A prospective, randomized, double-blind, placebo-controlled, multicenter study with an open-label extension period to investigate the efficacy and safety of NT 201 in the simultaneous treatment of upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral canthal lines)

Development phase:	Phase 3
Study identifier **EudraCT** **IND**	M602011070 / NCT04622254 2019-004113-13 100288
Indication:	Simultaneous treatment of horizontal forehead lines, glabellar frown lines, and lateral canthal lines in the upper face
Planned study period:	First subject first visit: Q4 2020 Last primary outcome visit: Q2 2021 Last subject last visit: Q3 2022
Investigational product(s):	NT 201, 100 Units, powder for solution for injection (active ingredient: NT 101, Botulinum neurotoxin type A free from complexing proteins, USAN: incobotulinumtoxinA) Reference product: matching placebo
Sponsor:	Merz Pharmaceuticals GmbH Eckenheimer Landstr. 100 60318 Frankfurt/Main Germany Telephone: +49 69 1503 0 Telefax: +49 69 1503 200
Responsible for the clinical study protocol content at the sponsor:	Clinical Project Manager: PPD Lead Medical Expert: PPD Biostatistician: PPD

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, including EU (Directive 2001/20/EG; General Data Protection Regulation) and German laws (German Medicines Act [AMG]; GCP-ordinance [GCP-V] and applicable data protection requirements). In addition, the clinical study protocol and informed consent form (ICF) are aligned with the requirements of the upcoming EU regulation No. 536/2014, as recommended by the EMA. The following individuals are responsible for the content of the clinical study protocol:

PPD

Date (dd-MMM-yyyy) Signature

PPD

Date (dd-MMM-yyyy) Signature

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

PPD

Date (dd-MMM-yyyy) Signature>

Statement of Compliance

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, as well as EU (Directive 2001/20/EG; General Data Protection Regulation) and German laws (German Medicines Act [AMG]; GCP-ordinance [GCP-V] and applicable data protection requirements).

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

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received a positive opinion from the responsible IEC before enrolling any subject in this study.
- Obtain informed consent for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, IEC review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC, or regulatory authority upon request.
- Use the IP and all study materials only as specified in the clinical study protocol.
- Report to the safety department of the CRO, within 24 hours, any adverse event of special interest and any serious adverse event immediately and under no circumstances later than 24 hours after learning of the event, whether considered treatment related or not.
- Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest.

Furthermore, I understand that:

- Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Merz and – as applicable – of the appropriate IEC 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>

<Study site stamp (if applicable)>

List of abbreviations and definitions of terms

AE	Adverse event
AESI	Adverse event of special interest
BP	Blood pressure
BoNT	Botulinum neurotoxin
BoNT-A	Botulinum neurotoxin type A
CFR	Code of Federal Regulation
CI	Confidence interval
ClinRO	Clinician Reported Outcome
CRO	Clinical research organization
eCRF	Electronic case report form
EDC	Electronic data capture
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration, US
G	Needle gauche
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GCP	Good clinical practice
GFL	Glabellar frown lines
HFL	Horizontal forehead lines
ICE	Intercurrent events
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IND number	Investigational new drug number, issued by the FDA
IP	Investigational product
IRB	Institutional review board
ISF	Investigator's Site File
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LCL	Lateral canthal lines
MAS	Merz Aesthetics Scale
MedDRA	Medical Dictionary for Regulatory Activities
MP	Main period

N	Number of subjects
OLEX	Open-label extension
PI	Principal investigator
PPS	Per protocol set
PRO	Patient Reported Outcome
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
U	Unit
UFL	Upper facial lines
WHO-ATC classification	World Health Organization Anatomical Therapeutic Chemical classification

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1 SYNOPSIS

Study title

A prospective, randomized, double-blind, placebo-controlled, multicenter study with an open-label extension period to investigate the efficacy and safety of NT 201 in the simultaneous treatment of upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral canthal lines).

Study phase

3

Indication

Upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral canthal lines).

Study objectives

Primary objective(s)

Efficacy of simultaneous intramuscular injections of NT 201 in subjects with moderate to severe upper facial lines [UFL] in comparison to placebo.

Secondary objective(s)

Efficacy and safety of simultaneous single and repeat-dose intramuscular injections of NT 201 in subjects with moderate to severe UFL.

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

A total of 360 male and female adults will be recruited.

Key inclusion criteria

- Outpatients (male or female) 18 years of age or older.
- Horizontal forehead lines [HFL], glabellar frown lines [GFL], and symmetrical lateral canthal lines [LCL] of moderate (score 2) to severe (score 3) intensity at maximum contraction as assessed by the investigator and subject according to Merz Aesthetics Scale [MAS]. The ratings of the investigator and the subject do not have to coincide as long as all ratings at maximum contraction are moderate or severe.

Key exclusion criteria

- Previous treatment with botulinum neurotoxin [BoNT] of any serotype in the face within the last 12 months before injection.
- Any facial cosmetic procedure within the last 12 months before baseline injection, such as dermal filling, chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment, ultrasound treatment, tattooing of eyebrows.
- Previous treatment with any biodegradable filler in the face within the last 12 months before injection.
- Any previous insertion of permanent material in the face including any insertion of treads in the upper face or at cheeks (regardless of the time between previous treatment and this study).
- Any medical condition that may put the subject at increased risk with exposure to NT201, including myasthenia gravis, Lambert-Eaton-Syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function.

Study design

This will be a prospective, randomized, double-blind, placebo-controlled, multicenter study with a placebo-controlled main period [MP] with one NT 201 injection cycle followed by an open-label extension period [OLEX] with two NT 201 injection cycles.

In the MP (Cycle 1), a total of 360 subjects will be randomized to three different treatment groups: UFL treatment (Group U), LCL treatment (Group L), and placebo (Group P) in a randomization ratio of 2:1:1. During the MP, subjects will be treated either with a total dose of 64 U NT 201 as simultaneous injections in all three facial areas (Group U), with 24 U NT 201 in the LCL area and placebo in the GFL and HFL area (Group L), or with placebo in all three facial areas (Group P). All randomized subjects will then be followed up for 120 days before they may enter the OLEX period. The duration of the MP (Cycle 1) will thus be 120 days plus the duration of individual screening (up to 14 days).

The OLEX period will comprise two additional treatment cycles, Cycle 2 and Cycle 3 with durations of 120 days each plus up to 30 days for eligibility reassessments per cycle (if required). During each cycle, eligible subjects will receive simultaneous injections of NT 201 at a total dose of 64 U in all three facial areas. Eligibility criteria will be evaluated before each reinjection.

Planned study period

First subject first visit: Q4 2020

Last primary outcome visit: Q2 2021

Last subject last visit: Q3 2022

Duration of treatment per subject

Subjects will receive investigational product (IP) at up to three injection visits.

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Endpoints for analysis

Efficacy endpoints

Primary efficacy endpoints

- Proportion of GFL-responders at Day 30

GFL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for GFL at maximum contraction as assessed by both the investigator and the subject.

- Proportion of HFL-responders at Day 30

HFL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for HFL at maximum contraction as assessed by both the investigator and the subject.

- Proportion of LCL-responders at Day 30

LCL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for both left and right LCL at maximum contraction as assessed by both the investigator and the subject.

Secondary efficacy endpoints

Key secondary efficacy endpoints:

- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for HFL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for both left and right LCL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the subject at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for HFL at maximum contraction as assessed by the subject at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for both left and right LCL at maximum contraction as assessed by the subject at Day 30 of MP.
- Global Aesthetic Improvement Scale (GAIS) as assessed by the subject at Day 30 of MP.

Further secondary efficacy endpoints:

- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for GFL at maximum contraction as assessed by the investigator
- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for HFL at maximum contraction as assessed by the investigator
- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for both left and right LCL at maximum contraction as assessed by the investigator
- GAIS as assessed by the investigator at Day 30 of MP

Safety endpoints

Primary safety endpoint

No primary safety endpoint was defined.

Secondary safety endpoints

- Incidence of related treatment-emergent adverse events (TEAEs) in the MP
- Incidence of related TEAEs in the OLEX period

Total number of subjects and number of countries

A total of 360 subjects will be recruited from Germany.

Number of study sites

It is planned to conduct the study in up to 12 sites in Germany.

Number of visits

A total of 7 study visits are planned during the MP (Cycle 1), plus 5 study visits during Cycle 2 of the OLEX period (plus optional reassessment visits), and 5 study visits during Cycle 3 of the OLEX period (plus optional reassessment visits).

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

NT 201 (active ingredient: NT 101, BoNT type A [BoNT-A], free from complexing proteins, US Adopted Name incobotulinumtoxinA) or matching placebo provided in 100 U vials.

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Statistical analysis methods

Adequate descriptive statistics will be provided for each efficacy endpoint and timepoint.

Primary and sensitivity analyses for primary efficacy endpoints will be based on the target population of main primary estimands which is defined as "Male and female adults (18 years of age or older) with HFL, GFL, and LCL of moderate (score of 2) to severe (score of 3) intensity at maximum contraction as assessed by the investigator and the subject according to MAS, as randomized in this study: Subset of subjects randomized to UFL treatment group or to Placebo treatment group, grouped by randomized treatment assignment." Further efficacy analyses will be based on the full analysis set (FAS) including all randomized subjects, if not otherwise specified.

The primary analysis of primary endpoints will be comparison of proportion of GFL-, HFL- and LCL-responders in treatment groups U and P by Mantel-Haenszel tests of the null hypothesis that the stratum-adjusted difference in response rates at Day 30 is zero, with study site serving as stratum variable.

The family-wise two-sided type I error level $\alpha = 0.05$ will be controlled by a hierarchical test procedure based on two-sided tests with $\alpha = 0.05$. First, a test for superiority of U versus P will be conducted for proportion of GFL-responders, then for proportion of HFL-responders and finally for proportion of LCL-responders. The test procedure will stop once statistical significance could not be reached.

Group L will not be part of the primary efficacy analysis.

All safety analyses will be performed on the SES.

Listings and tables displaying incidences of related TEAEs in MP and OLEX will be provided by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term by randomized study group and overall, for the total study period and by treatment cycle. For the analyses by treatment cycle, the denominator for the incidences will be adjusted to all subjects being treated in that treatment cycle.

2 STUDY ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	Function	Address
Merz Pharmaceuticals GmbH	Sponsor	Eckenheimer Landstrasse 100 60318 Frankfurt/Main Germany Telephone: +49-69-1503-0 Telefax: +49-69-1503-200
PPD	Clinical Project Manager	PPD
	Lead Medical Expert	
	Medical Expert	
	Biostatistician	
	Product Safety Officer	
	PPD	

2.2 External responsibilities

For multicenter studies, the sponsor will maintain a list of all country-specific coordinating investigators and principal investigators (PIs). The administrative structure for external responsibilities includes, but is not limited to, the following participants.

