A prospective, randomized, double-blind, multicenter study to investigate the safety and duration of effect of different NT 201 dose groups following the treatment of glabellar frown lines

Development phase:	Phase 2
Study identifier:	M602011015
NCT number:	NCT03806933
EudraCT number:	2018-002743-28
IND number:	100288
[redacted]	
Indication:	Glabellar frown lines
Planned study period:	First subject first visit: JAN-2019 Last primary outcome visit: SEP-2020 Last subject last visit: OCT-2020
Investigational product(s):	Clostridium botulinum neurotoxin type A (150 kDa), free from complexing proteins powder for solution for injection (NT 201)
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: [redacted] Medical Expert: [redacted] Biostatistician: [redacted]
Version date:	21-JUL-2023, Version 2.0 30-APR-2020, Version 1.0, Amendment 2 22-OCT-2019, Version 1.0, Amendment 1 01-OCT-2018, Version 1.0

SIGNATURE PAGE

The study will be conducted in compliance with the clinical study protocol, ICH–GCP principles, the Declaration of Helsinki, and regulatory authority requirements.
The following individuals are responsible for the content of the clinical study protocol:

Statement of Compliance

Study site(s)

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the case report form, International Conference on Harmonization (ICH)–Good clinical practice (GCP) principles, the Declaration of Helsinki, and regulatory authority requirements.

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

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate independent ethics committees (IECs)/ institutional review boards (IRBs) before enrolling any subject in this study.
- Obtain informed consent for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
- Use the IP and all study materials only as specified in the clinical study protocol.
- Report to the clinical CRO, within 24 hours, any adverse event (AE) that is serious, whether considered treatment related or not as well as any adverse event of special interest (AESI) (see Section 10.3 for definition).
- For United States (US) studies: Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest in accordance with 21 CFR Part 54 and a signed Food and Drug Administration (FDA) 1572 form according to 21 CFR Part 312.

Furthermore, I understand that:

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

Principal investigator (print name)	Date (dd-MMM-yyyy)	[redacted]

Study site stamp (for German sites only):

Changes to Previous Versions of this Protocol

Version and Date	Change
Version 2.0, 21-JUL-2023	Using the original 2018 (v1) clinical study protocol, as well as the two subsequent "stand alone" amendments/Summary of Changes documents from 2019 and 2020, this compiled study protocol was required for appropriate and transparent public disclosure and alignment with the final Statistical Analysis Plan (2021, v3).
Version 1.0, 30-APR-2020	A second protocol amendment became necessary due to government regulations and restrictions related to COVID-19. This amendment was needed to assure subjects' safety and mitigate the impact on safety and efficacy assessments in case subjects could not attend on-site visits. [redacted]
Version 1.0, 22-OCT-2019	A substantial amendment was required due to an error in the statistical analyses reported in the 2018 protocol for the primary efficacy variable and the two secondary "duration of effect" variables. [redacted]
Version 1.0, 01-OCT-2018	Original version

List of abbreviations and definitions of terms

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BDRM	Blind data review meeting
β-HCG	Beta-Human chorionic gonadotropin
BoNT(/A)	Botulinum neurotoxin (type A)
CETS	Combined endpoint treatment success
CRO	Contract research organization
DEM	Dose escalation meeting
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EU	European Union
EudraCT	European clinical trial database
FAS	Full analysis set
FDA	Food and Drug Administration, US
FWS	Facial wrinkle scale
[redacted]	
GCP	Good clinical practice
GFL	Glabellar frown lines
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND number	Investigational new drug number, issued by the FDA
IP	Investigational product
IRB	Institutional review board
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MP	Main period
OLEX	Open-label extension (period)
PI	Prescribing information

PRO	Patient-reported outcome
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SES	Safety evaluation set
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Serious treatment-emergent adverse event
U	Unit
US(A)	United States (of America)
V	Visit
WHO	World Health Organization

Table of Contents

1 SYNOPSIS

Study title

A prospective, randomized, double-blind, multicenter study to investigate the safety and duration of effect of different NT 201 dose groups following the treatment of glabellar frown lines

Study phase

2

Indication

Glabellar frown lines (GFL)

Study objectives

Primary objective

To assess the safety and duration of effect of different NT 201 dose groups following the treatment of GFL.

Secondary objective

To assess the efficacy of different NT 201 dose groups following the treatment of GFL.

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

The study will be a prospective, randomized, double-blind, dose-ranging, multicenter, phase 2 clinical study with two treatment stages.

Only subjects meeting all of the inclusion and none of the exclusion criteria at the Screening Visit V1 (Day -3 to -14) and/or the Baseline Visit V2 (Day 1) will be considered for study enrollment for stage 1 or 2 respectively.

Main inclusion criteria

- Male or female subject 18 years or over.
- Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed by investigator on the 4-point FWS.
- Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed by subject on the 4-point FWS.

Main exclusion criteria

- Previous treatment with Botulinum neurotoxin (BoNT) of any serotype in the facial area within the last 12 months before injection.
- Previous treatment with any facial cosmetic procedure (e.g., chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment, tattooing of eyebrows) in the glabellar area within the last 12 months before injection.
- Previous treatment with any biodegradable filler in the glabellar area within the last 12 months before injection.
- Inability to substantially reduce GFL by physically spreading them apart as assessed by the investigator.
- Excessively thick sebaceous skin or hypertrophic muscles in the upper third part of the face.
- Any surgery or scars in the glabellar area.
- Marked facial asymmetry.
- Eyelid ptosis.
- Marked brow ptosis and/or dermatochalasis.
- Ongoing severe or unstable medical conditions, e.g., systemic infection, or pulmonary disease, at the discretion of the investigator.

Study design

This multicenter Phase 2 clinical study will consist of a Main Period and the subsequent optional open-label extension (OLEX) Period. The Main Period will have a prospective, randomized, double-blind, dose-ranging, design with two treatment stages. In stage 1, the dose groups 20 units (U), 50 U, and 75 U will be investigated. Once all subjects of stage 1 completed Day 30±7 Follow-up Observational Visit V4, a dose escalation meeting (DEM) will be held. Stage 2 will be performed only if no safety concerns have been raised during DEM and will investigate the dose groups 20 U and 100 U. Subjects do not cross over from stage 1 to stage 2. A total number of up to 240 subjects with moderate to severe GFL at maximum frown as assessed by the investigator using the 4-point FWS is planned to be randomly assigned to one of up to four NT 201 dose groups (stage 1: 20 U, 50 U, 75 U and, if applicable, stage 2: 20 U and 100 U).

Study procedures will be identical in both stages. The subjects will receive intramuscular injection of NT 201 according to their respective randomized dose groups administered at

the Baseline Visit V2 (Day 1) of stage 1 or stage 2. The injection at Baseline Visit V2 (Day 1) of stage 1 or stage 2 and the following Observational Visits (up to V15) comprise the main period (MP) of the study.

Additionally, subjects who have relapsed to baseline status, will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GF [redacted] This injection and the subsequent follow-up visit constitutes an optional open-label extension (OLEX) period in this study.

MP

Stage 1 of the study

In stage 1 of the study, eligible subjects, who had a successful Screening Visit V1 (Day -3 to -14), will be randomized at the Baseline Visit V2 (Day 1) to one of three dose groups of 20 U (n=30), 50 U (n=60) or 75 U NT 201 (n=60) according to the randomization ratio 1:2:2.

Once all enrolled subjects for stage 1 have had their Day 30±7 Follow-up Observational Visit V4, a blinded evaluation of safety data will be performed in a DEM. Based on the stage 1 data, a decision to proceed with stage 2 of the study with a dose group of 100 U NT 201 will be made.

Stage 2 of the study

In the case where no safety concerns have been raised during DEM, stage 2 of the study will be started. After successful screening eligible subjects will be enrolled and randomized at the Baseline Visit V2 (Day 1) to one of two dose groups of 20 U (n=30) or 100 U NT 201 (n = 60) according to randomization ratio 1:2.

[redacted]

The observation period for each subject (in stage 1 and stage 2) will be at least 180 days. Subjects who have relapsed to baseline status of their GFL based on the investigator's assessment on the FWS at maximum frown up to Day 180, should complete the End of MP study visit at Day 180 of the study. Subjects who have not relapsed to baseline status of their GFL at Day 180 (V9) will continue to be observed for up to 180 additional days. For subjects who have relapsed to baseline status of their GFL between Day 180 and Day 360 the End of MP can be performed at each of the respective Observational Visits. If no relapse to baseline status is measured, the End of MP will be performed at Day 360 (V15).

Optional OLEX:

Subjects who have relapsed to baseline status of their GFL in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day 360. An OLEX Follow-Up Visit V16 will be performed 30 days after the optional injection to document the occurrence of adverse events (AEs)/adverse event of special interest (AESIs).

Study duration for each subject (in stage 1 and stage 2) will be at least 180 days, plus the individual duration of screening (up to 14 days), plus OLEX follow-up for subjects who elect to receive an optional follow-up treatment. The overall maximum study duration will be up to 390 days in case the subject will receive an optional follow-up treatment plus the individual duration of screening (up to 14 days) for each subject.

Subjects who withdraw or are withdrawn prematurely from the study will be requested to come to the End of MP study visit. Please note that subjects who receive the optional follow-up treatment but do not attend the OLEX Follow-Up Visit V16 for any reason will not be considered as discontinued prematurely from the study.

Planned study period

First subject first visit: JAN-2019
Last primary outcome visit: SEP-2020
Last subject last visit: OCT-2020

Duration of treatment per subject

There is one planned study treatment at the Baseline Visit V2 (Day 1) of stage 1 and stage 2 respectively and one optional follow-up treatment for subjects who have relapsed to baseline status of their GFL in the MP. The overall study duration for each subject will be at least 180 days, plus the individual duration of screening (up to 14 days), plus 30 days OLEX follow-up for subjects who elect to receive an optional follow-up treatment. The overall maximum study duration could be up to 390 days for subjects who receive an optional follow-up treatment, plus the individual duration of screening (up to 14 days) for each subject.

Variables for analysis

Efficacy variables

Primary efficacy variable

Duration of effect as defined by time between treatment and relapse to baseline status. Effect is defined as improvement at maximum frown as assessed by the investigator on the FWS.

If no improvement is observed on the FWS at any point after treatment, the time will be set to 0.

