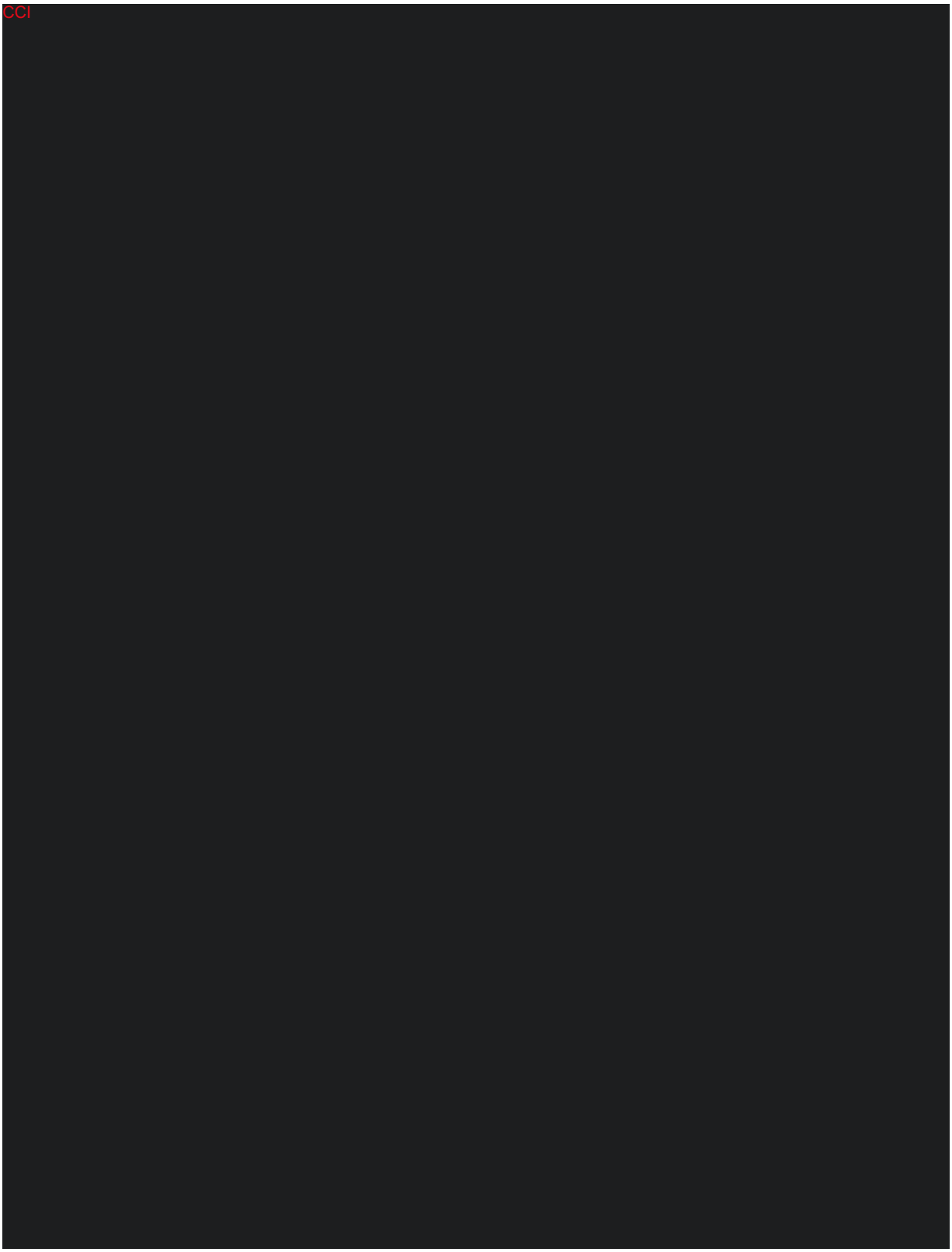
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# 9 STUDY ASSESSMENTS AND VISIT SCHEDULE

## 9.1 Assessments

All assessments will be performed as scheduled according to the study flow chart (Figure 1) and as detailed in the schedule of events table CCI

### *9.1.1 Clinical assessments*

Assessments performed by the subject should always be done independently from the investigator and study staff at the beginning of a study visit before any investigator's assessments take place to guarantee independence of self-ratings.

CCI The subject's assessments should be done in the following order: CCI

CCI the MAPS-D assessment (CCI ), CCI
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#### *9.1.1.1 Merz Aesthetic Platysma Scale - Dynamic (MAPS-D)*

##### 9.1.1.1.1 Investigator's assessment

The platysma area will be assessed live by the investigator at maximum contraction according to the validated five-point MAPS-D (CCI CCI ). As platysmal bands are most recognizable during speech or neck-muscle

flexion, subjects will be instructed to grimace while strongly pronouncing the letter ‘e’ to produce maximum platysmal-band contraction for condition grading.

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Assessments on the MAPS-D at maximum contraction by investigators are only to be performed by trained and qualified investigators. Training will take place prior to the first assessment and consist of an instructional session, followed by a qualification where trainees will score two sets of photographs representing a variety of different MAPS-D grades, at least two weeks apart. Any investigator that does not pass the qualification exercise will be retrained and requalified up to two times. If evaluator retention (e.g., change in personnel) becomes an issue during the study, new blinded evaluators must be trained by the sponsor, and respective qualification analyses must be performed. Qualification and training of blinded evaluators will be documented.

Ratings will be done at V1 and from V3 to V8. Ratings at V1 (screening) and V4 (Week 2) in an individual subject should be performed by the same treating investigator. For the sake of consistency, all efforts should be taken for all ratings of an individual subject to be performed by the same investigator throughout the study.