Name	Function	Address
CCI [redacted]	CCI [redacted]	CCI [redacted]
	Clinical research organization (CRO), Monitoring, serious adverse event (SAE) reporting, EC and Regulatory submissions	
	CRO (medical writing)	
	Data management/Electronic case report form (eCRF)/Biostatistics	
	Interactive web response system (IWRS) services	

Name	Function	Address
CCI	IP Distribution / Drug management	CCI
	Central laboratory	
	Photography Services	

2.3 Committees

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3 ETHICS

3.1 Independent Ethics Committee (IEC)

The following documents must be submitted to the responsible IEC and positive opinion obtained:

- The clinical study protocol.
- Any amendment to the clinical study protocol that is not solely of an administrative nature.
- The investigator's brochure and all updates.
- Subject information and informed consent forms, as well as updates (if applicable).
- Subject card
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable).
- Insurance statement/certificate and conditions
- Forms/Questionnaires for assessments to be completed by the subject (if applicable)
- Other documents will be provided if requested by the IEC.

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 and applicable regulatory requirements, including EU (Directive 2001/20/EG; General Data Protection Regulation) and German laws (German Medicines Act [AMG]; GCP-ordinance [GCP-V] and applicable data protection 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 IEC, or other regulatory authority will be obtained prior to initiation of the trial.

In case of a pandemic disease outbreak, e.g. new COVID-19 public health emergency, procedures that prioritize the reporting of protocol deviations that could impact subject safety to the IEC/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 IEC/IRB and notification to regulatory authorities (e.g. FDA, BfArM).

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. The subject will be informed that the treatment with NT 201 is not permanent and results in a temporary improvement of wrinkles for 4 – 6 months, in individual patients even longer, and that subjects will return to their baseline status afterwards. 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 including ICH revision R2, 2017), and the respective national regulations governing medical research and experimentation on humans, including EU (Directive 2001/20/EG; General Data Protection Regulation) and German laws (German Medicines Act [AMG]; GCP-ordinance [GCP-V] and applicable data protection requirements). 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).

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. For country-specific requirements, see Section 16.1.

In case of a pandemic disease outbreak, e.g. new COVID-19 public health emergency, if re-consenting of the subjects is deemed necessary due to significant changes made to the protocol and/or monitoring plan 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 be contacted via phone or video calls and provide verbal consent supplemented with written (e.g. e-mail) confirmation.
- Approved updated subject information sheet and consent form will be provided by e-mail, mail or courier to obtain a re-consent.
- All instances of consent that are 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 and randomization number and information that the subject is taking part in a study with botulinum toxin A in the indication UFL with a total dose of up to 64 U

In Cycle 1 of the study, subjects will receive one of the following 3 treatments:

- 20 U in the corrugator and procerus muscle, 20 U in the frontalis muscle and 12 U per side in the lateral orbicularis oculi muscle.
- 12 U per side in the lateral orbicularis oculi muscle and placebo in the corrugator and procerus.
- Placebo in all three areas.

In Cycle 2 and 3, the subjects receive a total of 64 U botulinum toxin A.

In case of AEs, treatment should be symptomatic, since no specific treatment is available.

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.

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 (pseudonymized) 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 (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 (e.g. (medical) monitors), auditors, regulatory authorities, or members of IECs) who have been bound to confidentiality. If the results of the study are published, the subject's identity will remain confidential.

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3.3.6 *Contact point*

All subjects will be provided with the subject informed consent form with a contact address where they may obtain further general information regarding clinical studies and data protection rights. The subject card will also contain the contact point of the study site and the responsible PI.

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 document conditions will be handed out to the subject.

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

The sponsor is usually not liable for injuries/cases of death that occur solely as a consequence of the subject's underlying disease or condition, or from diagnostic or therapeutic measures not specifically required by the clinical study protocol. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical study staff, and/or clinical research organization (CRO), including failure to act according to ICH-GCP principles or to comply strictly with the clinical study protocol. For detailed country-specific (i.e. Germany-specific) requirements, see Section 16.1.

3.5 Financing

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

4 INTRODUCTION

4.1 Study background

Investigational product

Botulinum neurotoxin type A [BoNT-A] is synthesized by a wild-type strain of the anaerobic bacterium *Clostridium botulinum*. BoNT-A is a part of a high molecular weight complex, which is formed by several hemagglutinins and other non-toxic non-hemagglutinin proteins.

BoNT-A acts selectively on peripheral cholinergic nerve endings, resulting in a temporary reduction in muscle contraction. Over the years, many indications in the field of aesthetic dermatology and plastic surgery have been found for BoNT-A preparations, such as hyperfunctional glabellar frown lines (GFL), lateral canthal lines (LCL) and HFL (horizontal forehead lines) due to muscle overactivity, and are treated commonly in daily practice and research [Carruthers 2009a, Imhof 2013, Jones 2010, Nestor 2011, Nettar 2011, Prager 2010, Prager 2013, Tamburic 2012].

BoNT-A weakens the power of the treated muscle by acting selectively on peripheral cholinergic nerve endings, inhibiting the release of the neurotransmitter acetylcholine and thereby paralyzing muscle contraction. The selective action of BoNT-A at its target requires a 3-step sequential process: binding to the acceptor site, internalization of the heavy chain of the BoNT-A molecule, and protrusion into the cytosol. In the cytosol, the zinc-dependent endopeptidase part of BoNT-A proteolyzes the synaptosomal-associated protein 25, a component of the transmitter vesicle fusion machinery. Thus, BoNT-A prevents exocytosis of acetylcholine into the synaptic cleft and inhibits signal transmission, e.g. at the muscular endplate [Burgen 1949].

NT 201 (United States [US] Adopted Name [USAN]: incobotulinumtoxinA) is a highly purified, freeze-dried formulation of BoNT-A, and was first approved on 31-MAY-2005 in Germany. CCI [redacted] CCI [redacted] CCI [redacted] NT 201 is marketed under the brand names Xeomin, Bocouture (EU/EEA only), Xeomin Cosmetic (Canada only for aesthetic use) and Xeomeen (Belgium and Mexico only).

In animal models, NT 201 has not shown any detectable immunogenicity [Jost 2007]. None of the subjects treated in aesthetic indications like GFL and LCL developed neutralizing antibodies that led to decreased clinical outcome (for further information please refer to the current investigator's brochure). NT 201 can be stored and transported at room temperature (between 2°C and 25°C) thus simplifying the handling of the compound.

Medical background

A youthful and aesthetically pleasant appearance is increasingly in-focus all over the world. Effective management of facial lines requires approaches that include aesthetic and dermatological treatments, such as peels, laser resurfacing, and fillers, as well as surgical treatments, such as rhytidectomy, eyebrow lift, and blepharoplasty [Cather 2002]. Since surgical techniques involve risks and recovery time, and rejuvenation and filler techniques may not achieve fully satisfactory results, minimally invasive local injection treatment with BoNT-A has rapidly become the standard treatment when the first representative of this drug class was approved for treatment of GFL.

BoNT-A treatment of facial wrinkles is a safe, effective, predictable, minimally invasive aesthetic procedure and was the leading non-surgical cosmetic procedure in 2018 in the US, with 7.4 million administrations [American Society of Plastic Surgeons 2018. Plastic Surgery Statistics Report 2018]. In Germany, the BoNT-A treatment is the most frequent and favored non-surgical minimally invasive cosmetic procedure [Deutsche Gesellschaft für Ästhetische-Plastische Chirurgie 2018, Statista 2018].

Treatment of GFL primarily targets corrugator and procerus muscles [Carruthers 1996]. The usual number of injection sites ranges from five to seven, with men typically requiring more sites and a higher dose. The approved standard dose of NT 201 in this indication is 20 units [U] [Bocouture EU Summary of Product Characteristics] but the dose may be increased by the physician to up to 30 U based on individual patient needs.

HFL result from contraction of the frontalis muscle and tend to be deeper in subjects who have low brows or blepharoptosis and who unconsciously elevate their brows to compensate. BoNT-A is effective in smoothing out these lines but does so at the expense of brow height. It is recommended that subjects with excessive brow ptosis should not get injected in the frontalis muscle to avoid excessive descent of the brows. If the subject wishes to have the GFL and HFL areas injected, a higher dose can be used than during a single treatment because the antagonistic brow depressors are weakened by GFL injections and there is less chance of brow ptosis developing [Carruthers 2004, Keen 1994].

Radial lines at the lateral aspect of the orbit, so-called LCL also known as crow's feet or lateral periorbital wrinkles/rhytids, are primarily caused by contraction of the orbicularis oculi muscle. However, the zygomatic muscles can play a significant role in subjects with crow's feet. Orbicularis fibers are superficial and can be readily identified by having the subject smile or squint. Three to five areas within the radial lines are usually injected [Hui 2007, Levy 2004, Lowe 2005].

There is a greater chance of bruising in this area because of the abundance of superficial vessels. Upper lip ptosis can occur from paralysis of the zygomaticus major muscle adjacent to the orbicularis oculi muscle. This can be prevented by avoiding injections

medial to a line dripped from the lateral canthus [Carruthers 2004, Kim 2003, Matarasso 2001].

Most subjects in clinical practice do not suffer from wrinkles in isolated areas. Instead more than one type of line in the upper face (i.e. GFL, LCL and HFL) is usually present in a single subject, and consequently holistic treatment is becoming increasingly popular and is a common approach in clinical practice worldwide [Blitzer 1997, Carruthers 2007, Carruthers 2009a, Carruthers 2009b, Lowe 2010, Olson 2007].

Wrinkle smoothing in more than one area at the same time provides a more refreshed, natural, and relaxed appearance and increases patient satisfaction [Carruthers 2005]. The combined treatment of different upper facial areas, such as GFL, HFL, and LCL during the same treatment session has become common practice.

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4.2 Study rationale

The combined treatment of wrinkles in the upper face produces a younger, more refreshed, natural and more relaxed appearance and is becoming increasingly popular. Treatment with BoNT-A in the upper face offers predictable results, has few adverse effects, and is associated with high patient satisfaction. The EU authorities agreed to mutually approve the indication UFL (simultaneous treatment of GFL, HFL, and LCL) on 15-March-2016. The sponsor received US FDA approval to NT 201 in the treatment of moderate to severe GFL in 2011. The sponsor intends to broaden the existing US aesthetic label for Xeomin (currently GFL only) to also enable simultaneous treatment of all three upper facial areas (GFL, HFL, and LCL) in the US.

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The planned study will add to a number of clinical studies that have been conducted in the field of aesthetics to support data regarding treatment of dynamic facial lines. The study accounts for the current trend of aesthetic physicians treating the aging face holistically rather than treating single folds or mimic muscle groups in order to achieve a more natural aesthetic outcome, in line with subjects' needs and goals.

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4.3 Risk-benefit assessment

The treatment of GFL, HFL, and LCL offers predictable aesthetic results, has few adverse effects, and is associated with high patient satisfaction.

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NT 201 was safe and well tolerated when all three facial areas were treated in combination, and no new safety concerns were identified during the pivotal EU UFL study. Moreover, there was no evidence of an increased incidence of treatment-emergent AEs [TEAEs], and especially those of special interest [treatment-emergent AESIs], in subjects undergoing repeat-dose treatment.

To date, all clinical studies with NT 201 in subjects with moderate-to-severe GFL, LCL or UFL (simultaneous treatment of GFL, HFL and LCL) conducted with maximum doses of up to 64 U NT 201 per treatment, have shown a good efficacy and comparable safety profile, with no evidence of new safety concerns. No new safety issues have been detected in the overall safety database. The safety results are consistent with the known safety profile of NT 201, and are supported by evidence from the comprehensive overall safety database.

In general, NT 201 is well tolerated (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.

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Additional risks that may arise in case a pandemic disease outbreak, e.g. new COVID-19 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).