Secondary efficacy variables

- Duration of effect whereby effect is defined by a score of none (0) or mild (1) at maximum frown as assessed by the investigator according to FWS

  This variable is defined as the time between treatment and the first point in time when the score is moderate (2) or severe (3) again. If no improvement is observed on the FWS at any point after treatment, the time will be set to 0

- Duration of effect whereby effect is defined as 2-point improvement from baseline at maximum frown as assessed by the investigator according to FWS

  This variable is defined as the time between treatment and the first point in time when the improvement is less than 2 points again. If no improvement is observed on the FWS at any point after treatment, the time will be set to 0

- Percentage of subjects rated as none (0) or mild (1) at maximum frown by investigator's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as none (0) or mild (1) at maximum frown by subject's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by investigator's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by subject's rating on FWS Subject at Day 180 (V9)

Safety variables

Primary safety variables

Occurrences of treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs), treatment-emergent adverse events of special interest (TEAESIs), related TEAEs and related TESAEs by dose group for the entire study period.

An AE is considered treatment-emergent with onset or worsening on or after date of the first administration of investigational product (IP).

Secondary safety variables

Not applicable.

Total number of subjects and number of countries

A total number of 240 subjects will be randomized.

Stage 1: In total 150 subjects: 30 subjects for the dose groups with 20 U and 60 subjects each for 50 U and 75 U (1:2:2 randomization).

Stage 2: In total 90 subjects: 30 subjects for the dose group 20 U and 60 subjects for 100 U (1:2 randomization).

The study will be conducted in the United States of America (USA) and Germany.

Number of study sites

It is planned to conduct the study in approximately 8 sites.

Number of visits

There will be up to 16 site visits during study course. [redacted]

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

In this study, all subjects will receive active treatment with NT 201 (active ingredient: NT 101, Clostridium botulinum neurotoxin type A (150kDa), free from complexing proteins) injected into the glabellar area after assignment to one of the following dose groups: 20 U, 50 U, or 75 U in stage 1 and 20 U or 100 U in stage 2 at Baseline Visit V2 (Day 1) of the respective stage. Subjects (in stage 1 and stage 2) who have relapsed to baseline status in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day 360.

[redacted] The treatment will be administered [redacted] to five intramuscular injection sites into the procerus and corrugator muscles. [redacted]

Statistical analysis methods

Efficacy variables

The efficacy analyses will be based on the full analysis set (FAS).

Primary efficacy variable

The primary endpoint will be described by Kaplan-Meier Curves per group and the respective medians of times.

[redacted] pairwise log-rank tests and Cox proportional hazards regression will be applied to compare differences between high dose groups and the 20 U group to explore statistical significance.

Secondary efficacy variables

The secondary duration of effect variables will be analyzed in analogy to the primary variable.

For the percentages of subjects fulfilling the criteria as described in the secondary efficacy variables two-sided 95% Pearson-Clopper confidence intervals will be computed for each dose group.

Safety variables

Primary safety variable

All safety analyses will be conducted on the safety analysis set (SES). Incidences (absolute and percentage) of TEAEs, TEAESIs, TESAEs, and related TEAEs will be calculated on the level of system organ class (SOC) and preferred term (PT).

Secondary safety variables

Not applicable

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
[redacted]	Clinical project manager	Telephone: Telefax: Email:
	Clinical project director Merz North America	Telephone: Mobile: Email:
	Medical expert	Telephone: Telefax: Email:
	Biostatistician	Telephone: Telefax: Email:
	Product safety officer	Telephone: Telefax: Email:
	Regulatory affairs manager	Telephone: Telefax: Email:

2.2 External responsibilities

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

The sponsor will maintain a list of all principal investigators and of all independent ethics committees (IECs)/institutional review boards (IRBs). Curriculum vitae of each investigator, names of all investigators as well as names and addresses of each IEC/IRB as well as additional vendors can be found in the trial master file.

Name	Function	Address
[redacted]		

Name	Function	Address
[redacted]		

2.3 Committees

No external committees are planned during this study. A DEM will be performed during the study. For more information, see Section 12.4.7.3.

3 ETHICS

3.1 Independent Ethics Committee/Institutional Review Board

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

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

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

3.2 Ethical conduct of the study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Conference on Harmonization (ICH)-Good clinical practice (GCP) and applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the study.

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

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 and their rights as study participants. This verbal and written information will be provided by the investigator (or authorized sub-investigator if applicable) according to the provisions set forth in the Declaration of Helsinki. The obligations of the investigator are set forth in the clinical study protocol, the ICH-GCP principles (effective as of 17-JAN-1997) and the respective national regulations governing medical research and experimentation on humans.

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

[redacted]

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 AEs, or poor tolerability to the 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.

[redacted]

This applies to sites that are temporarily closed for subject on-site visits or have subjects under a Stay-at-Home-Order or subjects who choose not to come to the site due to the pandemic.

To assure subject's safety, sites will monitor subject's safety via phone calls at planned visit dates based on subject's verbal consent.

a) being called for safety assessments (AEs, AESIs, change in medication and non-drug treatment, and occurrence of pregnancy) via phone and

b) being sent a printout of the Facial Wrinkle Scale [FWS] PhotoGuide, questionnaires [redacted] to perform their self-assessments of efficacy at home

After the verbal consent, the subject must also confirm his/her consent electronically in writing (via email) before sending out the documents required for the self-assessment to the subject.

During the next on-site visit, subject's consent to the phone visit and / or the self-assessment must be confirmed by the investigator and the subject in a signed supplemental ICF according to the procedures described above, including the requirements for traceability.

Every effort should be made to contact subjects via phone or letter. At least 3 documented attempts to contact the subject should be made. All the attempts are to be documented in the subject's source documentation.

3.3.3 Subject card

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

- The name, address, and telephone number of the investigator or institution, as the main contact for product information and emergency unblinding.
- A 24-hour hotline number for emergencies.

3.3.4 Post-study treatment

No specific post-study arrangements are made and no specific post-study care will be performed after this study. After study discontinuation, the subjects will be treated by their physician according to their medical condition and standard treatments in the country concerned.

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 (see Section 8.2.1). Access to non-coded data will be allowed solely to check validity, and such access will be limited strictly to authorized individuals (e.g., individuals authorized by the sponsor (e.g. (medical) monitors), auditors, regulatory authorities, or members of IECs/IRBs) who have been bound to confidentiality. If the results of the study are published, the subject's identity will remain confidential.

[redacted]

3.3.6 Contact point

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

[redacted]

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 required insurance documents will be handed out to the subject, if requested by the subject or if required by local law (as is the case e.g. in Germany).

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

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

[redacted]

3.5 Financing

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

[redacted]

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, a lot of indications in the field of aesthetic dermatology and plastic surgery were found for BoNT/A preparations such as hyperfunctional GFL due to muscle overactivity and are treated commonly in daily practice and research [Imhof 2013, Jones 2010, Nestor 2011, Nettar 2011, Prager 2013, Tamburic 2012].

NT 201 (United States Adopted Name [USAN]: incobotulinumtoxinA) is a highly purified, freeze-dried formulation of BoNT/A and was first approved on 31-MAY-2005 in Germany. [redacted] T 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).

Medical background

Vertical GFL between the eyebrows are caused by contraction of the corrugator muscles located above both eyebrows and the procerus muscle at the root of the nose [Carruthers 1996]. In subjects suffering from expression related GFL due to muscle overactivity, facial lines in this area become static lines fixed in the skin at rest early in the aging process.

[redacted] Effective management of facial lines requires approaches including aesthetic and surgical dermatological treatments such as peels, laser resurfacing, fillers, and 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 rapidly became the standard treatment when the first representative of this drug class was approved for treatment of GFL.

BoNT/A treatment is a minimally invasive aesthetic procedure and at 7 million was the leading non-surgical cosmetic procedure in 2016 in the USA [American Society of Plastic Surgeons 2017].

GFL are the historically first and most frequently treated aesthetic indication.

Treatment of GFL mainly targets the corrugators 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 [Jones 2017]. In GFL, local muscle relaxation is manifested as a reduction in the corresponding facial lines. The approved standard dose of NT 201 in this indication is 20 U [Merz Pharmaceuticals GmbH 2017, Merz Pharmaceuticals LLC 2018]. According to the EU summary of product characteristics (SmPC) the dose may be increased by the physician to up to 30 U if required by the individual needs of the patients. According to the American Consensus group about 30% of panel members use higher doses than the approved dose [Carruthers 2004b].

[redacted]

4.3 Risk-benefit assessment

There is an increasing demand for longer duration of effect following treatment with BoNT/A because this significantly influences patient satisfaction. [redacted]

Previous studies have indicated that a longer duration of effect might be achieved with increasing doses of BoNT/A while maintaining an acceptable safety profile. Doses of up to 80 U in the treatment of GFL in male patients were shown to be safe and well tolerated [Carruthers 2005a, Carruthers 2005b [redacted]].

[redacted]

In general, NT 201 is safe and well tolerated in the approved indications including facial aesthetic indications such as GFL and upper facial lines (please refer to the current IB). Doses of up to 64 U NT 201 in the indication upper facial lines have been found to be safe and well tolerated [redacted] and are already approved in the EU. And, as outlined above, there is literature evidence that doses of up to 80 U are safe. Therefore, 75 U is a reasonable highest dose in the first stage of the design.

The mechanism of action and potential AEs following treatment with BoNT/A are well known and qualitatively no new AEs are expected in this study. 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 and generally resolve spontaneously without intervention. [redacted]

Most of the complications of BoNT/A injections are related to needle misplacement [Alimohammadi 2017, Brodsky 2012, Rohrich 2003]. Detailed knowledge of the exact anatomical relationships between the muscles to be injected is very important to avoid the development of adverse effects.

For this study only investigators experienced in the treatment of GFL with BoNT/A will be selected. To ensure exact placement of the injections to targeted muscles, training of investigators during the investigator meetings will focus on individual anatomy of the underlying facial musculature and the physiologic interactions of the muscles. Moreover precise and standardized injection technique will be demonstrated during these trainings.

In this respect, it should further be considered that treatment areas and injection points are in line with the approved label claims in the EU SmPC and the US prescribing information (PI) as well as with international guidelines. Hence, the study design will not induce further procedure related risks.

In conclusion the sponsor believes that this clinical study M602011015 is carefully designed to minimize risks and to maximize potential benefits for the subjects. Based on available evidence, the benefit-risk-balance is considered as positive.