#### 9.1.1.1.2 Subject’s self-assessment

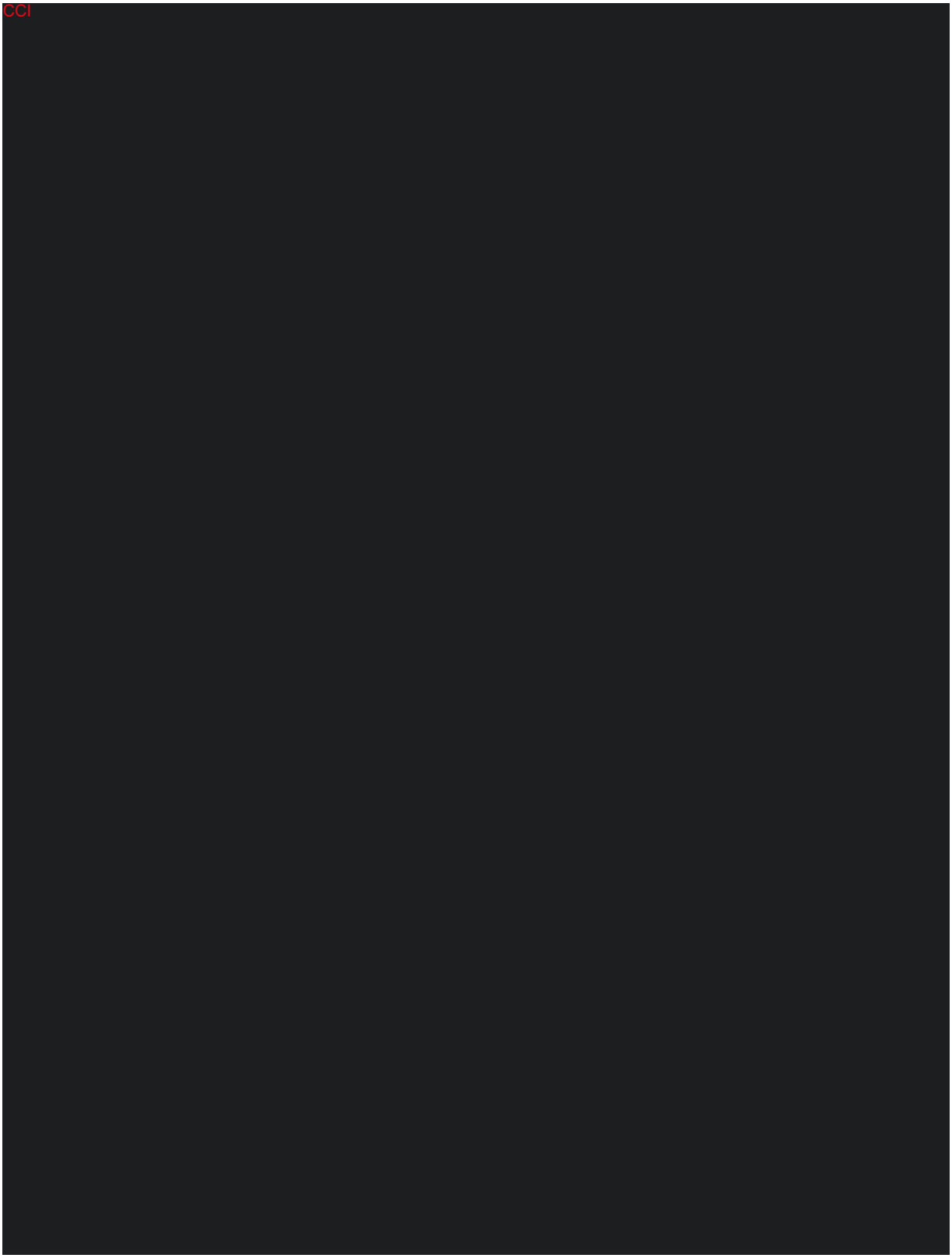
Subjects will self-assess their platysma at maximum contraction according to the validated five-point MAPS-D. CCI [redacted] The MAPS-D photo guide will be provided as reference.

Ratings will be done at V1 and from V3 to V8. The subject's ratings will be done prior to the assessment of the investigator and independently from the investigator.

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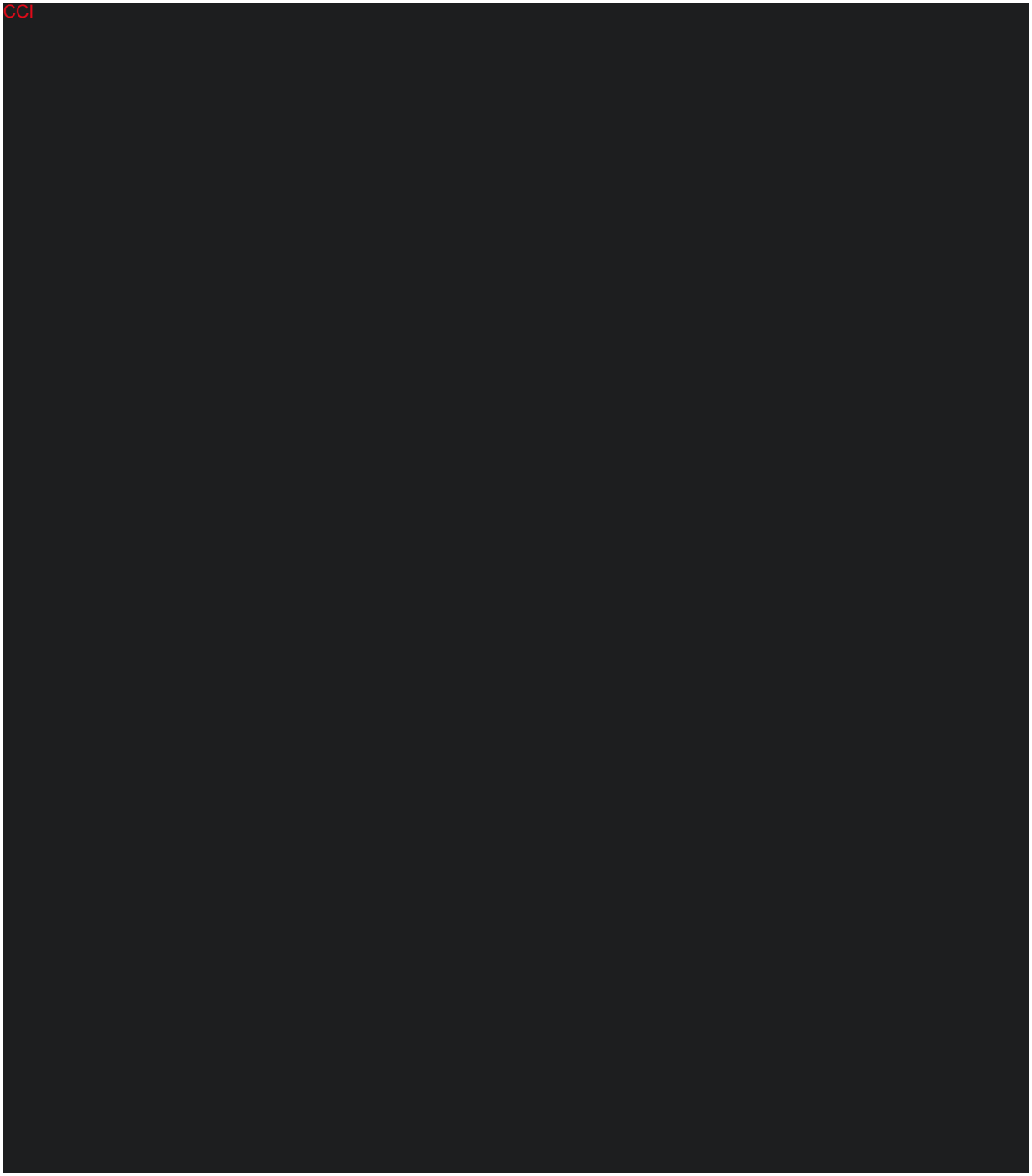
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#### 9.1.1.11 General assessments

General assessments include the following:

- Medical history and concomitant diseases, prior and concomitant medication, prior and concomitant non-drug therapies;
- Subject disposition;
- Physical examination;
- Vital signs;



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- Demographic data; and
- Body height (V1, screening) and weight (at V1 and V8, EOS visit).