5 STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of simultaneous intramuscular injections of NT 201 in subjects with moderate to severe UFL in comparison to placebo.

The secondary objectives are to assess efficacy and safety of simultaneous single and repeat-dose intramuscular injections of NT 201 in subjects with moderate to severe UFL.

6 INVESTIGATIONAL PLAN

6.1 Overall study design

This will be a prospective, randomized, double-blind, placebo-controlled, multicenter study with a placebo-controlled MP with one NT 201 injection cycle followed by an open-label extension period [OLEX] with two NT 201 injection cycles.

In the MP (Cycle 1), 360 subjects will be randomized 2:1:1 to three different treatment groups: the UFL treatment group (Group U), the LCL treatment group (Group L), and the placebo group (Group P) in a randomization ratio of 2:1:1. During the MP, subjects will be treated either with a total dose of 64 U NT 201 (UFL), or with 24 U NT201 in the LCL area and placebo in the GFL and HFL area, or with placebo in all 3 facial areas. For further details, see CCI [redacted] All randomized subjects will then be followed up for 120 days before they may enter in to the OLEX period. The duration of the MP (Cycle 1) will therefore be 120 days plus the duration of individual screening (screening: Days -14 to -3).

The OLEX period will comprise two additional treatment cycles, Cycle 2 and Cycle 3, with durations of 120 days each plus up to 30 days for eligibility reassessments per cycle. During each cycle, eligible subjects will receive simultaneous injections of NT 201 at a total dose of 64 U in all three facial areas. Eligibility criteria are being evaluated before reinjection. For further details see CCI [redacted] For details on the planned visits, see Section 9.2.

The overall study duration will be about 360 days plus the individual duration of screening (Day -14 to -3) at study start plus a maximum of 30 days after Cycle 1 and Cycle 2 for eligibility reassessment for entering the next treatment cycle, as applicable. Eligible subjects will receive one injection session with study treatment each at Day 1 of the respective treatment cycle.

This study will be conducted in up to 12 sites in Germany.

A clinical study report with all results from the MP and OLEX period will be prepared once all subjects completed the study.

6.1.1 End of study

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

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[redacted]

6.2 Discussion of study design, including choice of control groups

The prospective, randomized, double-blind, placebo-controlled, multicenter design of the MP of this Phase 3 study was chosen to investigate the efficacy and safety of simultaneous treatment of UFL with NT 201 with minimized risk of bias by including a placebo control. Robust results are expected from the study design.

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[redacted]

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The observation period of 120 days (4 months) (plus 30 days if subjects have not yet relapsed to enter the OLEX period) between first injection and reinjection, represents a reasonable time that the IP will have worn off in most of the treated subjects, so that reinjection in the OLEX period can be performed safely.

7 STUDY POPULATION

Subjects with HFL, GFL, and symmetrical LCL of moderate (score 2) to severe (score 3) intensity at maximum contraction as assessed by the investigator and the subject at study baseline visit according to the MAS will be enrolled in this study. The ratings of the investigator and the subject do not have to coincide as long as all ratings at maximum contraction are moderate or severe.

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, ethnic background, and pre-treatment status. This study population will therefore be expected to be a representative sample of the target population for the indication of moderate to severe UFL.

7.1 Selection of study population

A total number of 360 subjects are planned to be enrolled. Please refer to Section 12.1 for sample size calculation.

To support the recruitment process, recruitment advertisements approved by the responsible IEC will be published as required.

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 80-90% of subjects will be female; this represents the usual gender distribution in the daily practice among people seeking for cosmetic procedures.

7.2 Inclusion criteria

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

Inclusion Criteria	Rationale	Screening	Baseline
CCI [redacted]			
3. Outpatients (male or female) 18 years of age or older.	Safety	X	

Inclusion Criteria	Rationale	Screening	Baseline
4. HFL, GFL, and symmetrical[1] LCL of moderate (score 2) to severe (score 3) intensity at maximum contraction as assessed by the investigator and subject according to MAS. The ratings of the investigator and subject do not have to coincide as long all ratings at maximum contraction are moderate or severe.	Efficacy	X	X

CCI [redacted]

7.3 Exclusion criteria

Subjects meeting any of the following criteria at the screening and/or at the baseline examination (as indicated below) will not be included as subjects in this study; for details on individual medications, see also Section 8.3:

Exclusion Criteria	Rationale	Screening	Baseline
1. Previous treatment with BoNT of any serotype in the face within the last 12 months before injection.	Efficacy	X	X

[1] Symmetrical means that periorbital areas must present LCL of the same severity, e.g. either both are '2 - moderate', or both are '3 - severe'.

CCI [redacted]

Exclusion Criteria	Rationale	Screening	Baseline
2. Any facial cosmetic procedure within the last 12 months before baseline injection, such as dermal filling, chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment, ultrasound treatment, tattooing of eyebrows.	Efficacy	X	X
3. Previous treatment with any biodegradable filler in the face within the last 12 months before injection.	Efficacy	X	X
4. Topical or systemic retinoids within the last six months prior to injection	Efficacy	X	X
5. Any previous insertion of permanent material in the face including any insertion of threads in the upper face or at cheeks (regardless of the time between previous treatment and this study).	Efficacy	X	
6. Any medical condition that may put the subject at increased risk with exposure to NT 201, including myasthenia gravis, Lambert-Eaton-Syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function.	Safety concern	X	
7. Currently breastfeeding women.	Safety concern	X	X
CCI [redacted]			

Exclusion Criteria	Rationale	Screening	Baseline
CCI [redacted]			

Exclusion Criteria	Rationale	Screening	Baseline
CCI			

Exclusion Criteria	Rationale	Screening	Baseline
CCI [redacted]			

CCI [redacted]

CCI

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 (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's medical records) and the electronic Case Report Form (eCRF). Date and main 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 injection of IP. In case of pregnancy after a subject has received an injection, the subject can continue with applicable study visits until the end of the study but without any invasive procedure, e.g. injections, blood draw, or any other interventional procedure, see Section 10.6). However the subject is free to discontinue the study any time.
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.

- Intake of any other investigational drug.
- Administration of botulinum toxin of any serotype in the face except for IP.
- Treatment with any facial cosmetic procedure, such as dermal filling, chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment, ultrasound treatment, tattooing of eyebrows, during the entire course of the study.

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.

Subjects who discontinue the study because of AEs will be treated according to standard clinical procedures and will be followed up until the end of study 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 all investigators, the IEC/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 or at another clinical site (in case the primary site is closed e.g. due to quarantine).

Following discontinuation, the end of study 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 reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data on the IP do not justify a continuation of the study.

- The investigator or study site exhibits serious and/or persistent non-adherence to the clinical study protocol, the Declaration of Helsinki, ICH-GCP, and/or applicable regulatory requirements, including EU (Directive 2001/20/EG; General Data Protection Regulation) and German laws (German Medicines Act [AMG]; GCP-ordinance [GCP-V] and applicable data protection requirements).

- 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 IEC 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 IEC, 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. new COVID-19 public health emergency, it might not be feasible for a 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.

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.

8 TREATMENTS

8.1 Investigational product(s)

8.1.1 Description of investigational product(s)

NT 201, marketed under the brand names Bocouture (EU/EEA only) and Xeomin in the US (active ingredient: NT 101, BoNT-A free from complexing proteins; USAN: incobotulinumtoxinA) will be provided in quantities of 100 U in glass vials containing powder to be reconstituted for injection.

Placebo in glass vials containing powder for reconstitution, excipients only (sucrose, human serum albumin) without 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 24, D-06861 Dessau-Rosslau, Germany, and released by Merz Pharmaceuticals GmbH, Alfred-Wegener-Straße 2, 60438 Frankfurt/Main, Germany.

8.1.1.1 Instructions for preparation

CCI [redacted]

There is a vacuum in the vial which ensures that the lyophilized material remains integer as a block until addition of 0.9% sodium chloride. Therefore, the rubber stopper must not be penetrated with a needle without fluid. Otherwise the vacuum would be released and the powder dispersed on the inner walls of the vials.

After vertical insertion of the needle through the rubber stopper the solvent is injected gently into the vial in order to avoid foam formation. A CCI [redacted] short bevel needle is recommended for reconstitution. After removal of the syringe from the vial the product is mixed with the solvent by carefully swirling and inverting the vial and should not be shaken vigorously. If needed, the needle used for reconstitution should remain in the vial and the required amount of solution should be drawn up with a new sterile syringe suitable for injection.

All injectable solutions should be clear, colorless, and free from particulate matter otherwise it has to be discarded. The IP(s) should be reconstituted shortly before injection. However, the reconstituted IP(s) can be stored in the original vial for up to 24 hours in a refrigerator at 2°C to 8°C.

Any deviation to this will be documented on the drug accountability log and the sponsor has to be contacted. Reconstituted IP should not be stored in syringes. Any used syringes, spillages, or other materials that have been in contact with the test or reference product must be autoclaved. Any (partially) used or unused IP will be destroyed appropriately at the site, e.g. by autoclaving (Section 8.1.5).

The syringes for injection of NT 201 or placebo will be prepared by a trained and delegated study team member. To keep the investigator and subject blinded in all three treatment groups, the same injection volumes irrespective of active or placebo will be applied.

Either CCI needles must be used for injections.

CCI

Only the provided study material is allowed to be used in the study.

8.1.1.2 Instructions for administration

Only medical doctors trained and experienced in aesthetic BoNT treatment are allowed to inject. The number of investigators responsible for these tasks should be limited to a maximum of two per site in this study. In exceptional cases, an investigational site may train a third injector as a precaution to overcome eventual staff shortage during the new

COVID-19 pandemic outbreak. In any case, a third injector at an investigational site must be announced to and agreed by the sponsor in advance.

Before injections, the area to be treated will be cleaned. No massage, pre- or post-cooling, or local anesthetics are allowed. If bleeding occurs at the injection site, gentle pressure without rubbing can be applied until bleeding settles. For safety reasons, emergency equipment for treatment of anaphylactic reactions will be available at site.

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

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[redacted]

8.1.2 CCI

CCI [redacted] containing NT 201 or placebo vials for the MP will be sent to the sites. If necessary during the course of the study, sites will be replenished with all study materials. The site will dispense IP(s) to each subject during the double-blind and the open-label treatment periods.

In case of a pandemic disease outbreak, e.g. new COVID-19 public health emergency, considerations may be made to supply the investigator with sufficient study supplies to avoid resupply during the study.

CCI [redacted]

CCI [redacted] The IP will be labeled according to regulatory requirements in the participating countries. For the double-blind part of this study, the test product and reference product(s) will have the same printed label information on the outer medication packaging (box) and the inner containers (vials). See Section 8.5 for details of the blinding procedures planned for this study.

8.1.3 Storage of investigational product(s)

The IP(s) will be shipped at ambient temperature and a temperature logger will be included in the shipment. Unopened vials should be stored at a temperature between 2°C

and 25°C. During storage, the minimum/maximum temperature will be recorded in a temperature log each working day by a min-/max-thermometer provided by the Sponsor, CRO or central laboratory.

8.1.4 Accountability for investigational product(s)

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

Upon receipt of the IP(s), the investigator or pharmacist, according to applicable law, will visually inspect the shipment and verify the number and condition of the IP(s), check any temperature logger that was sent with the medication and acknowledge the receipt in the IWRS. An 'IP delivery form' will be completed and signed by the investigator or authorized site staff or pharmacist according to local law. The original completed, and signed form must be filed with the inventory/drug accountability records.