The COVID-19 pandemic may impact the conduct of this clinical trial. Subjects may no longer be able to come to the investigational site for planned safety and efficacy follow up visits due to quarantines, site closures, or travel limitations. Since ensuring the safety of the subjects is paramount, mitigation measures will be implemented. Subjects' safety will be monitored via phone calls at planned visit dates based on subjects' consent. Efficacy based on investigator assessments will not be possible under the circumstances mentioned above, however subjects' self-assessments can also be performed safely at home. Therefore, subjects will be asked if they consent to perform their self-assessments at home. On-site visits should be performed at the earliest possible date the subject is able to safely come to the site again. In conclusion the measures as outlined above are deemed appropriate to assure the safety of trial subjects and reduce the amount of missing data due to COVID-19 pandemic.

4.4 Justification of doses

In everyday practice some physicians do already use higher doses than the approved dose of 20 U in the treatment of GFL. According to the Consensus Recommendations on the use of BoNT/A in facial aesthetics [Carruthers 2004b] 30% of the panel members use doses of up to 120 U in the treatment of GFL.

The doses in this study were chosen in reference to publications and common use in aesthetic medicine.

5 STUDY OBJECTIVES

Primary objective

To assess the safety and duration of effect of different NT 201 dose groups following the treatment of GFL.

Secondary objective

To assess the efficacy of different NT 201 dose groups following the treatment of GFL.

6 INVESTIGATIONAL PLAN

6.1 Overall study design

This multicenter Phase 2 clinical study will consist of a Main Period and the subsequent optional open-label extension (OLEX) Period. The Main Period will have a prospective, randomized, double-blind, dose-ranging, design with two treatment stages. In stage 1, the dose groups 20 U, 50 U, and 75 U will be investigated. Once all subjects of stage 1 completed Day 30±7 Follow-up Observational Visit V4, a DEM will be held. Stage 2 will be performed only if no safety concerns have been raised during DEM and will investigate the dose groups 20 U and 100 U. Subjects do not cross over from stage 1 to stage 2. A total number of up to 240 subjects with moderate to severe GFL at maximum frown as assessed by the investigator using the 4-point FWS is planned to be randomly assigned to one of up to four NT 201 dose groups (stage 1: 20 U, 50 U, 75 U and, if applicable, stage 2: 20 U and 100 U).

Study procedures will be identical in both stages [redacted]. The subjects will receive intramuscular injection of NT 201 according to their respective randomized dose groups administered at the Baseline Visit V2 (Day 1) of stage 1 or stage 2. The injection at Baseline Visit V2 (Day 1) of stage 1 or stage 2 and the following Observational Visits (up to V15) comprise the MP of the study.

Additionally, subjects who have relapsed to baseline status in the MP, will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GF [redacted] This injection and the subsequent follow-up visit constitutes an optional OLEX period in this study. For more information on dosage, formulation, route of administration, and treatment groups, see Section 8.

MP:

Stage 1 of the study

In stage 1 of the study, eligible subjects, who had a successful Screening Visit V1 (Day -3 to -14), will be randomized at the Baseline Visit V2 (Day 1) to one of three dose groups of 20 U (n=30), 50 U (n=60) or 75 U NT 201 (n=60) according to the randomization ratio 1:2:2.

Once all enrolled subjects for stage 1 have had their Day 30±7 Follow-up Observational Visit V4, a blinded evaluation of safety data will be performed in a DEM. Based on the stage 1 data, a decision to proceed with stage 2 of the study with a dose group of 100 U NT 201 will be made. [redacted]

In addition to the blinded safety data evaluation (once all subjects of stage 1 completed Day 30±7 Follow-up Observational Visit V4), an interim analysis will be performed once complete 180-day data (V9) of stage 1 are available. Data will be unblinded for sponsor staff and vendor data management and biostatistics staff only with regard to stage 1 subject's assignment to treatment groups. The blind for subjects in stage 2 will be maintained. Stage 2 subjects, if applicable, will not be included in the 180-day interim analysis. For more details see Section 12.4.7.2.

An interim analysis of complete Stage 1 MP data will be performed as soon as data until and including the End of MP visit V15 from Stage 1 subjects' are completely available (except for missingness due to premature study discontinuation or intermittently missing visits). The analysis of Stage 1 MP data will serve to get further insights regarding duration of effect and occurrence of TEAEs over the entire Main Period of up to 360 days. Knowledge gained form the interim analysis at End of MP of Stage 1 will be useful to decide whether it is still meaningful to motivate affected Stage 2 subjects to re-assume on-site visits depending on the number of missing visits for the primary efficacy variable. Since ensuring the safety of subjects is paramount, this analysis will be valuable to balance the potential risks of further onsite visits against benefits such as avoidance of missing data and premature study discontinuations. Investigators and subjects, site staff and blinded monitor will be kept blinded throughout for both stages until final unblinding. The blind for subjects in Stage 2 will be completely maintained.

Stage 2 of the study

In the case where no safety concerns have been raised during DEM (see Section 12.4.7.3), stage 2 of the study will be started. After successful screening, eligible subjects will be enrolled and randomized at the Baseline Visit V2 (Day 1) to one of two dose groups of 20 U (n=30) or 100 U NT 201 (n = 60) according to randomization ratio 1:2.

The observation period for each subject (in stage 1 and stage 2) will be at least 180 days. Subjects who have relapsed to baseline status of their GFL based on the investigator's assessment on the FWS at maximum frown up to Day 180, should complete the End of MP study visit at Day 180. Subjects who have not relapsed to baseline status of their GFL at Day 180 (V9) will continue to be observed for up to 180 additional days. For subjects who have relapsed to baseline status of their GFL between Day 180 and Day 360 the End of MP can be performed at each of the respective Observational Visits. If no relapse to baseline status is measured, the End of MP will be performed at Day 360 (V15).

Optional OLEX:

Subjects who have relapsed to baseline status of their GFL in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day 360. An OLEX Follow-Up Visit V16 will be performed 30 days after the optional injection to document the occurrence of AEs/AESIs.

Study duration for each subject (in stage 1 and stage 2) will be at least 180 days, plus the individual duration of screening (up to 14 days), plus 30 days OLEX follow-up for subjects who elect to receive an optional follow-up treatment. The overall maximum study duration will be up to 390 days in case the subject will receive an optional follow- up treatment plus the individual duration of screening (up to 14 days) for each subject.

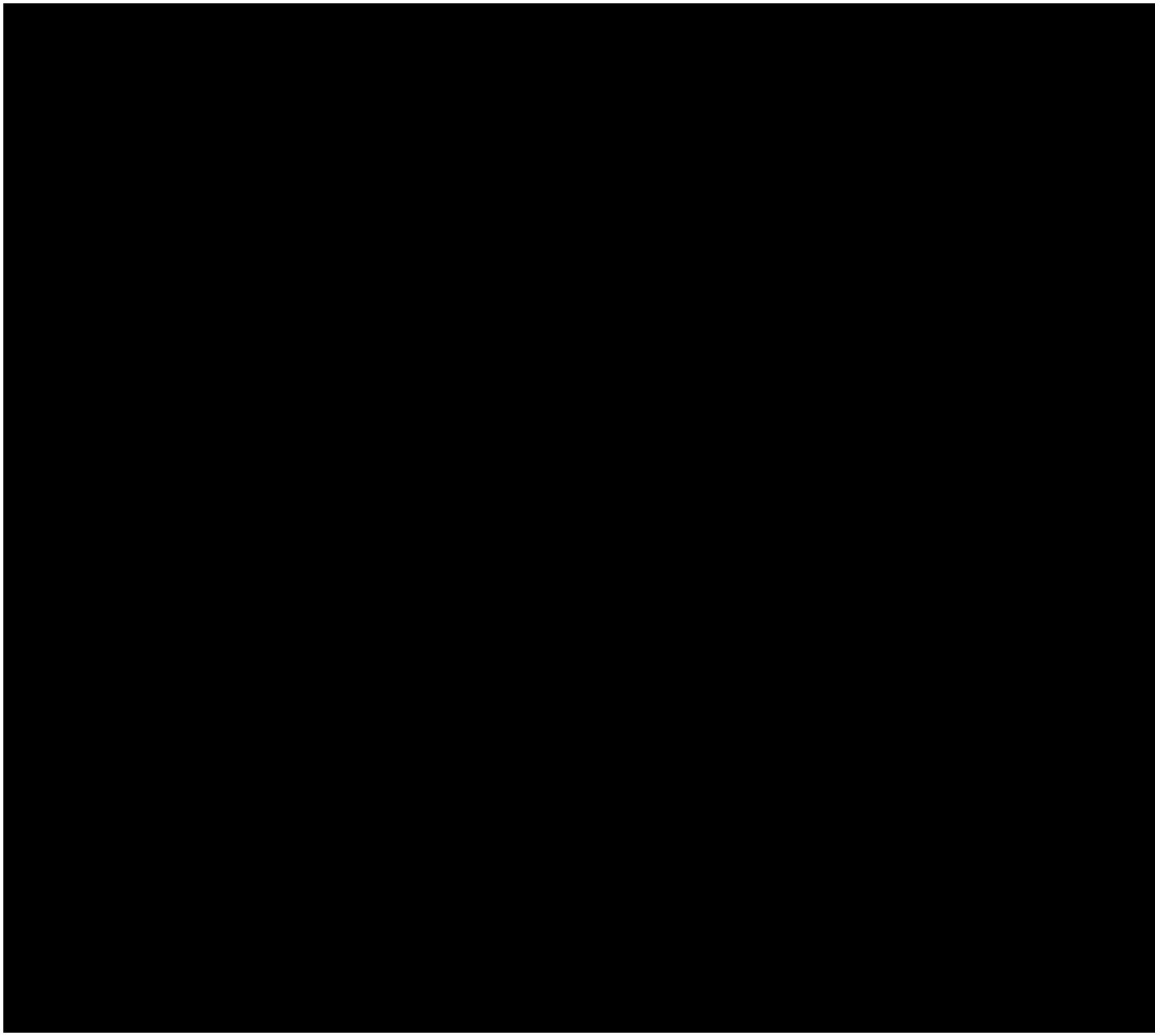
Subjects who withdraw or are withdrawn prematurely from the study will be requested to perform the End of MP study visit. Please note that subjects who receive the optional follow-up treatment but do not attend the OLEX Follow-Up Visit V16 for any reason will not be considered as discontinued prematurely from the study.

The study will be conducted in approximately 8 study sites in USA and Germany.

6.1.1 End of study

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

[redacted]



6.2 Discussion of study design, including choice of control groups

This prospective, randomized, double-blind, dose-ranging, multicenter, phase 2 clinical study is designed to investigate the safety and duration of effect of different NT 201 dose groups following the treatment of GFL.