At the beginning of the study, the subject's demographic data, relevant medical history all prior medication (within 30 days before screening) and all current and concomitant medications planned during the study will be recorded. Previous treatments with any facial cosmetic procedure and with botulinum toxin for any serotype in any body area must be recorded regardless of time of application. For prohibited and concomitant therapies, see Section 8.3. A review of this information will allow the investigator to assess whether the subject should be enrolled. Other data will be collected as required, including information obtained from physical examinations and vital signs. If counseling of subjects is deemed necessary, either before enrollment or during the study, counseling will be made available by the investigator involving other medical specialists, if necessary.

The following vital signs will be examined as scheduled according to the visit schedule CCI blood pressure and heart rate.

### *9.1.2 Laboratory evaluations*

#### *9.1.2.1 Clinical and research laboratory evaluations*

Blood samples for evaluation of clinical biochemistry and hematology will be drawn and pregnancy testing performed as described in the study visit schedule CCI Standard safety laboratory assessments will include the parameters as described in CCI The samples for hematology and clinical biochemistry, including serum pregnancy testing, will be analyzed at a central laboratory. Details with regard to the methods of sampling as well as the amount of blood to be taken will be described in the respective laboratory manual. See also Section 9.1.6.

Serum pregnancy testing in female subjects with childbearing potential will be performed at V1 (screening), with results available before administration of the IP, and at V8 (EOS visit). A urine pregnancy test will be done prior to injection at V2 (treatment).

If laboratory evaluations are missing or are unreliable (e.g., due to failed analysis) a re-test of these parameters has to be performed in the central laboratory. Reliable laboratory results for all required parameters have to be available prior to the subject's treatment visit (V2). The results of the re-test will be entered in the study data base.

Any laboratory results outside the normal range must be graded by the investigator or his/her delegate as 'abnormal, not clinically relevant' or 'abnormal, clinically relevant' in the subject file. After the injection of IP, a laboratory abnormality should be regarded as


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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.

An additional safety laboratory assessment can be performed 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 data base optionally if values are part of safety reporting.

If the investigator suspects that a subject presents with the symptoms associated with a public health emergency, 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 judgment of the investigator and local health care providers. All positive test results must be documented in the eCRF as an AE.


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### 9.1.3 Pharmacodynamics

Not applicable.

### 9.1.4 Pharmacokinetics

Not applicable.

### 9.1.5 Pharmacogenetics

Not applicable.



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### 9.1.6 Table of blood volume

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The blood amount corresponds to routine laboratory practice. Additional blood sampling may be necessary in case of missing values, e.g., due to failed analysis or if additional safety testing is deemed necessary by the investigator.

### 9.1.7 Specimen preparation, handling, storage, and shipping

Blood samples for clinical chemistry, hematology, and β-HCG will be determined by a central laboratory and will be handled according to the manual of the central laboratory. Blood samples will be stored at the central lab until the end of the study and destroyed after study completion.