To ensure proper storage and to verify the inventory, a drug supply inspection will be conducted at regular intervals by the monitor (Clinical Research Associate). Study records will be made available to appropriate individuals (e.g., monitor, auditor, and regulatory authorities) on request throughout the study.

Any study records will be reviewed during an audit if requested, whether it is stated in the protocol or not.

For further details, see Section 8.2.5.

In case of a pandemic disease outbreak, e.g. new COVID-19 public health emergency, considerations may be made to perform study -accountability procedures remotely and return of unused supplies may be delayed until site personnel are able to safely do so.

8.1.5 Destruction of investigational product(s)

Any used syringes, spillages, or other materials that have been in contact with the IP must be disposed adequately. Any reconstituted IP if (partially) used or unused must be inactivated appropriately at the site by one of the following methods:

- Autoclaving.

CCI [redacted]

CCI [redacted]

For all practical purposes, deactivation and denaturation will occur instantaneously.

In cases where reconstituted product has been spilled, dry, absorbent material should be used. If the product comes into contact with skin, the affected area should be abundantly rinsed with water. If product gets into the eyes, they should be rinsed thoroughly with plenty of water or with an ophthalmic eyewash solution. If product comes into contact with a wound or damaged skin, the area should be rinsed thoroughly with plenty of water and appropriate medical steps according to the dose injected should be taken.

Upon the completion or termination of the study, all unused and/or partially used IP(s) must be returned to the sponsor or another authorized party. The sponsor or another authorized party will destroy the IP(s) after completion of the clinical study report taking into account local legislation. Destruction of IP(s) at the study site may be allowed if written authorization is provided by the sponsor. If destruction at the study site is agreed upon, then a certificate of destruction must be given to the sponsor.

8.2 Treatments administered

In the MP (Cycle 1) subjects will be randomized to one of three treatment groups CCI [redacted]

- In Group U, subjects will receive 20 U NT 201 in the GFL area, 20 U NT 201 in the HFL area, and 24 U NT 201 in the LCL area (12 U per side).
- In Group L, subjects will receive placebo in the GFL area, placebo in the HFL area, and 24 U NT 201 in the LCL area, 12 U per side.
- In Group P, all three areas will be treated with placebo.

In the OLEX period (Cycles 2 and 3), all subjects will receive NT 201 in all three areas CCI [redacted]

Injections will be administered as described in Section 8.1.1.2.

CCI

In case of a public health emergency treatments may be halted or postponed.

8.2.1 Methods of assigning subjects to treatment groups

At baseline visit V2, subjects will be randomized 2:1:1 to one of the three treatment groups (Groups U, L, or P). Randomization will be done by using an IWRS. Randomization numbers and date of randomization will be recorded in the eCRF.

Randomization will be stratified by investigational site and will be in blocks of appropriate size. This will ensure an approximately equal ratio of treatment groups between sites. The block size will not be disclosed to investigators until the study is unblinded.

No other criteria for stratification of randomization will be applied.

If subjects are discontinued from the study during the MP, no replacement of subjects is planned.

In the MP, for each visit, the system will assign two medication boxes. The medication numbers are scrambled (they will not be in numerical order). Each site will receive scrambled medication numbers per delivery for the MP.

8.2.2 Selection of doses in the study

The choice of the doses per treatment area used in this study are justified by experience from prior studies performed with NT 201 [redacted] as well as by published results from clinical studies with other BoNT-A preparations.

[redacted] A placebo-controlled study with total doses of 64 U of BoNT-A injected in a comparable manner as planned in this study showed that this dose is safe and effective for the treatment of UFL [De Boulle 2018].

The doses chosen in this study are also in accordance with the treatment doses recommended in the labeling for [redacted]

8.2.3 Selection and timing of doses for each subject

In the MP (Cycle 1), subjects will be randomized to one of the three treatment groups as described in Section 8.2 [redacted]. Treatment (NT 201 or placebo) will be administered at the baseline visit V2 according to the instructions detailed in Section 8.1.1.2 and the [redacted] in [redacted]

After a 120 day observation period following injections in cycles 1 and 2, eligible subjects will receive NT 201 reinjection [redacted] at the next cycle baseline visit (V8 for Cycle 2 and V13 for Cycle 3) according to the instructions detailed in Section 8.1.1.2 and the injection scheme shown in [redacted] The end-of-Cycle 1 visit V7 and the Cycle 2 baseline visit V8, as well as the end-of-Cycle 2 visit V12 and the Cycle 3 baseline visit V13 should be on the same day if eligibility criteria are fulfilled at V7 and V12, respectively.

[redacted]

CCI

[redacted]

8.2.4 Duration of treatment per subject

Subjects will receive IP at up to three injection visits. The overall study duration for each subject will be approximately 360 days plus the individual duration of screening until baseline (up to 14 days) plus a maximum of 30 days after Cycle 1 and Cycle 2, respectively, for eligibility reassessment as applicable.

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

The IP(s) will be administered to the three facial areas by intramuscular injection performed by the investigator during the subject's visits at the site at study baseline (V2) and at cycle baselines in the OLEX period (V8 for Cycle 2 and V13 for Cycle 3). Thus, full treatment compliance is assured for each individual subject.

8.2.6 Treatment of overdose

An overdose is defined as any deviation from the specified dose in the protocol (doses that are higher than recommended). Any overdose must be recorded in the IP section, the AE section of the eCRF, and the source documents. Any case of overdose leading to serious adverse events (SAEs) or AEs of special interests (AESI) must be reported to the CRO in an expedited manner using the appropriate reporting form (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 estimated to be very 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.

CCI

[redacted]

There is no significant information regarding overdose from clinical studies in adults with GFL. In the event of an overdose, the investigator or treating physician is advised to use best clinical judgement 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 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 [Arnon 2001]. 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 patients whose clinical signs were consistent with those of naturally occurring botulism [Chertow 2006].

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-diamino-pyridine) 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 [Marchini 1997].

Subjects should be advised to seek immediate medical care 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 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 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.

In addition, the following previous treatments should be checked and listed before enrollment:

- Previous treatment with BoNT of any serotype at any body region at any time[5].
- Previous treatment with any facial cosmetic procedure[6] CCI [redacted] including also biodegradable filler and insertion of permanent material[7] CCI [redacted] in the face at any time.

In general, medications, therapies, and procedures that may violate the in- and exclusion criteria (Section 7.2 and Section 7.3) are not permitted during the study.

The following concomitant medications are not permitted during the study:

- Anticoagulants such as heparin, cumarines, non-vitamin K antagonists, oral anticoagulants like CCI [redacted] for prophylactic or therapeutic reasons within 10 days prior to injection to 4 days after injection (aspirin and other platelet-aggregation inhibitors CCI [redacted] (exclusion criterion no. 20).
- Aminoglycoside antibiotics, or other agents that might interfere with neuromuscular function such as D-penicillinamine, curarine-type muscle relaxants, succinylcholine, or that might interfere with the action of BoNT, such as chloroquine, within 14 days prior to injection and during the entire course of the study) (exclusion criterion no. 25).
- Other agents that might interfere with neuromuscular function, i.e. drugs listed in World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) classification class M03 Agents that might induce the production of antibodies

[5] As previous treatment with BoNT of any serotype in the facial area within the last 12 months before injection is an exclusion criterion (exclusion criterion no. 1), the exact body area of BoNT injection must be documented.

[6] Subjects with previous treatment with any facial cosmetic procedure or biodegradable filler in the face within the last 12 months before injection are excluded from this study (exclusion criterion no. 2)

[7] Subjects with any previous insertion of permanent material such as silicone, polyacrylamide etc. in the face including any insertion of threads in the upper face or at cheeks, regardless of the time between previous treatment and this study are excluded from study participation (exclusion criterion no. 5)

against acetylcholine receptors (e.g., D-penicillamine), within 14 days before injection and during the entire course of the study[8].

- Retinoids (exclusion criterion no. 4)
- BoNT treatment of any serotype for any treatment indication during the entire course of the study.
- Any other investigational drug during the entire course of the study.

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

8.4 Restrictions during the study

Not applicable. For restrictions regarding previous and concomitant therapies, see Section 8.3.

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[8] Previous treatment within 14 days prior to injection with agents that might interfere with neuromuscular function or with the action of BoNT is an exclusion criterion (exclusion criterion no. 24).

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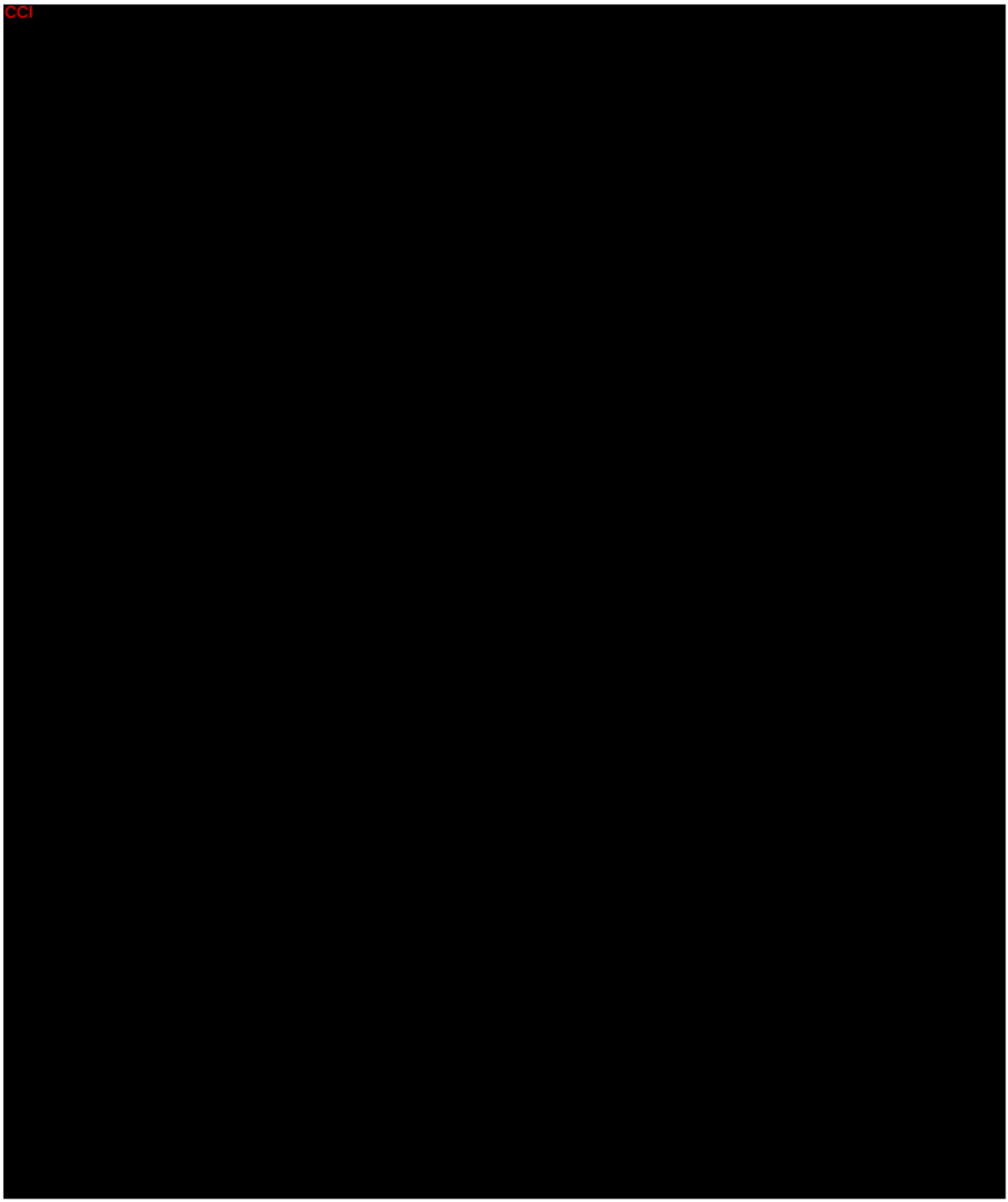

9 STUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 Assessments

Instructions for use of the clinical outcome assessments at site visits in this study will be described in a respective outcome manual (provided by Merz). All assessments will be performed as scheduled according to the study flow chart provided in CCI in Section 9.2. An overall description of the study plan is provided in Section 6.1 and in the flow chart in Section 6.1.2.