The recommended dose of 20 U NT 201 used in the US and the 20 to 30 U used in the EU for the treatment of GFL has been proven effective and safe in numerous clinical studies and there is a long term experience in clinical practice. In this study, higher doses of NT 201 (50 U, 75 U, and 100 U) are compared to this currently approved dose. The focus of the study is the safety and duration of effect.

To reduce the risk of subjects, a two-stage design was chosen and the highest dose (100 U) is only investigated when acceptable safety based on predesigned criteria was proven for the 50 U and 75 U doses (see Section 12.4.7.3). To ensure blinding and comparability of the results, subjects will be enrolled in the 20 U dose group in both stages.

The DEM will be performed when all enrolled subjects for stage 1 have had their Day 30±7 Follow-up Observational Visit. Selection of this time point ensures timely decision on the continuation with stage 2 as well as an accurate measurement of safety as the treatment will already have reached its peak effect.

Both stages use a randomized double-blind design. Although an unblinded interim analysis will be performed on the 180-day data of stage 1 subjects, the blind will be maintained for investigators, subjects, site staff and monitors to ensure unbiased continuation of the study.

Subjects will be enrolled regardless of gender, age, ethnic background and pre-treatment status to represent the average target population that is seeking GFL treatment.

Wash out period for BoNT/A treatment in the targeted areas before the study is 12 months, ensuring that no BoNT/A activity from former treatments is left.

The primary efficacy endpoint of the study is duration of effect. The observation period of up to one year, represents a reasonable time that the IP will have worn off in most of the treated subjects, considering the higher doses applied, and ensuring that the primary efficacy endpoint can be measured in a reasonable number of subjects.

[redacted] subjects who have relapsed to baseline status in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day 360. [redacted]

7 STUDY POPULATION

7.1 Selection of study population

Subjects with moderate (score = 2) to severe (score = 3) GFL at maximum frown as assessed by the investigator and subject using the 4-point FWS at screening will be enrolled in this study.

Treatment-naïve subjects or pre-treated (non-naïve) subjects may enter the study. Pre-treated subjects must not have received treatment with BoNT of any serotype in the facial area within the last 12 months before injection.

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

Distribution of gender

No stratification regarding gender is planned. Subjects will be recruited regardless of their gender, ethnicity and age. This study population will therefore be expected to be a representative sample of the target population for the indication of moderate to severe GFL.

7.2 Inclusion criteria

Only subjects meeting all of the following inclusion criteria at the Screening Visit V1 (Day -3 to -14) and/or the Baseline Visit V2 (Day 1) (as indicated below) will be considered for study enrollment for stage 1 or 2 respectively.

Inclusion Criteria	Rationale	Screening	Baseline
[redacted]			
Male or female subject 18 years or over.	Administrative	X	
Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed by investigator on the 4-point FWS.	Efficacy	X	X
Moderate (score = 2) to severe (score =3) GFL at maximum frown as assessed by subject on the 4-point FWS.	Efficacy	X	X
[redacted]			

7.3 Exclusion criteria

Subjects meeting any of the following criteria at the Screening Visit V1 (Day -3 to -14) and/or the Baseline Visit V2 (Day 1) (as indicated below) will not be included as subjects in this study for stage 1 or 2 respectively:

[redacted]

Exclusion Criteria	Rationale	Screening	Baseline
[redacted] Previous treatment with BoNT of any serotype in the facial area within the last 12 months before injection.	Efficacy	X	X
[redacted] Previous treatment with any facial cosmetic procedure (e.g., chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment, tattooing of eyebrows) in the glabellar area within the last 12 months before injection.	Efficacy	X	X
[redacted] Previous treatment with any biodegradable filler in the glabellar area within the last 12 months before injection.	Efficacy	X	X
[redacted] Inability to substantially reduce GFL by physically spreading them apart as assessed by the investigator.	Efficacy	X	X
[redacted] Excessively thick sebaceous skin or hypertrophic muscles in the upper third part of the face.	Efficacy	X	
[redacted]			
[redacted] Any surgery or scars in the glabellar area.	Safety concern	X	
[redacted]			
[redacted] Marked facial asymmetry.	Efficacy	X	X
[redacted]			
[redacted] Eyelid ptosis.	Safety concern	X	X
[redacted] Marked brow ptosis and/or dermatochalasis.	Safety concern	X	X

Exclusion Criteria	Rationale	Screening	Baseline
[redacted]			
[redacted] Ongoing severe or unstable medical conditions, e.g., systemic infection, or pulmonary disease, at the discretion of the investigator.	Safety concern	X	X
[redacted]			

7.4 Removal of subjects from treatment or assessment

7.4.1 Discontinuation of subject's study participation

In accordance with the Declaration of Helsinki and the informed consent form, the subject may end his/her participation in the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled (see Section 7.4.3). Both the fact and the reason(s) why the subject's participation in the study was prematurely discontinued must be recorded in the source documentation (e.g. subject file) and the electronic case report form (eCRF). Date and discontinuation circumstances should be stated.

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

- Withdrawal of informed consent.
- Pregnancy prior to 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). However the subject is free to discontinue the study at any time.
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.

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 MP if no optional treatment was received or the OLEX Follow-up Visit V16 if optional treatment was received (see Section 6.1) 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.

Following discontinuation the End of MP is to be documented. 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). Please note that subjects who receive optional follow-up treatment but do not attend the OLEX Follow-Up Visit V16 for any reason will not be considered as discontinued prematurely from the study.

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(s) do not justify a continuation of the study.
- The investigator or study site exhibits serious and/or persistent non-adherence to the clinical study protocol, the Declaration of Helsinki, ICH–GCP, and/or applicable regulatory requirements.
- 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/IRB has decided to withdraw or suspend approval for the study, the study site, or the investigator.

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

7.4.3 Provision of care for subjects after discontinuation of the study

After study discontinuation, the subjects will be treated by their physician according to their medical condition and standard treatments in the country concerned.

8 TREATMENTS

8.1 Investigational product(s)

8.1.1 Description of investigational product(s)

[redacted]

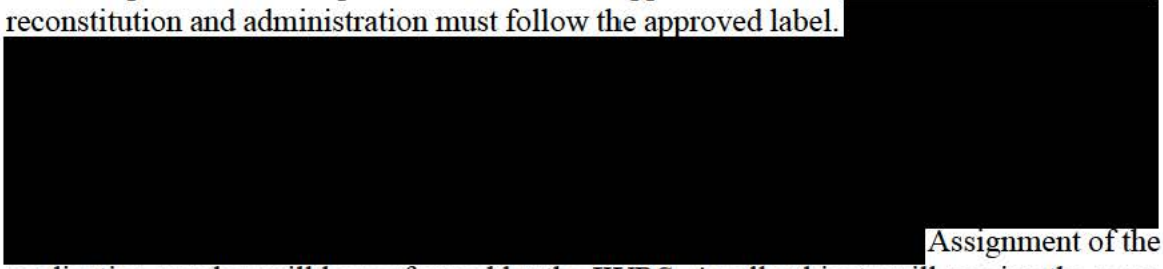
Investigational product:	NT 201, (active ingredient: NT 101, Clostridium botulinum neurotoxin type A (150kDa), free from complexing proteins), [redacted] powder for solution for injection (manufactured by Merz Pharma GmbH & Co. KGaA, Am Pharmapark, 06861 Dessau-Rosslau, Germany) is released by Merz Pharmaceuticals GmbH, Eckenheimer Landstr. 100, D-60318 Frankfurt/Main, Germany.
International non-proprietary name of active ingredient:	An international non-proprietary name for the drug substance has not been assigned. The assigned United States Adopted Name (USAN) for the active ingredient is incobotulinumtoxinA.
Excipients:	Sucrose, human serum albumin.

[redacted]

8.1.1.1 *Instructions for preparation*

Preparation of the IP will be performed by an unblinded study nurse or pharmacist, who receives a precise training. The unblinded study nurse/pharmacist must be a separate person not involved in any other study procedures to ensure blinding of the investigators, other study staff, and subjects. By using the IWRS the dose group according to randomization and the medication number of the medication box to be used will be provided following log-in with a separate password for the unblinded staff. The unblinded study nurse/pharmacist will then reconstitute the IP for each subject according to the randomized dose group assignment. The syringe to be used for injection must be labelled with the medication number provided with the IP kit. Reconstitution according to each dose group assigned by IWRS will be documented in a separate unblinded folder not accessible to blinded study staff. The medication number for each subject will be recorded in the eCRF. The investigator will be blinded to dose group as only the syringe will be provided for treatment.

For the optional follow-up treatment with the approved standard dose of 20 U NT 201, reconstitution and administration must follow the approved label.



Assignment of the medication number will be performed by the IWRS. As all subjects will receive the same dose for this follow-up injection, no other procedures on treatment assignment are necessary.

All injectable solutions should be clear, colorless, and free from particulate matter, otherwise it has to be discarded.

The IP should be reconstituted shortly before injection. However, the reconstituted solution can be stored in the original vial for up to 24 hours in a refrigerator at 2-8°C (36- 46°F). Any deviation should be documented on the drug accountability log. Reconstituted study medication is not to be stored in syringes. 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,
e.g. by autoclaving (please also refer to Section 8.1.5).

8.1.1.2 Instructions for administration

Before injections, the area to be treated will be cleaned per each site's standard practice and dry.

For safety reasons, emergency equipment for treatment of anaphylactic reactions will be available at site.

The treatment will be administered to five intramuscular injection sites into the procerus and corrugator muscles. As the position and the size of these muscles can differ, the investigator should identify the muscles by touching and holding them gently between the fingers

Only medical doctors trained and experienced in aesthetic BoNT treatment are allowed to inject subjects. The number of investigators responsible for these tasks should be as small as possible.

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

8.1.2 Packaging and labeling

An adequate number of medication boxes [redacted] will be sent to the study sites by Merz or a designee. The medication box [redacted] also contains a sticker with the medication number for labeling of the reconstituted IP syringe. Assignment of the medication number to the subject is given to the investigator via the IWRS or is given to the investigator on a printed note accompanying the syringe stating subject/screening number and medication number. [redacted]
The investigator must administer the IP to the subject during the injection visits only. IP must not be handed over to subjects.

The IWRS will assign IP to each subject at baseline or at V15 for the optional follow-up treatment. If an IP vial should be broken, or becomes unusable for any reason, the medication-box / vial must be replaced from the site stock of study medication and the medication number and reason for unusability will be recorded in the IWRS.