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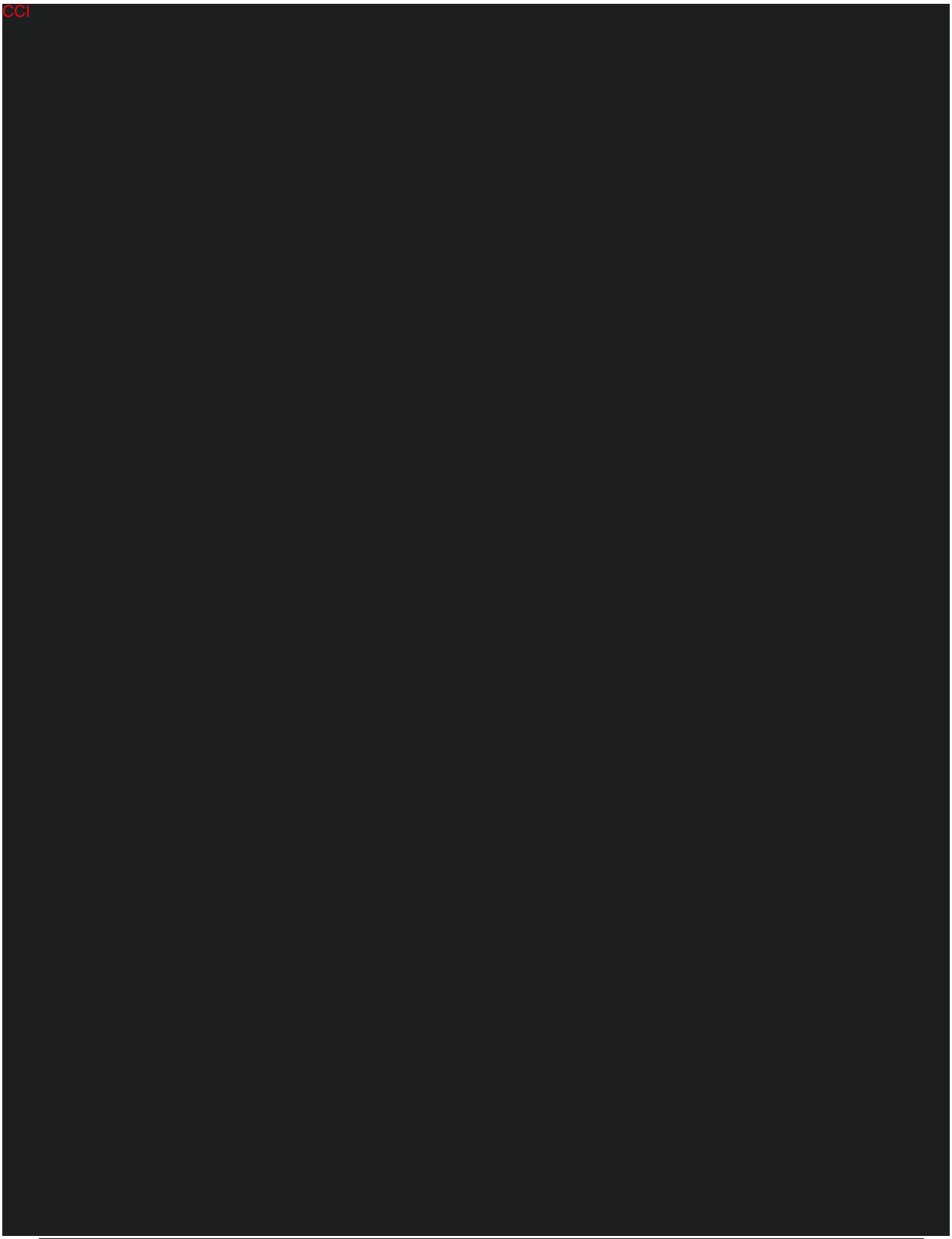
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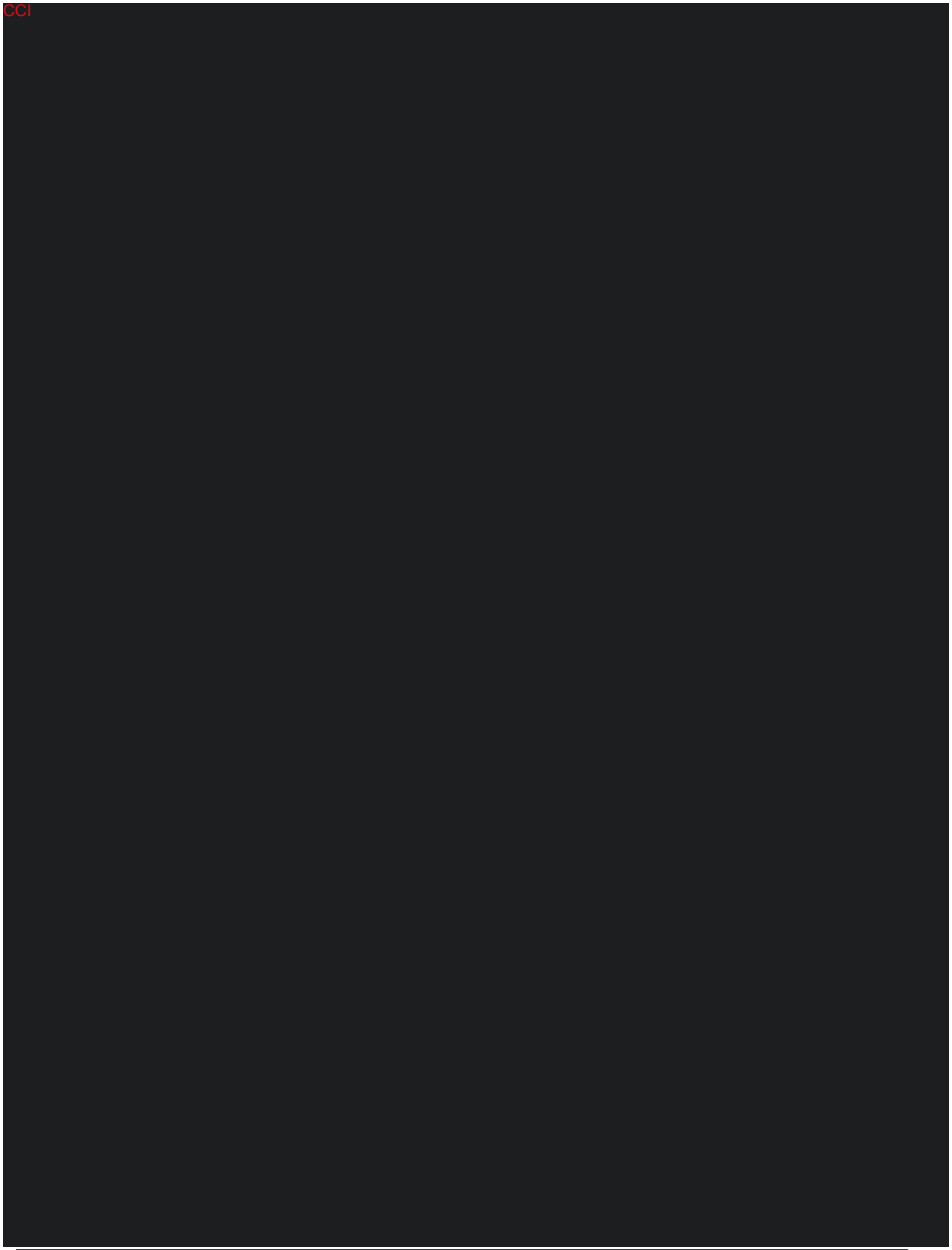



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### 9.2.1 Modified visit schedule during a pandemic

In case a pandemic disease outbreak, e.g., a new public health emergency, affects the clinical study conduct, it is our primary goal to ensure the safety and well-being of the participating subjects.

- In general, limit the visit schedule to those visits necessary for subject safety, clinical care, or follow-up of AEs;
- Use phone or virtual study visits for routine, mandated safety follow-up as described in the study protocol;
- Determine if efficacy data can be collected remotely; and
- Arrange flexibility where possible of any required procedures, e.g., subject imaging, photography, lab sampling, if applicable.

Public health emergency mitigation rules for this protocol:

- Screening: up to two re-screenings are allowed. In case the subject quarantines, site closures, travel limitations do not allow subject on-site randomization, re-screening of subjects will be allowed after relaxation of public restrictions;
- Increase the visit time window to ± 7 days for V4 and ± 14 days for visits V5 to V8 for on-site visits;
- If on-site visits are not possible due to subject quarantines, site closures, travel limitations, interruptions to the supply chain for the IP, or other considerations, if site personnel or trial subjects become infected:
    - Visits should be conducted remotely (e.g., via phone) to collect subject safety data;



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- Investigator' assessments can be conducted via a video assessment, if the technical prerequisites are available at the site and subject level under consideration of applicable data protection laws;
- Collection of standardized photography and platysmal band length measurement will need to be done during an on-site visit, with the increased visit time window of ± 7 days for V4 and ± 14 days for visits V5 to V8;
- Subject's self-assessments of efficacy should be conducted at the subject's home if the subject consents to this; and
- CCI [redacted]


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# 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. Information on expected and unexpected AEs is available in the IB.

Changes in efficacy endpoints (e.g., subject-reported outcomes [questionnaires and scales] during the course of the study) need not be documented as AEs, because these changes will be recorded as efficacy endpoints. Elective treatments planned before screening and which are documented in the subject's source data are usually not regarded as AEs.

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.

The period of observation for an AE extends from the time when the informed consent form was signed until Week 17 ± 7 days after administration of IP. Any medical occurrence during the observation period is an AE and has to be documented in the subject file.