9.1.1 Clinical assessments

9.1.1.1 Efficacy 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.

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To ensure consistent conditions for all subjects, all make-up and evident jewelry has to be removed from the face prior to any standardized photography, the clinical assessments and self-assessments. The study staff will ensure that the subject and investigator can perform assessments independently at a place with adequate lighting and without disturbance at the beginning of the respective study visit. Furthermore, a mirror will be provided so that subjects can control respectively for their facial appearance.

Entries in the source documents need to be dated and signed by the investigator or by the subject.

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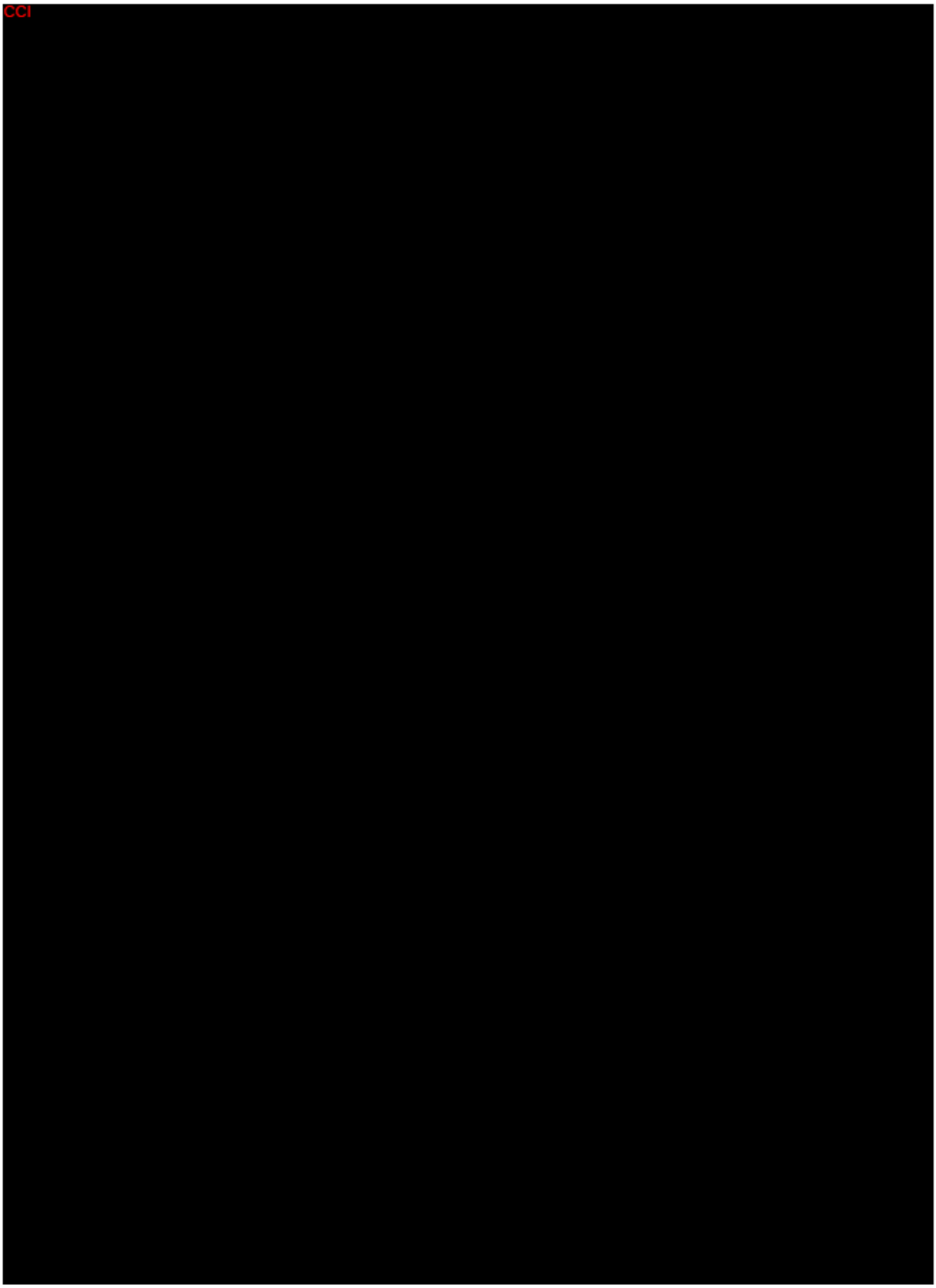

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[redacted]


CCI


CCI

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9.1.1.2 General assessments

General assessments include the following:

- Medical history and concomitant diseases, prior and concomitant medication, prior and concomitant non-drug therapies.

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- Subject disposition.
- Demographic data.
- Body height at V1 (screening) and weight at V1 (screening) and V17 End of Study Visit.

At the beginning of the study, the subject's demographic data, relevant medical history, concomitant diseases, all prior medication (within 30 days before screening) and all current and concomitant medications and non-drug treatments planned during the study will be recorded. Previous treatments with any facial cosmetic procedure and CCI [redacted] must be recorded regardless of time of application. For prohibited prior 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.

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 schedules for the MP CCI [redacted] and OLEX period CCI [redacted] 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.

In case of pathological laboratory findings, the investigator will discuss these with the subject, if agreed in the informed consent form.

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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 baseline visit. The results of the re-test will be entered in the study database.

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

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9.1.3 Pharmacodynamics

Not applicable for this study.

9.1.4 Pharmacokinetics

Not applicable for this study. Currently, there are no tests sensitive enough to measure BoNT in peripheral blood.

9.1.5 Pharmacogenetics

Not applicable for this study.

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.

9.1.7 Specimen preparation, handling, storage, and shipping

Blood samples for clinical chemistry, hematology, and ß-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.

9.2 Visit schedule

The MP consists of a screening visit V1, which will be performed between Day -14 and Day -3 prior to randomization at baseline (V2; Day 1).

The purpose of the screening visit is to determine subject eligibility for study participation.

Baseline is defined as Day 1, which is the day of randomization and first administration of the IP.

During the double-blind MP, subjects will receive NT 201 or matching placebo once at baseline and will be followed up during five subsequent control visits (V3 to V7). V7 is also the end-of-Cycle 1 visit.

To capture long-term safety and efficacy data for this indication, eligible subjects of all three randomization groups from the MP (Cycle 1) will continue in Cycle 2, where they will receive treatment with NT 201 for all three facial areas at the Cycle 2 baseline visit V8. The end-of-Cycle 1 visit V7 and the Cycle 2 baseline reinjection visit V8 can be performed on the same day if all required eligibility criteria and none of the exclusion criteria of the OLEX period (Section 7.43) are met at V7. Reassessment for eligibility is possible within 30 days after V7 (Section 8.2.3). After treatment in Cycle 2, subjects will

be followed up during four control visits (V9 to V12) for 120 days. Control visit V12 is also the end-of-Cycle 2 visit.

After completion of Cycle 2, eligible subjects will continue in Cycle 3, where they will receive treatment with NT 201 for all three facial areas at the Cycle 3 baseline visit V13. The end-of-Cycle 2 visit V12 and the Cycle 3 baseline reinjection visit V13 can be performed on the same day if all required eligibility criteria and none of the exclusion criteria of the OLEX period (Section 7.43) are met at V12. Reassessment for eligibility is possible within 30 days after V12 (Section 8.2.3). After treatment in Cycle 3, subjects will be followed up during four control visits (V14 to V17) for 120 days. Control visit V17 is also the end-of-Cycle 3 and end-of-study visit.

The study activities and visit schedules are shown in CCI for the MP and in CCI for the OLEX period. The clinical study protocol allows for a window of ± 7 days in scheduling of study visits for all post-baseline visits, except V3 where only a ± 3-day window is allowed. The IP(s) must be injected by the investigator, who is trained and experienced in aesthetic BoNT treatment, at the study site. Following administration of IP(s), subjects will be observed for a minimum of 30 minutes at the site and will be asked by the investigator if any AEs have occurred since administration. Vital signs will be taken at the beginning of each study visit to ensure subject safety.

The last primary outcome visit will occur at Day 30 ± 7 (V4) for each subject. For subjects not fulfilling the reinjection criteria, also not at the reassessment visit, the end-of-study visit will be performed directly and the subject will be discontinued from the study. For all other subjects, the end-of-study visit V17 will occur at Day 120 ± 7 after last administration of the IP in Cycle 3. Unscheduled visits may be required in the case of AEs or premature discontinuation of the study. In this case, the final assessments as described for V17, will be performed as soon as possible. If additional safety follow-up is necessary after this visit, subjects may be contacted by telephone or be assessed in the clinic, depending on the nature of the follow-up required.

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10 SAFETY ASSESSMENTS

Safety assessments include AEs, AESIs, standard clinical biochemistry and hematology, vital signs, physical examination, pregnancy test as described in Section 12.3.5 and according to the visit schedules of the MP [redacted] and OLEX period [redacted]

10.1 Definition of an adverse event

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

Changes in efficacy endpoints (e.g., subject-reported outcome endpoints (questionnaires and scales) during the course of the study) 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.

Any untoward medical occurrence that happens between the time when the informed consent form was signed and the first administration of IP(s) 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 during or after the first administration of IP(s) up to and including final study visit. In case no final visit is performed, all AEs reported during a time period corresponding to the expected cycle length will be regarded as treatment-emergent.

New AEs reported to the investigator during the observation period after the last administration of IP(s) must be documented, treated, and followed up like all other AEs. Non-serious AEs will not be followed up after the final study visit, which is scheduled 120 ± 7 days after last administration of IP(s).

Pre-existing conditions noted in the medical history and previous to study drug administration 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 significant.

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 of onset.
- Date of worsening (e.g. if an AE turns from mild to moderate, the date has to be given).
- Intensity (see Section 10.1.1).
- Causal relationship (not related, related).
- Causal relationship to COVID-19 (not related, related)
- Serious (yes or no).
- Outcome (Section 10.1.4).
- AE leading to discontinuation of the study (yes or no).
- Stop date.

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 CRO immediately, 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.

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."