The study medication must be labeled according to regulatory requirements in the participating countries. The label will include as minimum information the name and address of the sponsor, study reference number, European clinical trial database (EudraCT)/ Investigational new drug (IND) number, medication number, the dosage form, route of administration, quantity of dosage units, batch number, directions for use, storage conditions, period of use, and the warning 'For clinical study use only'. German labels will include the name and address of the CRO. Labels for USA only, must include: 'Caution: New Drug – Limited by Federal (or US) law to investigational use'. Parts of the study medication may be subject to a reduced labeling according to the applicable regulations. [redacted]

8.1.3 Storage of investigational product(s)

The IP will be shipped at ambient temperature. Shipment will be performed under temperature control. Unopened vials should be stored within a temperature range from +2 to +25°C (36-77°F). It is recommended not to freeze the study medication. During storage the minimum/maximum temperature must be recorded in a temperature log. During storage at the site the temperature log must be maintained weekly on a predefined business day (e.g. every Thursday ± one business day). For storage of reconstituted IP, see Section 8.1.1.1. IP must be stored in a locked place during all study periods.

8.1.4 Accountability for investigational product(s)

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

Upon receipt of the IP(s), the investigator - pharmacist according to local law - must visually inspect the shipment and verify the number and condition of the IP(s), and acknowledge the receipt in the IWRS. An 'IP supply and return form' must 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. Instead of paper forms IWRS print-outs can be used, if applicable.

To ensure proper storage and to verify the inventory, a drug supply inspection will be conducted at regular intervals by the unblinded monitor. The results of the inspection will be made available to the authorized individuals (e.g., unblinded monitor, auditor, and regulatory authorities) on request throughout the study.

For further details, see Section 8.2.5.

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, e.g. by autoclaving [redacted].

[redacted]

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 used and unused vials of IP must be returned to the sponsor or another authorized party. 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

During this study, all subjects will receive active treatment with NT 201 once at the Baseline Visit V2 (Day 1) of stage 1 or stage 2.

In stage 1, all subjects will receive active treatment with NT 201 at the Baseline Visit V2 (Day 1) [redacted] injected into the glabellar area [redacted] in one of three dose groups: 20 U, 50 U, or 75 U. Injection in stage 2 will be performed on the Baseline Visit V2 (Day 1) [redacted] in the dose groups 20 U or 100 U.

Subjects (in stage 1 and stage 2) who have relapsed to baseline status in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for treatment of their GFL between Day 180 and Day 360 [redacted].

[redacted]

8.2.1 Methods of assigning subjects to treatment groups

This study is planned as a multinational, multicenter study. At the Baseline Injection Visit (V2; Day 1) of each stage, subjects will be randomly assigned to dose groups stratified by center by using IWRS. For stage 1, groups 20, 50 and 75 U will be randomized with a randomization ratio of 1:2:2. For stage 2, subjects will be assigned randomly to the groups 20 U or 100 U with a randomization ratio 1:2. Randomized subjects discontinued from the study will not be replaced.

Randomization in blocks of appropriate size and by IWRS will ensure appropriate control of stratification. The block size will not be disclosed to investigators until the study is unblinded. Subjects will receive a subject /screening number through the IWRS, as well as a randomization number, if randomized.

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

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

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

The randomization schedules for stage 1 and 2, respectively, will be sealed and locked at the sponsor's site and will not be accessible to any blinded functions in the study prior to applicable unblinding.

As all subjects will receive 20 U of NT 201 in the optional follow-up treatment, no further randomization is required. The unique medication number of the IP kit for the optional follow-up treatment as assigned to the subject by IWRS will the recorded in the eCRF.

8.2.2 Selection of doses in the study

In the present study 20 U, 50 U and 75 U NT 201 are used in stage 1 and 20 U and 100 U are used in stage 2.

The dose of 20 U is the currently approved dose of NT 201 for the treatment of GFL.

According to the Consensus Recommendations on the use of BoNT/A in facial aesthetics [Carruthers 2004b] 30% of panel members use doses of up to 120 U in the treatment of GFL. [redacted]

The optional follow-up treatment is administered with the approved standard dose of 20 U NT 201. Reconstitution and administration follows the approved label.

8.2.3 Selection and timing of doses for each subject

In this study, all subjects will receive active treatment with NT 201 injected into the glabellar area [redacted] in one of following dose groups: 20 U, 50 U, or 75 U in stage 1 and 20 U or 100 U in stage 2 at the Baseline Visit V2 (Day 1) of the respective stage.

Subjects (in stage 1 and stage 2) who have relapsed to baseline status in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day 360.

For more details see Section 8.1.1.2 and Section 8.2.1.

8.2.4 Duration of treatment per subject

There is one planned study treatment at the Baseline Visit V2 (Day 1) of stage 1 and stage 2 and one optional follow-up treatment for subjects who have relapsed to baseline status of their GFL in the MP. The overall study duration for each subject will be at least 180 days, plus the individual duration of screening (up to 14 days), plus 30 days OLEX follow-up for subjects who elect to receive an optional follow-up treatment. The overall maximum study duration could be up to 390 days for subjects who receive an optional follow-up treatment, plus the individual duration of screening (up to 14 days) for each subject.

8.2.5 Treatment compliance

The IP(s) will be administered by intramuscular injection performed by the investigator during the subject's visit to the investigational site. Thus, full treatment compliance is assured for each individual subject.

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

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 of the eCRF and the source documents. Any case of overdose leading to AEs, SAEs or AESIs must be reported to the CRO in an expedited manner using the appropriate reporting form (see Section 10.1).

As treatment with IP is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this study is estimated to be very low.

[redacted]

[redacted]

There is no significant information regarding overdose from clinical studies in adults with GFL as they will be treated in this clinical study. In the event of an overdose, the investigator/treating physician should closely monitor the subject for any AE/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 hrs 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 anti-toxin will no longer be effective because the neurotoxin has already irreversibly blocked the transmitter release. Compounds releasing acetylcholine (e.g., physostigmine, guanidine, 3,4- diaminopyridine) might be helpful. However, there is no experience with a specific antidote to BoNT including NT 201 in the clinical management of overdose. A published case report describes the successful treatment of dysphagia with intranasal neostigmine [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 (see 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 prior 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/use 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 enrollmen[redacted]:

- Previous treatment with BoNT of any serotype at any body region at any time[redacted].
- Previous treatment with any facial cosmetic procedure[redacted], including also biodegradable filler[redacted] and insertion of permanent material[redacted] (such as silicone, polyacrylamide etc) in the glabellar area at any time.

The following procedures and concomitant medications are not permitted during the study (please see also Section 7.3):

- Procedures in the face that may violate in- and exclusion criteria. For details, please refer to in- and exclusion criteria.
- Any other investigational drug.

[redacted]

- Aminoglycoside antibiotics, or other agents that might interfere with neuromuscular function (e.g., D-penicillinamine, curarine-type muscle relaxants, succinylcholine) or might interfere with the action of BoNT (e.g., chloroquine) within 14 days prior to injection and during the entire course of the study.
- Other agents that might interfere with neuromuscular function, i.e. drugs listed in World Health Organization (WHO) Anatomical Therapeutic Chemical classification

[redacted]

(ATC class M03 *Agents that might induce the production of antibodies against acetylcholine receptors (e.g., D-penicillamine)* (please see Section 16.3).

- BoNT treatment of any serotype at any body region.

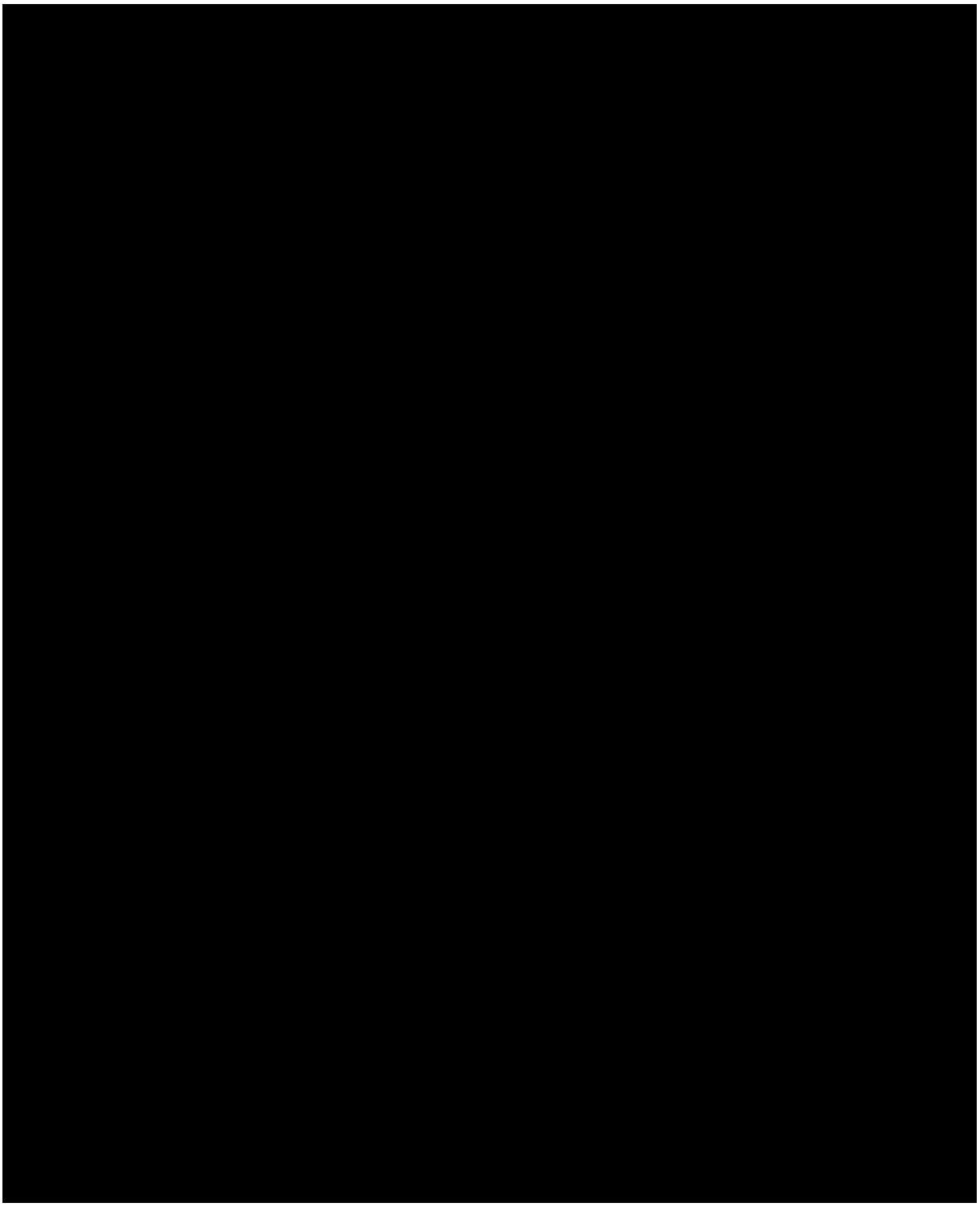
The following concomitant non-drug therapies are not permitted during the study (please see also Section 7.3):

- Treatment with any cosmetic procedure in the face (e.g., dermal filling, chemical peeling, photo rejuvenation, mesotherapy, photodynamic therapy, laser treatment).
- Any surgery in the face.