Any untoward medical occurrence that happens between the time when the informed consent form is signed, and IP administration is an AE and has to be documented in the subject's file and in the eCRF AE report form. These AEs are called non-TEAEs.

TEAEs are defined as AEs with onset or worsening on or after date and time of first dose of study treatment.

New AEs reported to the investigator during the observation period after IP administration must be documented, treated, and followed up like all other AEs. Non-serious AEs will not be followed up after the EOS visit, which is scheduled 17 weeks ± 7 days after IP administration. Information on SAE follow-up is presented in Section 10.2.

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 observation period. To determine whether a condition has worsened, it is compared to the condition of the subject at screening. Abnormal laboratory values obtained during the subject's screening period will only meet AE criteria if newly detected and if considered clinically relevant.


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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 (see Section 10.1.1);
- Causal relationship (not related, related);
- Serious (yes or no);
- Reason for seriousness;
- Outcome (see Section 10.1.3);
- 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 report form and report it to the CROimmediately, as described in Section 10.2.

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.


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*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 report 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 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 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]

[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.


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

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 planned before screening 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 by telefax, telephone or e-mail within 24 hours of knowledge of the event. SAE report forms are provided in the Investigator's 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;
- An identifiable reporting source (investigator/study site identification); and
- An event or outcome that can be identified as serious:

The report must be delivered to the individual(s) listed below.

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[redacted]

[7] 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."



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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 product safety database 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 study database.

## 10.3 Adverse events of special interest (alert terms)

AEs that are thought to possibly indicate toxin spread are defined as AESIs. To ensure the safety of the subjects and to assess for any potential AEs, subjects will return for an in person visit at 1 week (visit 3) and 2 weeks (visit 4) following injection. The subject will be actively asked by the investigator at each visit starting with V2 (treatment) if any of the AESI terms listed in CCI below occurred since the last contact. The standardized active assessment for signs and symptoms of systemic toxin spread, including focused physical examination, will be performed as detailed in the AESI manual. AESI questioning at V2 (treatment) will be done prior to treatment and will facilitate recording of pre-existing conditions and/or possibly undetected (S)AEs that could confound AESI questioning post-treatment of IP. AESIs occurring after signature of informed consent until treatment are defined as non-TEAESIs and will be entered in the source documents and on the AE pages of the eCRF.

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. Thus, they should be closely monitored and reported to the sponsor within 24 hours.

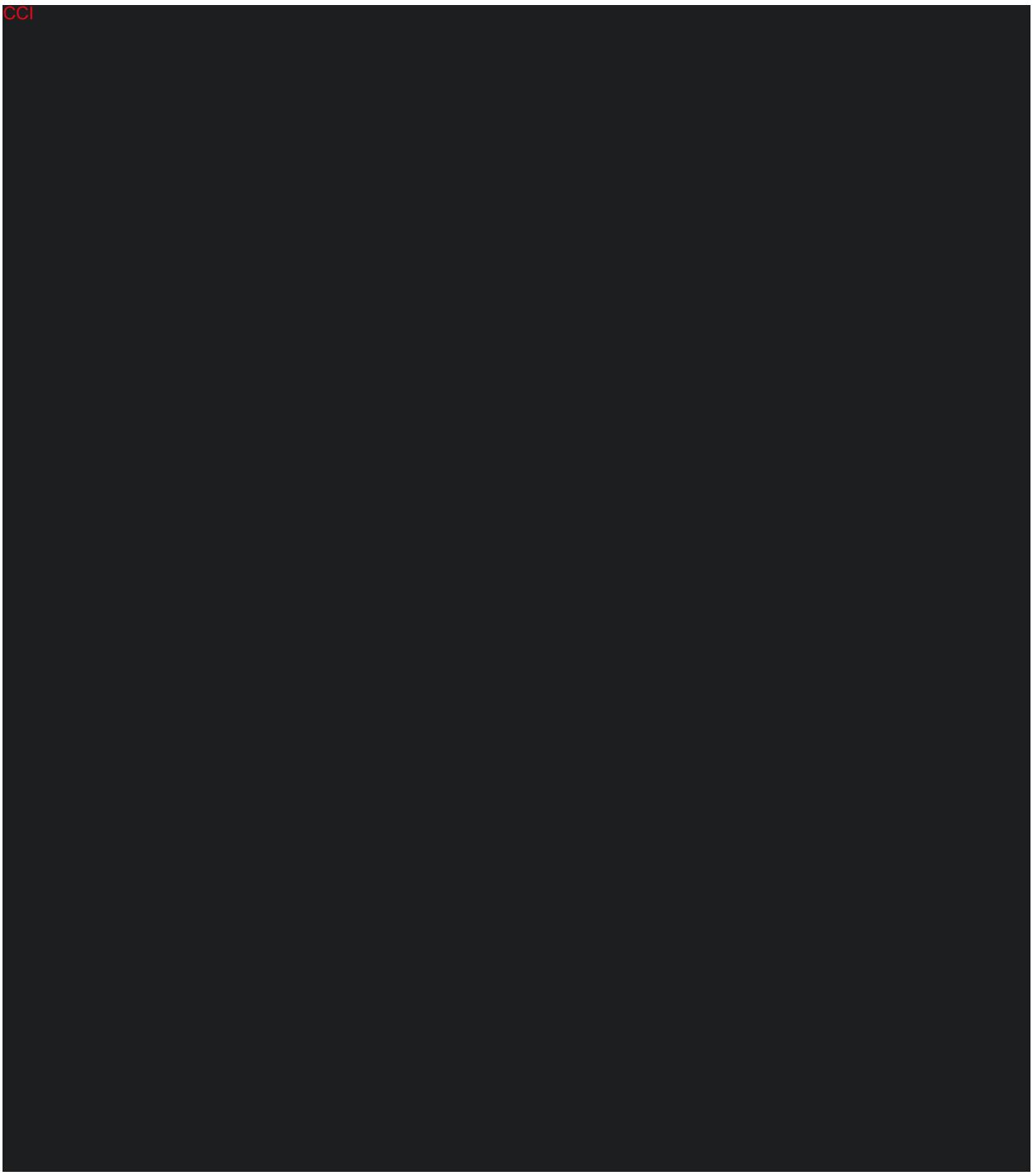
The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, by telephone, telefax, or e-mail to the responsible CRO within 24 hours of knowledge of the event. Each AESI must be reported by the site on the AESI reporting form. Moreover, AESIs should 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 pages 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 this study, the following AEs are defined as key AEs of special interest:


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As described in Section 4.3 above, transient instances of the following key AESIs have been reported after platysmal prominence treatment with BoNT/A: dysphagia, neck muscle weakness, hoarseness (i.e., dysphonia) and dry mouth. Dysphonia and dysphagia would typically occur 12 to 72 hours after exposure [7, 22]. Merz intends to closely monitor the occurrence of these transient events during the phase 2 study.