10.1.4 Categories of outcome

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

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered/resolved with sequelae.
- Fatal.
- 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.[9]
- Requires inpatient hospitalization, or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Consists of any other medically important condition.[10]

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 immediately and under no circumstances later than 24 hours after learning of the event by telefax, telephone or email. 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).

[9] 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.

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

- An event or outcome that can be identified as serious.

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

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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.

Moreover, SAEs are to be documented on the general pages of the AE eCRF as well as in the subject's file. The eCRF pages for medical history/concomitant diseases and for previous/concomitant medication and non-drug treatment are to be faxed/sent along with the SAE reporting form.

SAEs occurring after final study visit (V17) 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 clinical study database. These reports will be entered into the Safety Database.

10.3 AESIs / alert terms

AEs occurring after treatment that are thought to possibly indicate toxin spread are defined as AESI. The subject will be actively asked by the investigator at each visit after screening (starting with baseline visit V2) if any of the AESI terms listed in CCI [redacted] below occurred since the last contact. AESI questioning at V2 will facilitate recording of pre-existing conditions and/or possibly undetected (S)AEs that could confound AESI questioning post injection of IP. The questioning and documentation of answers will be standardized.

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(s) or not, by telefax or email to the responsible CRO within 24 hours of knowledge of the event. The CRO will transmit these AESIs to Merz Pharmaceuticals GmbH. Each AESI must be reported by the site on the AESI reporting form. Moreover, AESIs are to be documented on the general pages of the AE eCRF as well as in the subject's file. The eCRF 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. The AEs in CCI are defined as AESIs for this study.

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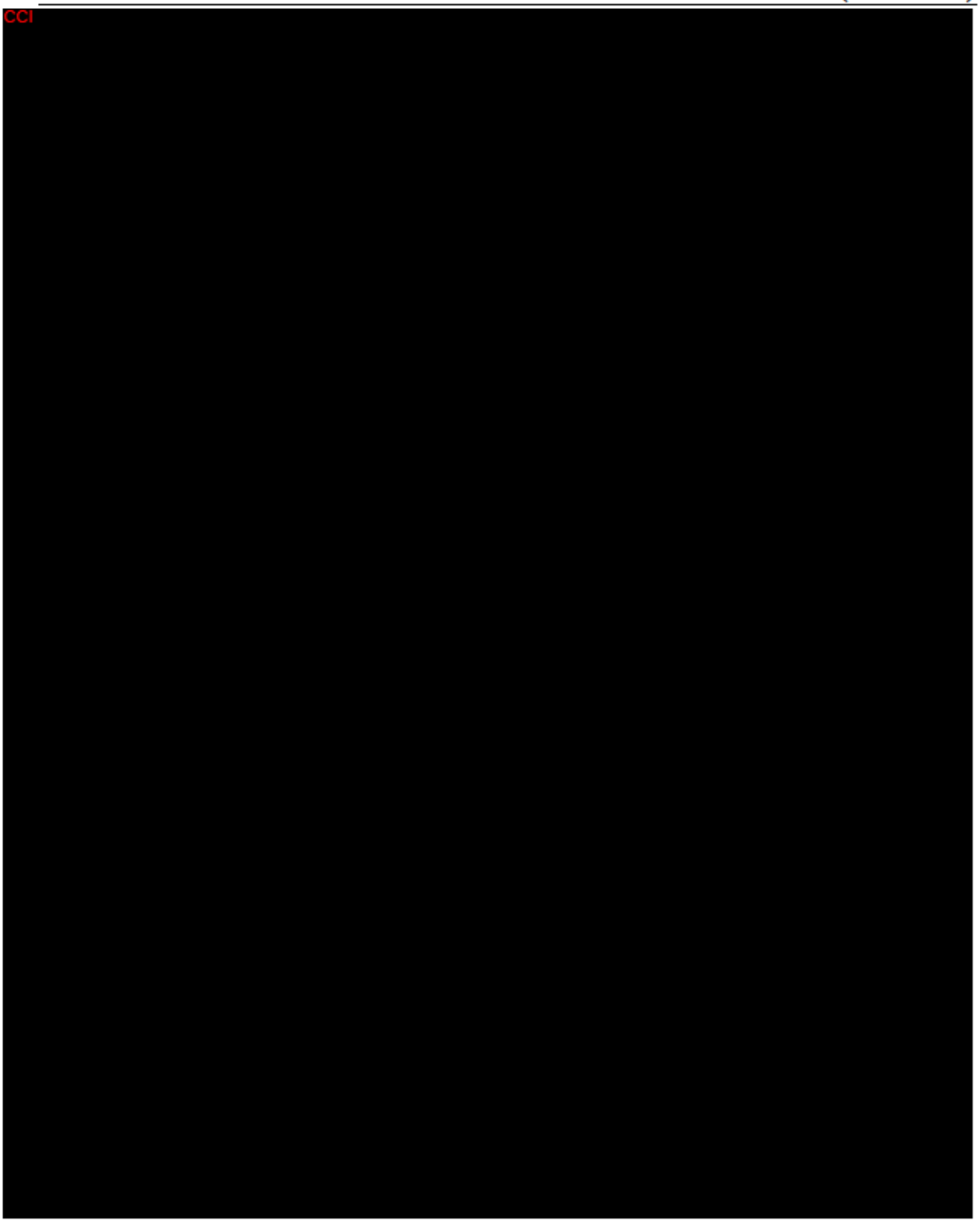

10.4 Expected adverse events

Expected AEs are those described in Section 7.1. 'Company Core Safety Information' of the investigator's brochure for NT 201.

10.5 Unexpected adverse events

Unexpected AEs are those not described in Section 7.1. 'Company Core Safety Information' of the investigator's brochure 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 exposure before or during pregnancy). Any abnormal pregnancy or pregnancy outcome is to be reported as SAE (on an SAE form). In case a pregnancy occurs prior to first injection, the subject must not be randomized. If a pregnancy occurs after a subject has received injection, the subject can continue with applicable study visits until the end of the corresponding cycle but without any invasive procedure (e.g. injections, blood drawing) and no further injection treatments will be given. However, the subject is free to discontinue the study at any time.

11 DATA QUALITY ASSURANCE

Inspections by regulatory authority representatives and IEC are possible at any time, even after the end of study. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC 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).

This study will be monitored regularly by a qualified monitor from the CRO according to ICH-GCP and the respective SOPs (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 (Section 3.3.2). The investigator must also confirm by written statement in the source documentation that all inclusion criteria and all exclusion criteria were checked prior to inclusion of the subject. In addition to this statement, the subject's meeting or non-meeting of the in- and exclusion criteria and eligibility criteria have to be traceable on the basis of the documentation in the subjects file. The childbearing potential of female subjects and their used method of birth control 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, subject diary, laboratory report). Scales or questionnaires assessed by the investigators and subjects on paper forms CCI [redacted] will be considered as source data and will be transferred into the eCRF by the site.

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 the CRO. 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 electronic data capture system; answers to queries or changes to the data will also be documented in this system directly by an authorized member of the investigator's site staff.

The audit trail in the electronic data capture system documents all changes. Edit checks generate automatic queries during data entry when a field is not populated according to specifications defined in the data validation plan. Manual queries (to be answered by site staff) can be raised during source data verification, medical or safety review and data management review.

Laboratory 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 CRO's data management function (see Section 2.2) will be responsible for clinical data-processing, in accordance with the sponsor's data management procedures as far as possible.

Data from the independent rater panel will be received electronically and merged with the eCRF data (but not uploaded into the EDC system). Further details will be specified in the Data Management Plan.

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.

In case of a pandemic disease outbreak, e.g. new COVID-19 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.
- 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 clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements, including EU (Richtlinie 2001/20/EG; Datenschutzgrundverordnung; the upcoming EU regulation No. 536/2014) and German laws Arzneimittelgesetz [AMG]; GCP-Verordnung Datenschutzbestimmungen). Monitoring will also be aimed at detecting any misconduct or fraud. In addition, the monitor will check whether all AEs, SAEs, AESIs or 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.
- Record all IP(s) dispensed in the eCRF and the drug inventory records.

All subjects who are screened, but not included in the study, will be listed on the subject screening/enrollment log. Monitoring will be systematic, prioritized, and risk-based.

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

In case of a pandemic disease outbreak, e.g. new COVID-19 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.
- 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).

12 STATISTICAL METHODS

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

Any deviations from planned analyses, the reason(s) for such deviation(s), and all alternative or additional statistical analyses that may be performed before database close or unblinding, respectively, will be described in amendments to the clinical study protocol or the SAP. All deviations and/or alterations will be summarized in the clinical study report.

In case of a pandemic disease outbreak, e.g. new COVID-19 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 statistical analysis plan:

- 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.
- Consider the need for involvement of an independent Data Monitoring Committee particularly if trial sample size changes are anticipated.

12.1 Determination of sample size

Overall, 360 subjects are planned to be randomized to three treatment groups (UFL, LCL or Placebo) with a randomization ratio of 2:1:1 at baseline visit V2.

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These sample sizes provide sufficient power also to assess efficacy under conservative assumptions. For proportions of 20% LCL-responders in Group U and 5% in Group P, a power of 93% is achieved for one-sided Fisher's exact test at $\alpha = 2.5\%$. Moreover, if proportions of HFL- and GFL-responders of at least 40% for Group U and at most 5% for Group P are assumed, the samples sizes provide power close to 100%.

In conclusion, when randomizing 180 subjects to Group U and 90 subjects each to Groups L and P, the study will have at least 90% power to establish efficacy of NT 201 using a hierarchical procedure for comparisons of proportions of GFL-, HFL-, and LCL-responders between Groups U and P. Assuming that about 15% of subjects will not complete the MP period, the proposed sample size will result in more than 150 completed subjects in Group U in this study. This number of completed patients in this study is considered sufficient to support the overall safety profile of NT 201 for simultaneous treatment of UFL.

12.2 Analysis sets

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

Safety evaluation set (SES)

The SES is the subset of all subjects who were exposed to IP at least once. Subjects in the SES analyses will be analyzed as treated.

Full analysis set (FAS)

The FAS will consist of all randomized subjects. Subjects in FAS analyses will be analyzed as randomized.

Per protocol set (PPS)

The PPS is the subset of subjects in the FAS without major protocol deviations. Major protocol deviations will be defined during the blinded data review meeting.

12.3 Endpoints and main estimands for analysis

12.3.1 Efficacy endpoints and main efficacy estimands

12.3.1.1 Primary efficacy endpoints and main primary efficacy estimands

The following three endpoints will be used for primary efficacy analysis during the MP:

- Proportion of GFL-responders at Day 30

  GFL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for GFL at maximum contraction as assessed by both the investigator and the subject.

- Proportion of HFL-responders at Day 30

HFL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for HFL at maximum contraction as assessed by both the investigator and the subject.

- Proportion of LCL-responders at Day 30

  LCL-response is defined as a score of 0 (no) or 1 (mild) and at least two-grade improvement from baseline to Day 30 of MP on MAS for both left and right LCL at maximum contraction as assessed by both the investigator and the subject.

Main estimands for primary efficacy endpoints (see CCI for GFL, CCI for HFL, CCI for LCL) describe the treatment effects of interest for the three treatment areas. For each main primary estimand, the variable attribute corresponds to the respective primary endpoint.