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.



9 S TUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 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 assessments performed by the investigator take place to guarantee independence of self-ratings (as described in more detail in the outcome manual). [redacted] o facilitate consistent conditions for all subjects all make-up and evident jewelry has to be removed from the face prior to any clinical assessments and self-assessments. The study staff will ensure the subject 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 [redacted] GFL appearance.

[redacted]

If on-site visits due to COVID-19 restrictions are not possible, efficacy live assessments by the investigator cannot be performed and will inevitably lead to missing data.

Subjects who provide their consent for self-assessment of efficacy at home will be re-instructed on how to perform their self-assessments during the safety call. Subjects will be reminded to wear no make-up and evident jewelry during self-assessment. Moreover, subjects will be requested to perform their self-assessment at a place with adequate lighting and without disturbance and to use a mirror to assess their [redacted] GFL appearance. Subjects will be asked to fill in, sign and date the questionnaires [redacted] at the time of the planned study visit dates, if possible during/shortly after the respective safety call. The documents sent to the subjects (FWS PhotoGuide, completed questionnaires [redacted]) will be returned to the investigational site at next possible on-site visit.

The eCRF should be updated by the site staff to collect reasons for missing data: For each planned study visit that was not performed at the study site, the site staff should document whether it was performed as virtual visit due to COVID-19 pandemic, not performed due to COVID-19 pandemic or not performed (due to other reasons). Also, it should be documented if a subject is discontinued from the study due to COVID-19 pandemic.

9.1.1 Clinical assessments

At the Screening Visit V1 (Day -3 to -14), the subject's demographic data, relevant medical history, concomitant diseases, and all concomitant therapies (medications and non-drug treatments) planned during the study will be recorded. All prior medication(s) used by the subject during the last 30 days prior to the Screening Visit V1 (Day -3 to -14) must be documented. Previous treatments with BoNT treatment of any serotype and for any body region and any other facial cosmetic procedur [redacted] in the glabellar area must be recorded regardless of time of application [redacted]. 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, vital signs, and body weight and height measurement (see below). 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.

[redacted]

9.1.1.1 Facial Wrinkle Scale (FWS)

The FWS is a widely used 4-point standardized assessment scale for the assessment of the severity of GFL, which has been used in several studies investigating facial wrinkle treatment [Ascher 2004, Carruthers 2004a, Rzany 2006] including respective GFL studies with NT 201 [Carruthers 2013, Hanke 2013]. Analogue investigator (investigator's FWS) and subject (subject's FWS) versions will be used (see Section 16.4).

9.1.1.1.1 Investigator's Facial Wrinkle Scale (FWS)

Trained investigators will assess status of GFL according to the 4-point FWS [redacted] at maximum frown. The FWS [redacted] at maximum frown will assess the severity of GFL [redacted]

[redacted]

A photo guide comprising sample photos of each of the four grades will support the rating by FWS together with descriptors for the four severity grades. The investigator must use the FWS photo guide together with the respective severity grade descriptors for each assessment.

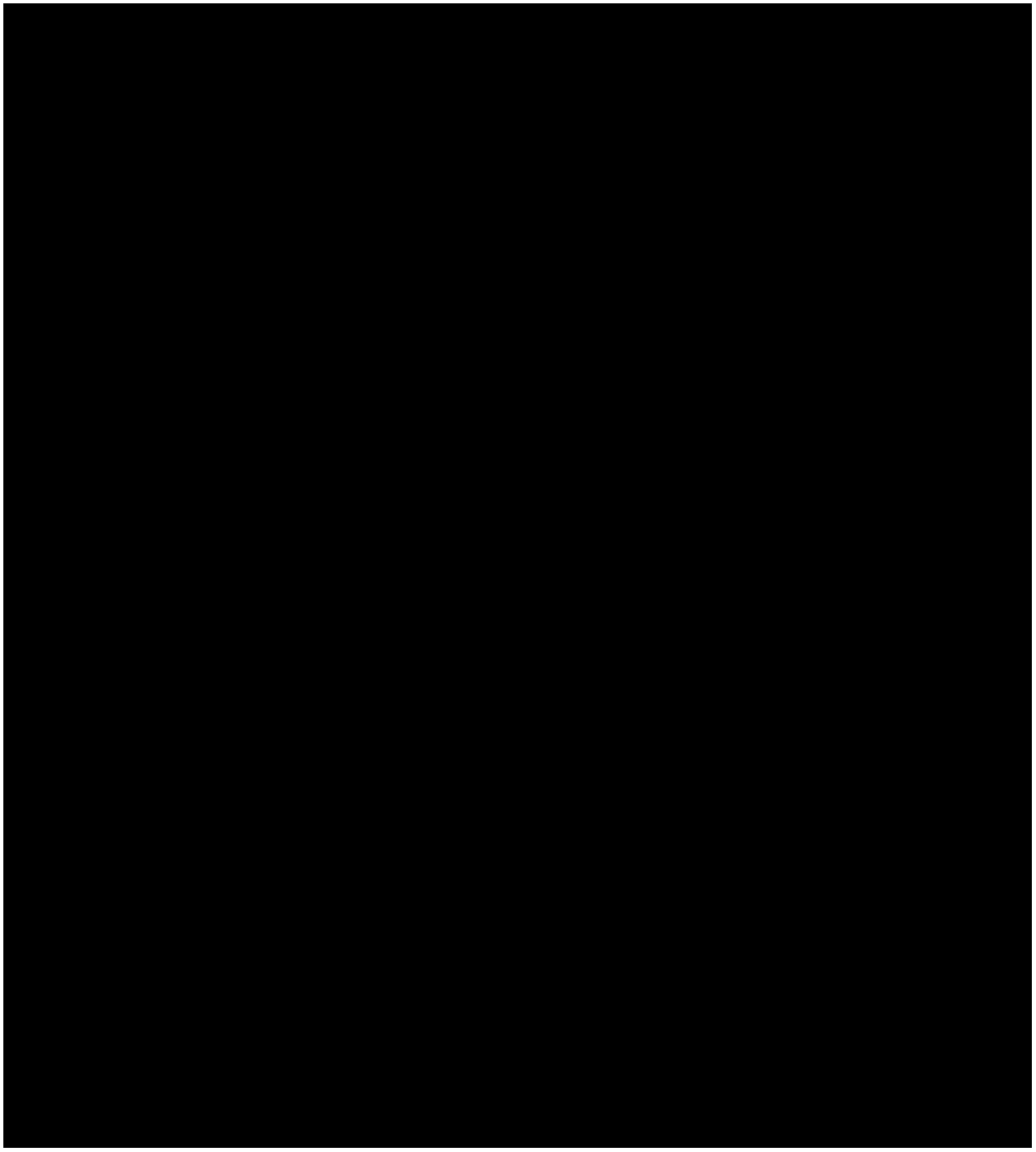
[redacted]

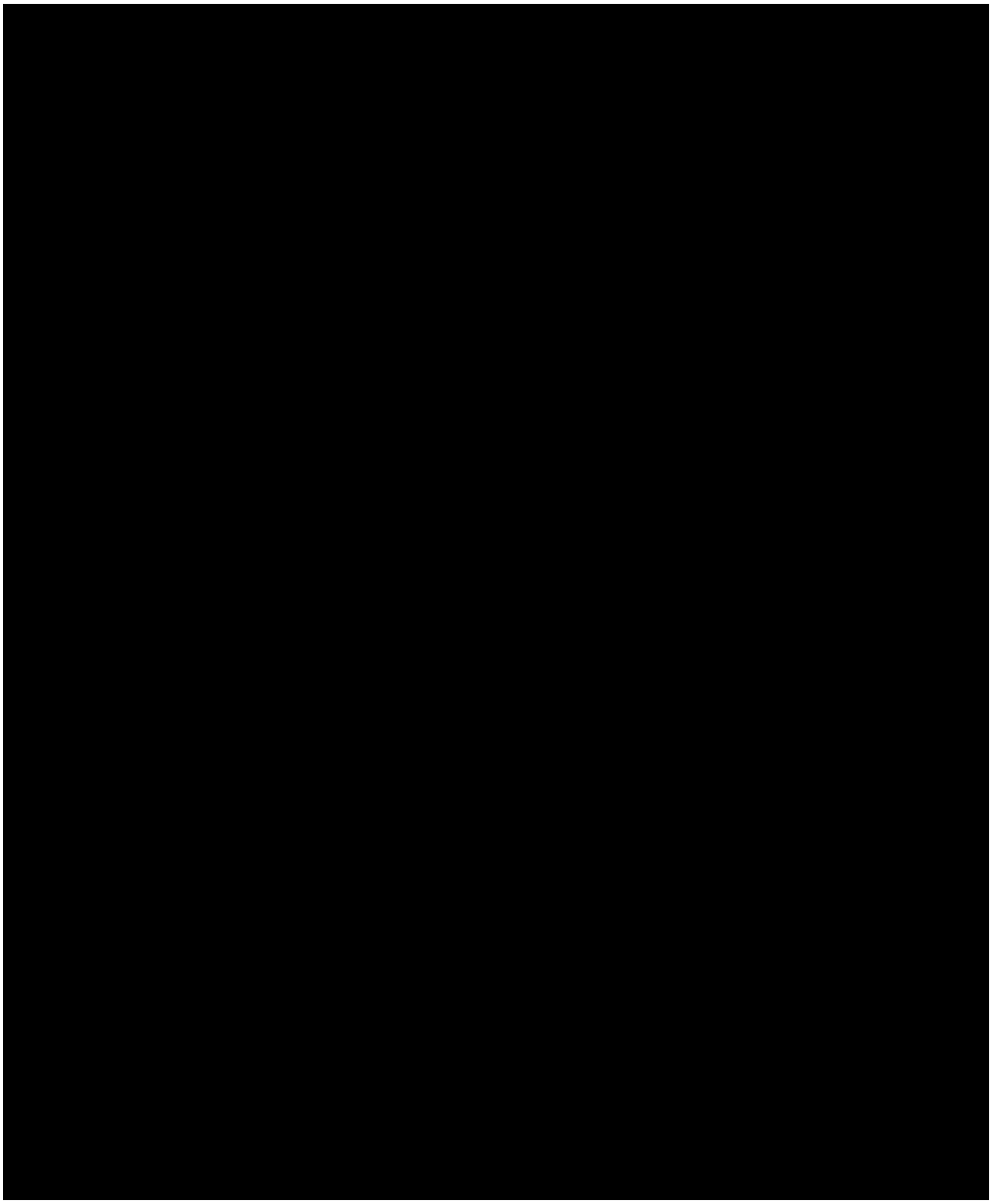
Investigators must pass the prior training qualification for use of the FWS before their first study rating.