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If either one of the above mentioned key AESIs (dysphagia, neck muscle weakness, hoarseness (i.e., dysphonia) and dry mouth) is reported at an investigational site as an event of moderate to severe intensity, administration of treatment to additional subjects will be paused at the affected site and the treating investigator will be retrained on appropriate injection technique if needed. After retraining, the site may resume treatment of subjects.

Additionally, if there are three or more instances of moderate to severe events of either dysphagia, dysphonia, neck muscle weakness or dry mouth at either site or if multiple sites report the same event, administration of treatment to additional subjects will be paused at the affected sites and a DMC will be conveyed. The DMC will evaluate the safety data on the affected subjects and make recommendations to the sponsor if any changes to the study conduct are deemed necessary to ensure subject safety.

The clinical intensity of key AESIs will be classified on the basis of its associated signs and symptoms and following the National Cancer Institute Terminology Criteria for Adverse Events where applicable as shown in CCI

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## 10.4 Expected adverse events

Expected AEs are those listed in the reference safety information of the current IB for NT 201.

## 10.5 Unexpected adverse events

An unexpected AE is an AE not previously reported in nature, severity, or incidence in the reference safety information of the current IB for NT 201.

## 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



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exposure before or during pregnancy). Any abnormal pregnancy or pregnancy outcome is to be reported as serious adverse event (on an SAE -form).

## 10.7 Other safety assessments

Other safety assessments include:

- Assessment of standard clinical biochemistry and hematology at V1 (screening) and V8 (EOS visit) (for detail see Section 9.1.2.1);
- Vital signs of blood pressure and heart rate at V1, V4, V5, and V8 (EOS visit);
- Physical examination at V1 (screening) and V8 (EOS visit);
- Serum pregnancy test at V1 (screening) and V8 (EOS visit) and urine pregnancy test at V2 (treatment) prior to treatment (only for females of childbearing potential[8]); and
- Subjects will be contacted by telephone 24 to 72 hours after each treatment and will have an unscheduled visit if indicated by safety concerns.

[8] Childbearing potential is defined as not premenarche, permanently sterilized, or postmenopausal (i.e., 12 months with no menses without an alternative medical cause).


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# 11 DATA QUALITY ASSURANCE

Inspections by regulatory authority representatives and IRBs are possible at any time, even after the EOS. 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 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, and validation methods).

Assessments on the MAPS-D CCI [redacted] by investigators are only to be performed by trained and qualified investigators (see Section 9.1.1.1.1 and Section 9.1.1.2.1).

This study will be monitored regularly by a qualified monitor from the CRO according to ICH-GCP and the respective 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 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 etc.). Scales assessed by the investigators and subjects on paper forms (i.e., MAPS, CCI [redacted]) will be considered as source data and will be transferred into the eCRF by the site.


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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 are to be recorded in the web-based eCRFs (electronic data capture [EDC] system) provided by CCI [redacted]. All users who will enter data into the eCRF will be previously trained. Successful completion of the training will be a prerequisite for the access to the eCRF. The access to the eCRF is password-controlled and conforms with 21 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 EDC 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 EDC 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.

Laboratory and platysmal band length data will be received electronically and merged with the eCRF data (but not uploaded into the EDC system). Plausibility checks will be performed to ensure correctness and completeness of these data. The data management/biostatistics vendor CCI [redacted] will be responsible for data-processing, in accordance with the sponsor's data management procedures.

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


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In case of a pandemic disease outbreak, e.g., new public health emergency, and by this, if data entry and cleaning is limited or not possible due to site closures, travel limitations, or other considerations if site personnel become infected, the following mitigations should be considered for data cleaning processes:

- Data entry and response to data clarifications will proceed depending on availability of study nurses, coordinators and investigators;
- Depending on the content of data clarifications, the necessity of source data review of the response will be re-assessed by the sponsor;
- Self-evident corrections of obvious query responses might be allowed. These will be documented thoroughly (e.g., using a list of self-evident corrections to be approved before database lock);
- If applicable, risk-based assessment of closing long open queries will be done considering their impact on trial conclusion and data validity; and
- Assessment will be done if data clarifications and/or eCRF pages are to be signed by staff that is not yet on the delegation log. The delegation log is to be updated, if applicable.

## 11.4 Monitoring

This study will be monitored regularly by a qualified monitor from the CRO according to GCP guidelines and the respective SOPs. During these visits, 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 CSP, 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/AESIs/pregnancies 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.


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All subjects who are screened, but not included in the study, will be listed on the subject screening/enrollment log.

Regular monitoring tasks will be performed by a blinded monitor. Compliance with the IRT randomization and inventory/drug accountability will be monitored by an unblinded monitor.

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.

In case of a pandemic disease outbreak, e.g., new public health emergency, and by this, if 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 should be considered and assessed in an updated monitoring plan:

- On-site monitoring visits might be cancelled and/or the period between monitoring visits extended. When planned on-site monitoring visits are not possible, the reason should be clearly documented and made available for review during audits and/or inspections;
- Phone and/or video visits will be implemented when feasible, considering site closures, reduced staff and any other circumstances;
- Remote monitoring or central monitoring could substitute on-site monitoring, when technically feasible; and
- Protocol deviations will be tracked and documented if deviations occurred due to the public health emergency.

Current local regulations, including data privacy regulations will be considered when accessing source data remotely.

## 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).


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# 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 CSP or the SAP. All deviations and/or alterations will be summarized in the clinical study report.

In case of a pandemic disease outbreak, e.g., new public health emergency, if 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 should be considered and assessed in an updated SAP:

- Describe changes to planned and additional analyses due to the public health emergency. Thoroughly assess amount and patterns of missing values and sources of bias such as missing values and virtual instead of live assessments (if applicable);
- Include systematic identification of protocol deviations due to the public health emergency; and
- Consider the need for involvement of an independent DMC, particularly if trial sample size changes are anticipated.

## 12.1 Determination of sample size

A total sample size of 68 randomized subjects (i.e., 17 subjects per treatment group) was chosen in order to have at least 64 evaluable subjects at the primary endpoint visit (V4, Week 2) assuming a drop-out rate of maximal 5% within the first two weeks. The sample of 64 evaluable subjects will have a power of at least 90% under the following assumptions:

- Mean change NT 201 = -1.7 (assumption for NT 201 Groups 1, 2, and 3);
- Mean change placebo (assumption for Group 4) = -0.5;
- Standard deviation = 1;
- Two-sided, alpha = 0.05;
- Randomization ratio 1:1:1:1; and
- Power at least 90%.