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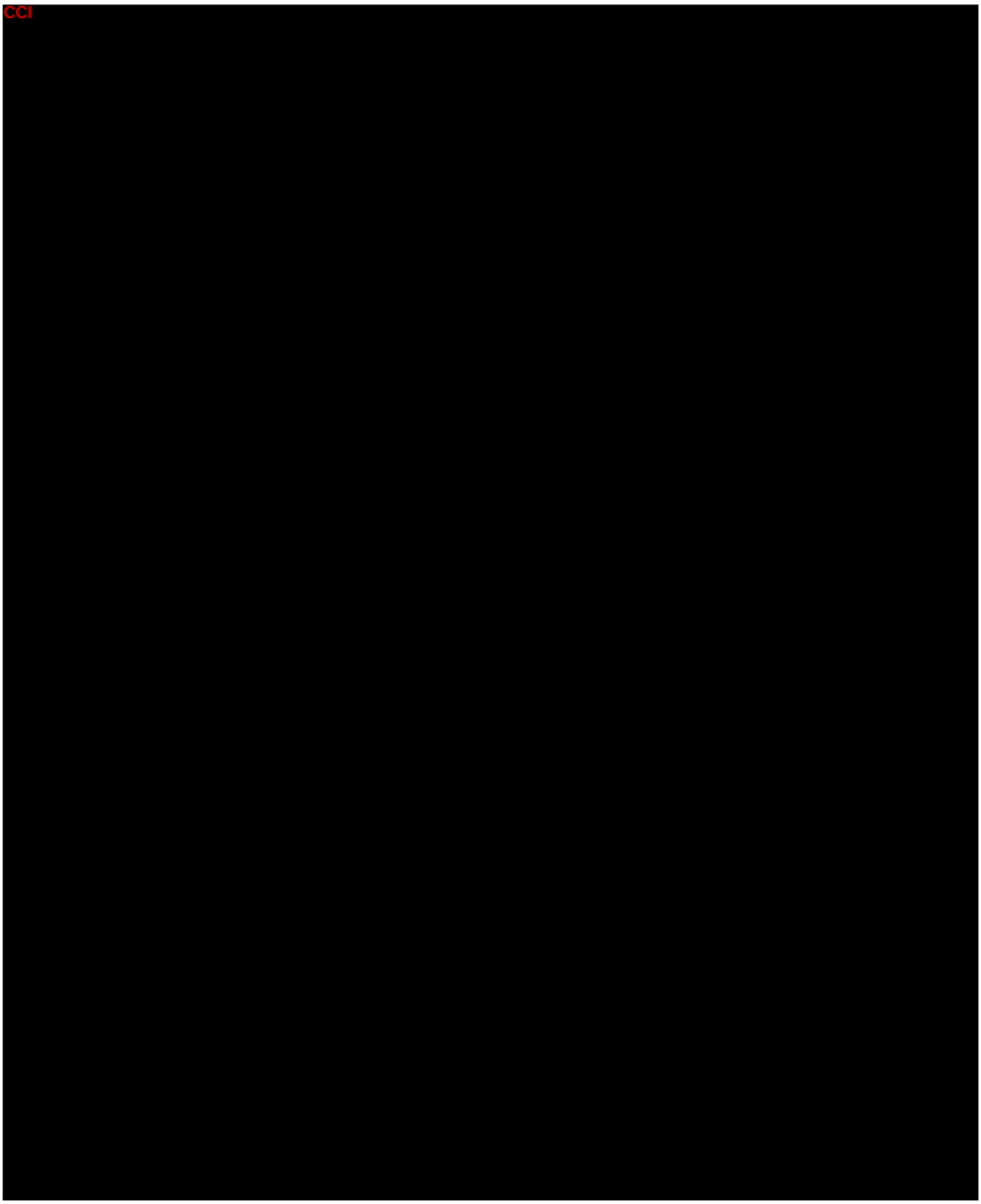

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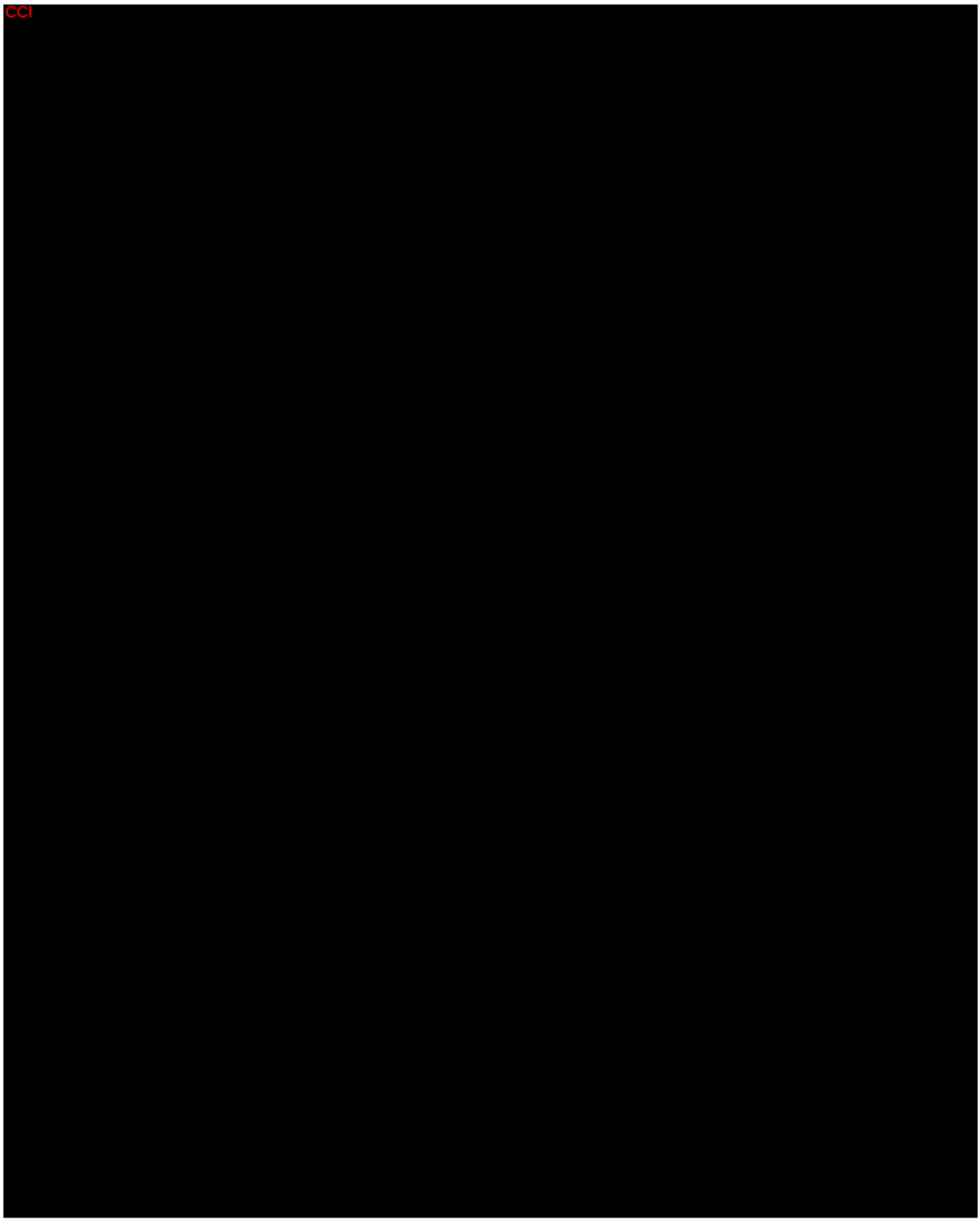
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12.3.1.2 *Secondary efficacy endpoints and main secondary efficacy estimands*

Key secondary efficacy endpoints:

- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for HFL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for both left and right LCL at maximum contraction as assessed by the investigator at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the subject at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for HFL at maximum contraction as assessed by the subject at Day 30 of MP.
- Proportion of subjects with a score of 0 (no) or 1 (mild) on MAS for both left and right LCL at maximum contraction as assessed by the subject at Day 30 of MP.
- GAIS as assessed by the subject at Day 30 of MP

Main estimands for MAS-based key secondary efficacy endpoints are specified in full detail in CCI [redacted]. All key secondary estimands per treatment area were derived from the respective main primary estimand as specified in Section 12.3.1.1. Definitions of attributes treatment, target population, other intercurrent events and population level summary are identical. The variable attributes of key secondary estimands were adapted according to the above-defined key secondary endpoints for the respective treatment area based on the investigator/ subject assessment on the MAS at maximum contraction. For example, the variable attributes of the main estimands for the two key secondary efficacy endpoints for treatment area GFL are defined as "GFL response defined as a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the investigator at Day 30" and "GFL response defined as a score of 0 (no) or 1 (mild) on MAS for GFL at maximum contraction as assessed by the subject at Day 30", respectively.

The main estimand for the key secondary endpoint based on subject's GAIS at Day 30 of MP is presented in CCI [redacted]

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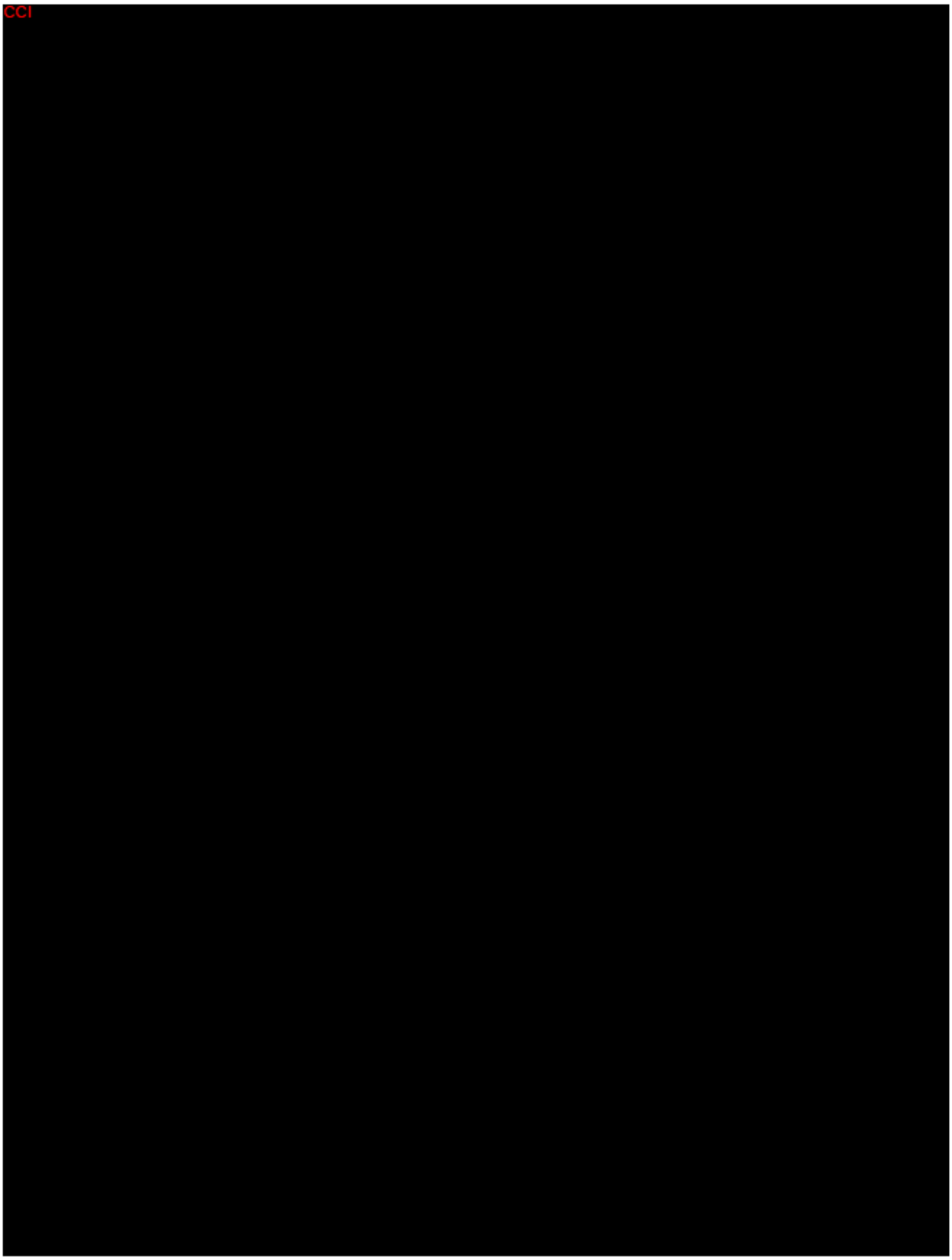