Ratings at Baseline Visit V2 (Day 1), Day 30±7 (V4), Day 120±7 (V7), Day 180±7 (V9) and the End of MP in an individual subject should be performed by the same investigator. For the sake of consistency all efforts should be taken that all FWS assessments in an individual subject will be performed by the same investigator.

9.1.1.1.2 Subject's Facial Wrinkle Scale (FWS)

The subject will self-assess GFL [redacted] at maximum frown according to the subject's FWS together with the photo guide as reference. The descriptors for each scale grade will be provided together with instructions on how to perform the assessments on a separate subject rating sheet. The site staff will be trained during the investigator meeting or the site initiation visit on how to instruct the subject on the self-assessment.





[redacted]

[redacted]

9.1.1.5 Physical Examination

The investigator will perform physical examinations for subjects at the Screening Visit V1 (Day -3 to -14) and the End of MP. The physical examination will cover standard physical examinations. Any abnormal findings will be documented in the subject's medical file. The investigator will confirm the conduct of these investigations in the eCRF.

9.1.1.6 Vital Signs

Vital signs (i.e., blood pressure and heart rate) will be assessed at each visit from the Screening Visit V1 (Day -3 to -14) to Day 180 (V9), and at End of MP. Vital signs will be recorded in sitting or lying position after the subject has rested for at least 5 minutes.

In case on-site visits are not possible due to COVID-19 restrictions, vital signs cannot be assessed. [redacted]

9.1.1.7 Body height and weight

Body height will be assessed at the Screening Visit V1 (Day -3 to -14) and weight will be assessed at the Screening Visit V1 (Day -3 to -14) and End of MP.

9.1.2 Laboratory evaluations

9.1.2.1 Clinical and research laboratory evaluations

[redacted]

Blood samples for evaluation of clinical biochemistry and hematology (approx. 9 mL) plus serum pregnancy test (1 mL), if applicable, will be collected at the Screening Visit V1 (Day -3 to -14) and the End of MP.

Pregnancy testing (to be done prior to enrollment, with results available prior to administration of IP[s]) will be performed in female subjects with childbearing potential in serum at the Screening Visit V1 (Day -3 to -14) and the End of MP. A urine pregnancy test will be performed at the Baseline Visit V2 (Day 1) prior to injection and prior to optional follow-up treatment, if applicable.

The samples for hematology and clinical biochemistry, including serum pregnancy test (if applicable), will be analyzed at the central laboratory. Details with regard to the methods of sampling will be described in the respective laboratory manual.

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 subjects' Baseline Visit V2 (Day 1). 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.

9.1.3 Pharmacodynamics

Not applicable

9.1.4 Pharmacokinetics

Not applicable.

9.1.5 Pharmacogenetics

Not applicable.

9.1.6 [redacted] blood volume

Blood samples will be taken for general safety testing (clinical biochemistry and hematology) and also for serum pregnancy testing.

[redacted]

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 β-HCG will be determined by a central laboratory and will be handled according to the manual of the central laboratory.

9.2 Visit schedule

[redacted] Study procedures will be identical in stage 1 and stage 2 (if applicable).

The purpose of the Screening Visit V1 (Day -3 to -14) is to determine subject eligibility for study participation. The screening evaluation must be completed between Day -14 to -3 prior to Baseline. Subjects who fail screening are allowed to be re-screened one time. Subjects who are re-screened will be assigned a new screening number.

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

The clinical study protocol allows a window of ±7 days in scheduling of study visits for all post-baseline visits, except V3, where only a ±1 day window is allowed. The IP(s) should be injected at the study site by the investigator trained and experienced in aesthetic BoNT treatment. 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 the administration of study treatment.

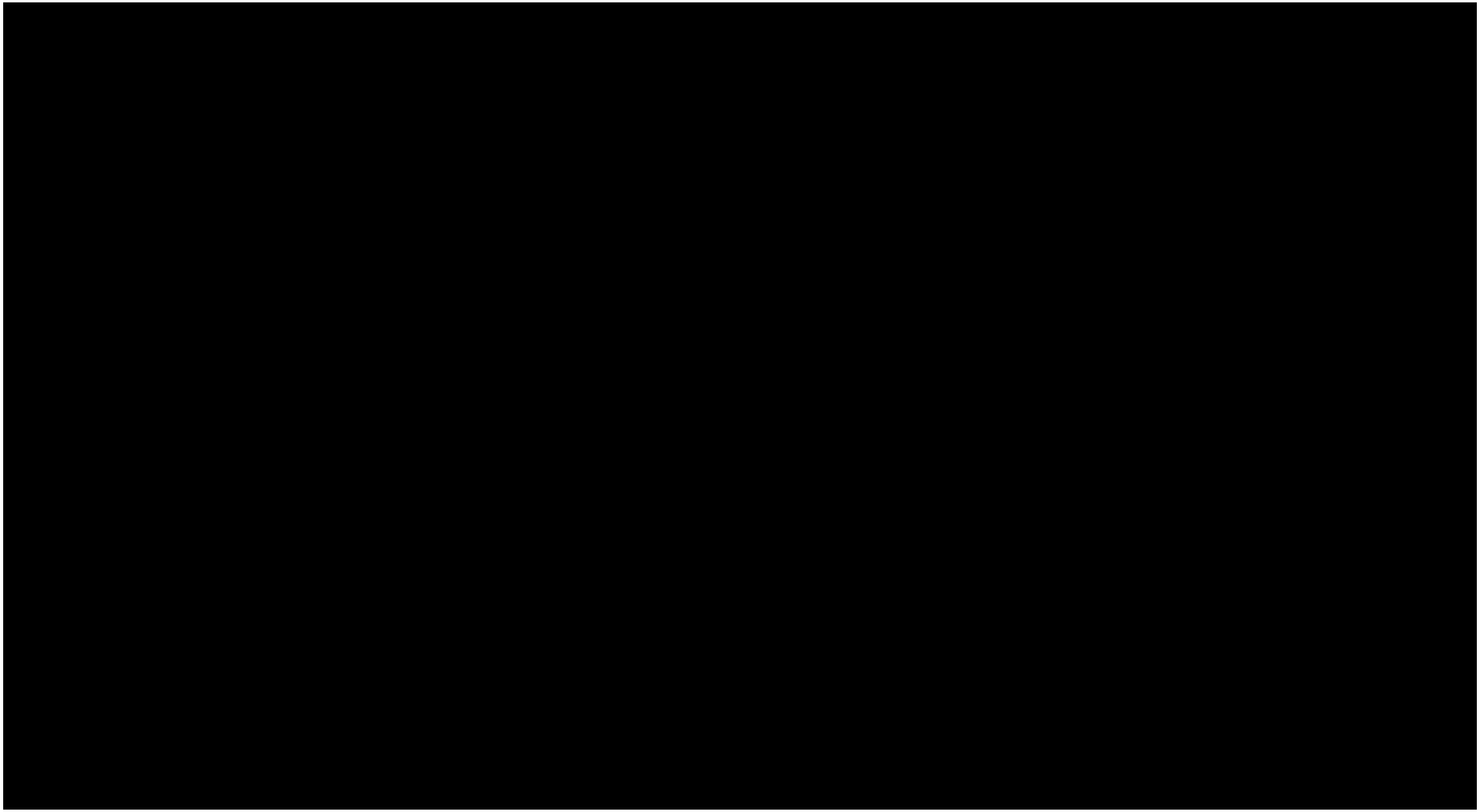
[redacted] he End of MP will be performed between Day 180 and Day 360 for all subjects who relapsed to baseline based on the investigator's assessment on the FWS at maximum frown.

If planned on-site visits cannot be performed due to COVID-19 situation, safety data will be collected via phone calls and the subjects will do their self-assessments at home if they previously consented to this procedure.

In addition, on-site visits should be performed at the earliest possible date that the subject is able to safely come to the site again. Any missing visit data and the reason should be documented as instructed in Section 9.1.

Additionally, subjects (in stage 1 and stage 2) who have relapsed to baseline status in the MP will have the option to receive a follow-up treatment with the market approved dose of 20 U NT 201 for their GFL between Day 180 and Day
360. An OLEX Follow-up Visit V16 will be performed for all subjects who receive the optional follow-up treatment.

Unscheduled visits may be required in the case of AEs or premature discontinuation of the study. In this case, a final assessment will be performed as soon as possible. If additional safety follow-up is necessary after this assessment, subjects may be contacted by telephone or assessed in the clinic, depending on the nature of the follow-up required.



10 SAFETY ASSESSMENTS

10.1 Definition of an adverse event

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

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

The period of observation for an AE extends from the time when the informed consent form was signed until the End of MP if no optional treatment was received or the OLEX Follow-up Visit V16 if optional treatment was received (see Section 6.1). Any medical occurrence during the observation period is an AE and has to be documented in the subject's file. For screening failures AEs are not to be documented in the eCRF. For randomized subjects that experienced AEs during the screening period these have to be entered into the eCRF. Non-serious AEs will not be followed up after the End of MP or the OLEX Follow-up Visit V16 if optional treatment was received.

Pre-existing conditions noted in the medical history should not be reported as an AE, unless the condition worsens or the disease reoccurs during the observation period. To determine whether a condition has worsened, it is compared to the condition of the subject at screening. Abnormal laboratory values obtained during the subject's screening period will only meet AE criteria if newly detected and if considered clinically significant. However, if laboratory values resulting from pre-existing conditions worsen to clinical relevance during the course of the study AE criteria are met.

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.

If on-site visits are not possible due to COVID-19 pandemic and the subject provides his/her consent to safety assessments on the phone, safety assessments (AEs, change in medication and non-drug treatment, and occurrence of pregnancy) will be performed via phone calls and the results documented in the source data first and in the eCRF subsequently (see also Section 11.2).