An estimated total number of 64 subjects will provide 90.7% power to show a statistically significant difference between CCI dose group (Group 3 with N = 16 subjects) and the placebo (Group 4 with N = 16 subjects) at an alpha level of 0.05 (two-sided t-test,


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Statistical Analysis System software® Version 9.4). Further dose groups 104 U vs. placebo and 78 U vs. placebo will be tested in a hierarchical manner and no alpha adjustment will be performed.

Prager and colleagues [12] conducted an investigator-initiated trial (IIT) in which 23 subjects were treated with CCI of NT 201 in total. The mean change from baseline in mean scores at maximum tension on the published 5-point scale for platysmal bands [25] to Week 2 in was -1.696. As no data for higher doses is available, a mean change from baseline of approximately -1.7 was assumed for all NT 201 treatment groups (Groups 1, 2, and 3) in this sample size estimation even if it might be even stronger especially in Group 2 CCI and Group 3 CCI As there was no data available for placebo and for standard deviation in Prager's study the assumption for mean change in placebo group and for standard deviation are based on clinical experience in other indications.

The sample size has been determined for the primary objective of the phase 2 study which is assessing the efficacy of different NT 201 doses for treatment of moderate to severe platysma prominence by demonstrating superiority of NT 201 versus placebo. The sample size of 68 randomized subjects is also considered adequate for the secondary objective of the phase 2 study which is assessing the safety of different NT 201 doses for treatment of moderate to severe platysma prominence. Seventeen (17) subjects per dose group is considered a sufficient number of subjects to have a first safety assessment of each dose without exposing a too large number of subjects to risk and discomfort of potential AEs.

## 12.2 Analysis sets

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

**Safety evaluation set**

The SES is the subset of all subjects who were exposed to IP at least once.

**Intention to treat set**

The ITT is the subset of all randomized subjects.


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## 12.3 Endpoints for analysis

### *12.3.1 Efficacy endpoints*

#### *12.3.1.1 Primary efficacy endpoint*

The primary efficacy endpoint is:

- Change from baseline on the MAPS-D score at maximum contraction, as assessed live by the investigator at V4 (Week 2).

Note that the MAPS-D investigator's assessment conducted at the screening visit will be used as the baseline value for MAPS-D scores.

The main primary estimand is defined as follows in CCI


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#### 12.3.1.2 Secondary efficacy endpoint

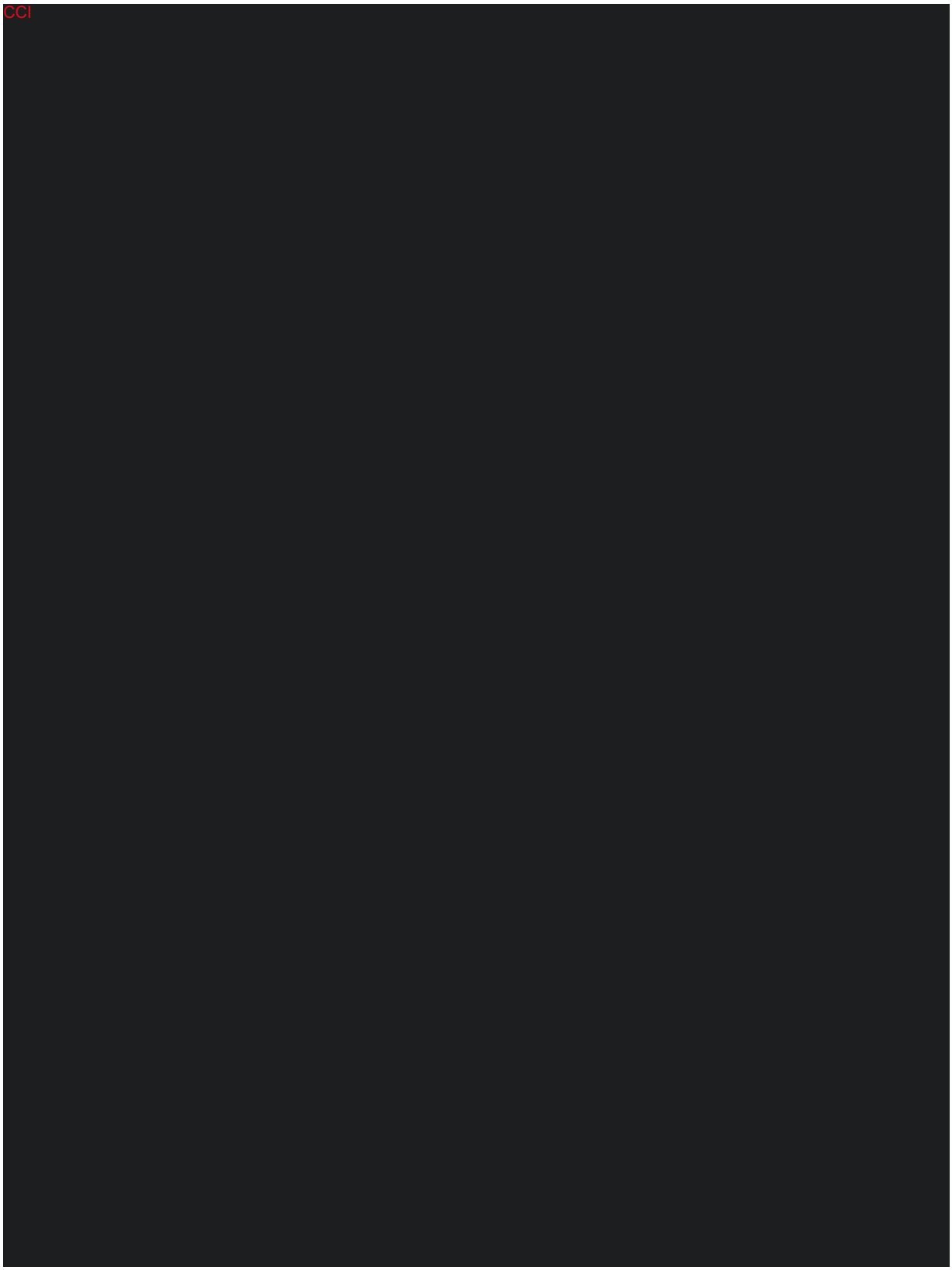
The secondary efficacy endpoint is:

- Change from baseline on the MAPS-D score at maximum contraction, as assessed by the subject at V4 (Week 2).

Note that the MAPS-D subject's assessment conducted at the screening visit will be used as the baseline value for MAPS-D scores.



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[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

Not applicable.