Further secondary efficacy endpoints:

- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for GFL at maximum contraction as assessed by the investigator.
- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for HFL at maximum contraction as assessed by the investigator.
- Proportion of subjects with at least one-grade improvement from baseline to Day 30 of MP on MAS for both left and right LCL at maximum contraction as assessed by the investigator.
- GAIS as assessed by the investigator at Day 30 of MP.

No estimands are defined for further secondary endpoints.

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12.3.2 Pharmacodynamic endpoints

Not applicable.

12.3.3 Pharmacokinetic endpoints

Not applicable.

12.3.4 Pharmacogenetic endpoints

Not applicable.

12.3.5 Safety endpoints

12.3.5.1 Primary safety endpoint

No primary safety endpoint has been defined.

12.3.5.2 Secondary safety endpoints

- Incidence of related TEAEs in MP
- Incidence of related TEAEs in OLEX period

For the definition of TEAEs, see Section 10.1.

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12.4 Statistical analysis methods

12.4.1 Efficacy endpoints and efficacy estimands

Primary and sensitivity analyses for primary efficacy endpoints (see Section 12.4.1.1) will be based on the target population of the three main primary estimands as defined in Section 12.3.1.1. Further efficacy analyses will be based on the FAS if not otherwise specified. Statistical tests will be two-sided hypothesis tests for between treatment differences in general. Adequate descriptive statistics will be provided for all endpoints. Continuous endpoints (values and changes from baseline) will be summarized by number of subjects (N), mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative endpoints, absolute and percent frequencies (N, %) and, if applicable, shift

tables will be displayed. Confidence limits and descriptive p-values will be given, where appropriate.

12.4.1.1 Primary efficacy endpoints and primary efficacy estimands

The primary endpoints will be proportions of GFL-, HFL- and LCL-responders as defined in Section 12.3.1.1. These proportions will be compared for treatment groups U and P (as described in [redacted] It should be noted that Group L is not part of the primary efficacy analysis which has the objective to compare efficacy of simultaneous treatment of UFL with NT 201 versus placebo. Group L will be considered in the secondary and other analyses.

The three main primary efficacy estimands are defined in Section 12.3.1.1 (see [redacted] for GFL, [redacted] for HFL, and [redacted] for LCL).

Main estimators for main primary estimands: Primary analysis of primary endpoints

For comparison of proportion of GFL-, HFL- and LCL-responders in treatment groups U and P, Mantel-Haenszel stratum weights and the Sato variance estimator will be used to calculate the stratum-adjusted risk difference, with study site serving as stratum variable. For each anatomical region, the the stratum-adjusted (common) difference in response rates between treatment Group U and Group P (reference) will be provided with two-sided p-value and 95% Mantel-Haenszel confidence interval (CI). The null hypothesis of the Mantel-Haenszel test is that the common difference in response rates is zero. The family-wise two-sided type I error level $\alpha = 0.05$ will be controlled by a hierarchical test procedure based on two-sided tests with $\alpha = 0.05$ as described in Section 12.4.7.4.

[redacted]

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[redacted]

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[redacted]

12.4.1.2 *Secondary efficacy endpoints and secondary efficacy estimands*

Secondary efficacy endpoints and estimands for key secondary endpoints are described in Section 12.3.1.2. Definitions of MAS-based key secondary estimands are provided in CCI [redacted] and of the subject's GAIS-based key secondary estimand in CCI [redacted]

12.4.1.2.1 Key secondary efficacy endpoints and key secondary efficacy estimands

Main estimators for main key secondary dichotomous MAS-based efficacy estimands correspond to main estimators for main primary estimands (see Section 12.4.1.1). For all three anatomical regions and for investigator's as well as subject's assessments on the MAS, stratum-adjusted differences in proportions for overall comparisons of treatment Group U versus P (reference) with corresponding 95% Mantel Haenszel CIs and p-values will be provided.

Main estimator for the main key secondary estimand based on subject's GAIS CCI [redacted] will be analysis of covariance with factors treatment group and site, and mean of baseline MAS for HFL, GFL, and LCL at maximum contraction assessed by subject as covariate. Missing data on subject's GAIS at Day 30 will be handled following the same conservative imputation strategy as defined for missing MAS data at Day 30 in the main estimator of main primary estimands (see Section 12.4.1.1).

Multiplicity adjustment strategy for comparisons of treatment groups U and P on key secondary endpoints is described in Section 12.4.7.4.

Supplementary analyses of key secondary endpoints for all three regions will be performed using the same methods as described for supplementary analyses of primary endpoints on the FAS, the PPS and on observed cases in FAS and PPS (Section 12.4.1.1).

12.4.1.2.2 Further secondary endpoints

Similar analysis strategy by region as described for the supplementary analysis of primary endpoints on observed cases in FAS/PPS will be applied for the further secondary dichotomous MAS-based efficacy endpoints defined for the MP. In particular,

proportions of subjects with at least one-point improvement in treatment groups U and P will be compared by stratum-adjusted differences in proportions with corresponding 95% Mantel Haenszel CIs and p-values.

Moreover, 95% CIs for proportions and difference in proportions will be provided.

Group L will only be considered for statistical analyses of MAS of the LCL region but not of the GFL and HFL regions.

GAIS as assessed by the investigator at Day 30 of the MP will be analyzed using analysis of covariance with factors treatment group and site, and mean of baseline MAS for HFL, GFL, and LCL at maximum contraction assessed by investigator as covariate.

Results for all further secondary endpoints will only be interpreted descriptively.

For further secondary endpoints only observed cases will be analyzed. Analyses will be provided for FAS and PPS.

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. The analysis of safety endpoints will be based on observed cases and only TEAEs will be analyzed. AEs will be coded according to the MedDRA version in effect at the time the database is closed. Only TEAEs will be analyzed, which are defined as AEs with onset or worsening on or after date of the first administration of IP up to end of study visit.

12.4.5.1 Primary safety endpoint

No primary safety endpoint has been defined.

12.4.5.2 Secondary safety endpoints

Listings and tables displaying incidences of related TEAEs in MP and OLEX will be provided by system organ class and preferred term by study group and overall, for the total study period and by treatment cycle. For the analyses by treatment cycle, the denominator for the incidences will be adjusted to all subjects being treated in that treatment cycle.

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[redacted]

12.4.7 Special statistical/analytical issues

12.4.7.1 Discontinuations and missing data

Reasons for premature discontinuation of study will be summarized descriptively. Discontinued subjects will not be replaced.

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[redacted]

12.4.7.2 Interim analyses

Not planned.

12.4.7.3 Committees

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[redacted]

12.4.7.4 *Multiple comparisons/multiplicity*

The family-wise two-sided type I error level $\alpha = 0.05$ for comparisons of treatment groups U and P on the primary and key secondary endpoints will be controlled by a hierarchical test procedure based on two-sided tests with $\alpha = 0.05$.

The hierarchical procedure for primary analysis (Section 12.4.1.1) will be performed as described below. First, using the Mantel-Haenszel test of the null hypothesis that the common difference in response rates at Day 30 is zero, Group U versus Group P will be tested for superiority for proportion of GFL-responders, second for proportion of HFL-responders, and third for proportion of LCL-responders. The test procedure will stop once statistical significance could not be reached.

In case statistical significance can be established for all three primary efficacy endpoints, the procedure will proceed to key secondary endpoints (Section 12.4.1.2.1): As next steps, Mantel-Haenszel tests for superiority of Group U versus Group P will be conducted for proportion of subjects with a score of 0 (no) or 1 (mild) on MAS at maximum contraction as assessed by the *investigator* at Day 30 of MP for GFL, then HFL and finally LCL anatomical region. Thereafter, Mantel-Haenszel tests for superiority of Group U versus Group P will be conducted for proportion of subjects with a score of 0 (no) or 1 (mild) on MAS at maximum contraction as assessed by the *subject* at Day 30 for GFL, then HFL and finally LCL anatomical region.

Finally, GAIS as assessed by the subject at Day 30 of MP will be tested as described in Section 12.4.1.2.1.

The hierarchical test procedure will stop once statistical significance could not be reached.

For any other statistical tests on primary or key secondary endpoints (e.g. comparison of treatment groups L and P), no type I error adjustment will be performed. The same accounts for any statistical analyses of further secondary and other endpoints.

12.4.7.5 *Examination of subgroups*

The primary analysis of primary endpoints will be conducted for two subgroups according to pre-treatment status. Subjects will be distinguished on whether they have been treated with BoNT-A prior to randomization at any time for any treatment indication or not (treatment naïve).

Dichotomized endpoints which are based on MAS at rest will be analyzed in subgroups of subjects with baseline score of at least 2 on the corresponding MAS at rest as assessed by both subject and investigator. Since scores at rest are in general lower than scores at maximum contraction, some subjects may have a score of 0 (none) or 1 (mild) at baseline on MAS at rest. These subgroup analyses will be more meaningful and sensitive to treatment effects than analyses of the total FAS as they consider effects in 'symptomatic'

subjects, i.e. subjects with 0 (none) or 1 (mild) on corresponding MAS will not be analyzed.

13 DATA HANDLING AND RECORDKEEPING

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

13.1 Corrections to data

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

If corrections are necessary, an authorized member of the investigator's site staff will enter the correct data into the web-based eCRF. The audit trail in the electronic data capture system will document 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 and sign it off. The investigator is not allowed to make any changes to these documents.

Database closing will occur only after quality assurance procedures have been completed.

13.2 Recordkeeping

Essential documents should be retained until at least two years after the last approval of a marketing application (whether pending or contemplated) in an ICH region, or at least two years have elapsed since the formal discontinuation of IP clinical development. These documents are to be retained for a longer period, 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 medical records).
- 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 year of birth.
- A signed copy of the final clinical study protocol and any amendment.
- CDs/DVDs with PDF-files containing subjects' 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 IEC 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.
- 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.

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 (such as clinicaltrials.gov and EudraCT), 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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