#### 12.3.5.2 Secondary safety endpoint

The secondary safety endpoint is:

- Incidence of related treatment emergent adverse events (related TEAEs).

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## 12.4 Statistical analysis methods

### *12.4.1 Efficacy endpoints*

Unless indicated otherwise, all efficacy analyses will be based on the ITT. Efficacy analyses will be performed per randomized treatment group. Statistical tests will be two-sided hypothesis tests for between-treatment differences in general. Continuous variables (values and changes from baseline) will be summarized by N, mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (N, %) will be tabulated. Confidence limits and descriptive p-values will be given, where appropriate.

#### *12.4.1.1 Primary efficacy endpoint*

The primary efficacy endpoint is defined in Section 12.3.1.1.

**Main estimators**

The primary efficacy analyses will be based on the target population of main primary efficacy estimands, defined in CCI [redacted] Metric descriptive statistics by randomized treatment group will be provided.

A baseline-adjusted repeated measures ANCOVA ($\alpha = 5\%$, two-sided) with randomized treatment group and study site as fixed factors will be used for the analysis of the primary efficacy endpoint. The covariates will be MAPS-D at baseline and age at screening. LS means of the change from baseline to V4 (Week 2), calculated by the model described above, will provide an estimate for the average treatment effect of both body sides and it will be used to test the difference of each NT 201 group to placebo in a hierarchical manner as follows:



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[redacted]

- Only if Group 3 CCI vs. placebo is statistically significant will Group 2 CCI vs. placebo be tested in a confirmatory way;
- If Group 2 CCI vs. placebo is also statistically significant, then Group 1 CCI vs. placebo will be tested in a confirmatory way; and
- If one of the tests is not statistically significant vs. placebo the subsequent test(s) will be interpreted in an exploratory manner.

Handing of missing values is described in Section 12.4.7.1.

**Sensitivity estimators**

In addition to the primary efficacy analyses based on the target population of main primary efficacy estimand as described above, the same analyses based on observed cases will be performed on the ITT for sensitivity purposes.

#### *12.4.1.2 Secondary efficacy endpoint*

The secondary efficacy endpoint is defined in Section 12.3.5.2. The secondary efficacy analyses will be based on the ITT. For the secondary efficacy endpoint, no replacement of missing values will be done, i.e., observed cases will be analyzed.

For the secondary efficacy endpoint, responder rates will be summarized as frequency tables with absolute and percent frequencies (N, %) and by two-sided 95% Wilson score confidence intervals. Responder rates of each NT 201 group will be compared with the placebo group using two-sided 95% Newcombe confidence intervals based on Wilson scores for the risk difference.

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### 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

All safety analyses will be performed on the SES per actual treatment group and for total active group. AEs will be coded according to the Medical Dictionary for Regulatory



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Activities (MedDRA) version in effect at the time the database is closed. Only TEAEs will be analyzed.

#### *12.4.5.1 Primary safety endpoint*

Not applicable.

#### *12.4.5.2 Secondary safety endpoints*

The main analysis for the secondary safety endpoint will be the overall TEAE rate of related TEAEs. Furthermore, incidences will be calculated for subjects with related TEAEs and number of related TEAEs on the MedDRA system organ class (SOC) level and on the preferred term (PT) level.




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### 12.4.7 Special statistical/analytical issues

#### 12.4.7.1 Discontinuations and missing data

Discontinued subjects will not be replaced.

The amount of missingness of the primary efficacy endpoint is expected to be low. In case the primary efficacy endpoint is missing for more than 10% of the subjects in the target population of main primary efficacy estimand, multiple imputation (MI) using the SAS procedure PROC MI with 1000 iterations and seed 602011078 will be applied on the target population of main primary efficacy estimands. The variables statement will consider the variables randomized treatment group, study site, age at screening, and MAPS-D at baseline, V3 and V4. Due to the lack of information about the missing data pattern in MAPS-D values over time, the fully conditional specification option will be chosen for the model. All missing MAPS-D values for the post baseline visits V3 and V4 will be replaced. The multiple ANCOVA results will be combined with SAS PROC MIANALYZE.

In addition, observed cases analysis will be performed as sensitivity analysis. If the primary efficacy endpoint is missing for only 10% or less subjects the observed cases analysis is considered the main analysis.

For the secondary and other efficacy analyses, no replacement of missing values will be done, i.e., observed cases will be analyzed.

#### 12.4.7.2 Interim analyses

Not applicable.

#### 12.4.7.3 Committees

If any of the conditions described in Section 10.3 of this protocol are met, a DMC will be established to advice the sponsor regarding the safety of trial subjects. Procedures for the evaluation of safety data will be documented in a separate DMC charter.

#### 12.4.7.4 Multiple comparisons/multiplicity

The family-wise two-sided type I error level $\alpha = 0.05$ for comparisons of NT 201 dose groups and placebo on the primary efficacy endpoint will be controlled by a hierarchical test procedure based on two-sided tests with $\alpha = 0.05$.

For primary efficacy endpoint the three NT 201 dose groups will be tested versus placebo in a hierarchical manner as follows:


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- Only if Group 3 CCI vs. placebo is statistically significant will Group 2 CCI vs. placebo be tested in a confirmatory way;
- If Group 2 CCI vs. placebo is also statistically significant, then Group 1 CCI vs. placebo will be tested in a confirmatory way; and
- If one of the tests is not statistically significant vs. placebo the subsequent test will be interpreted in an exploratory manner.

The hierarchical test procedure will stop once statistical significance could not be reached. All further test will be of descriptive nature only.

#### *12.4.7.5 Examination of subgroups*

Descriptive summaries of the primary efficacy variable by MAPS-D baseline value will be provided. Due to the small sample size of only 17 subjects per group, no further subgroup analyses are defined.


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# 13 DATA HANDLING AND RECORDKEEPING

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

## 13.1 Corrections to data

All data required by this CSP 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 EDC system documents all changes.

If corrections in the subject diary or 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 is not allowed to make any changes to these documents.

The data management/biostatistics vendor (CCI [redacted]) 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 Record-keeping

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, however, 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 CSP and any amendment;


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- Disks (CD/DVD, USB) with PDF files of eCRF data and audit trail (preferably provided to site during close-out visit), and any associated subject-related source data (or, where applicable, authorized copies of source data);
- Signed informed consent forms;
- Copies of site investigators' and co-workers' curricula vitae;
- Copies of all direct correspondence with the IRB and with the regulatory authority(ies);
- Copies of laboratory normal ranges and 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 PI 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.


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# 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 sponsor ensures that the study is registered and study results are disclosed in at least one public clinical study registry (i.e., clinicaltrials.gov), 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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# 16 APPENDICES

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