For all adverse events that are collected during telephone visits, it is up to the medical judgement of the investigator to refer a subject to a specialist if deemed necessary, thus ensuring the safety of the subject and the accuracy of the data.

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.
- Intensity (maximum observed; see Section 10.1.1).
- Causal relationship (not related, related).
- Serious (yes or no).
- Outcome (see Section 10.1.3).
- 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 AE of special interest [redacted] the investigator must also complete an SAE report form or AE of special interest 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.'

10.1.3 Categories of outcome

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

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered/resolved with sequelae.
- Fatal.
- 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.[8]
- Requires inpatient hospitalization, or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect.

[8] 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.

- Consists of any other medically important condition.[9]

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

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

All SAEs that occur during the study period whether considered to be related to IP(s) or not, must be reported by telefax or e-mail within 24 hours of knowledge of the event. SAE report forms are provided in the investigator's site file.

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

[9] 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.'

If the report is sent via email then the completed and signed SAE report form must be attached to the email. A simple notification email of the event is not sufficient.The CRO will transmit all SAE reports within one business day to Merz product safety.

The investigator, Merz Pharmaceuticals GmbH, and the CRO will comply with the applicable regulatory requirements related to the reporting of SUSARs to the regulatory authorities and the IEC(s)/IRB(s).

Furthermore the investigator has to report the SAE to the responsible IEC/IRB according to local requirements.

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

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

10.3 Adverse events of special interest (alert terms)

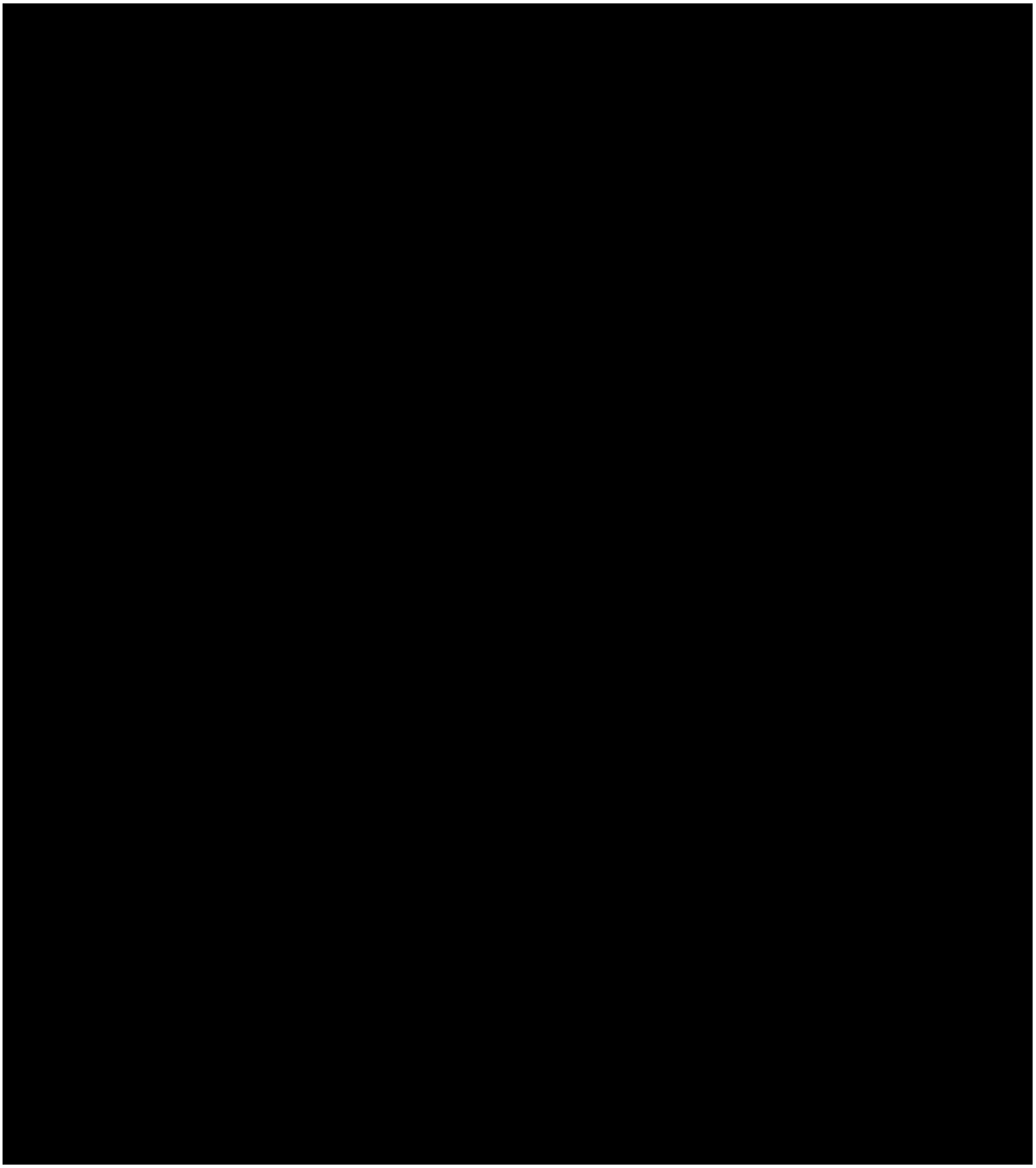
AEs occurring after treatment that are thought to possibly indicate toxin spread are defined as AESIs [redacted].

During the entire study, the subject will be actively asked by the investigator at each visit after injection (starting with Baseline Visit V2) if any [redacted] AESI [redacted] occurred since the last contact. [redacted]

Due to COVID-19 situation questioning of AESIs will be done via phone if on-site visits are not possible.
The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, by telephone, telefax, or e-mail to the responsible CRO within 24 hours of knowledge of the event. 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 should be documented on the general pages of the AE CRF as well as in the subject's file.

The AE form in the eCRF as well as the pages for medical history / concomitant diseases and for previous / concomitant medication and non-drug treatment are to be faxed/sent along with the AESI reporting form.



10.4 Expected adverse events

Expected AEs are those listed in the reference safety information of the current IB [Merz Pharmaceuticals GmbH 2018].

10.5 Unexpected adverse events

An unexpected AE is an AE not previously reported in nature, severity, or incidence in the reference safety information of the current IB [Merz Pharmaceuticals GmbH 2018].

10.6 Pregnancy

Each pregnancy that starts during the study must be reported by the investigator to 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 injection, the subject must not receive any injection treatment and the End of MP will be conducted right away without any invasive procedures (such as blood drawing) performed.

If a pregnancy occurs after a subject has received injection, the subject can continue with applicable study visits until the end of the study but without any invasive procedure (e.g. injections, blood drawing). However, the subject is free to discontinue the study at any time.

11 DATA QUALITY ASSURANCE

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

11.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, and validation methods).

This study will be monitored regularly by qualified monitors from the CRO according to ICH-GCP and the respective Standard operating procedures (SOPs) (see Section 11.4).

11.2 Source documentation requirements

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

To assure subject's safety, sites that are temporarily closed for subject on-site visits or have subjects under a Stay-at-Home-Order or subjects who choose not to come to the site due to the pandemic will monitor subject's safety via phone calls at planned visit dates.

During the next on-site visit, subject's consent to the phone visit and / or the self-assessment must be confirmed by the investigator and the subject in a signed supplemental ICF according to the procedures described above, including the requirements for traceability.

If safety assessments were performed via phone, it must be documented in the eCRF that the visit was virtually conducted by phone due to COVID-19 pandemic. If a planned visit cannot be performed at all, it must be documented in the eCRF whether this was due to COVID-19 pandemic or due to other reasons.

Every effort should be made to contact subjects via phone or letter. At least 3 documented attempts to contact the subject should be made. All the attempts are to be documented in the subject's source documentation.

11.3 Data management

Data required according to this protocol is to be recorded in the web-based eCRFs (electronic data capture system)[redacted]. All users who will enter data into the eCRF will be previously trained. After the successful completion of the training all participants will receive a training certificate, which will be a prerequisite for the access to the eCRF. The access to the eCRF is password-controlled and conforms with CFR part 11.

Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data capture system; answers to queries or changes to the data will also be documented in this system directly by an authorized member of the investigator's site staff. The audit trail in the electronic data capture system documents all changes. Edit checks will 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.

AEs, medical history/concomitant diseases and non-drug treatment will be coded according to the MedDRA version in effect at the time the database is closed.

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 data management / biostatistics vendor [redacted] will be responsible for data-processing.

After all necessary data for DEM (when all enrolled subjects for stage 1 have had their Day 30±7 Follow-up Observational Visit V4) have been entered, a database snapshot will be taken.

For the final analysis, 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 according to respective SOP.

An analogous procedure will be applied prior to the interim analysis after 180 days (V9) of stage 1. Once the data is cleaned, a database snapshot is saved.

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 the integrity of the source data with the eCRF entries, for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements. Monitoring will also be aimed at detecting any misconduct or fraud.

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

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

- Have all data properly recorded in the source documentation and the eCRF prior to each monitoring visit.
- Have the source documentation available at the monitoring visits.
- Record all IP(s) dispensed in the eCRF and the drug inventory records.

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

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.

Off-site and centralized monitoring are already conducted during the study as described in the monitoring manual and will be continued to be performed while on-site monitoring visits are not possible due to COVID-19 restrictions. If no on-site source data verification [SDV] is possible due to COVID-19 restrictions, a "data confirmation call" will be arranged with the site and documented. During this call, site personnel will be

asked to read aloud selected data from the source data to the study monitor; the study monitor will compare these data with the eCRF entries. During the next on-site visit, the CRA will verify the data fields confirmed via phone when reviewing the source data in person to complete the SDV process on-site and will tick the respective SDV-data fields in the eCRF at that time. Details of "data confirmation call" will be provided in the monitoring manual.

During COVID-19 pandemic the monitors are in close contact with site staff to monitor the local situation and well-being of study subjects and staff. On-site monitoring visits will be done as soon as possible.

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 STATIS TICAL 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.

12.1 Determination of sample size

In total, 60 subjects in the high dose groups are deemed required for the objectives of the study. For the low dose group, 30 subjects suffice in case the study stops after stage 1 as the side effects and efficacy of a dose of 20 U are well characterized in previous studies.

12.2 Analysis sets

Safety evaluation set

The SES is the subset of all subjects who were exposed to study medication.

Full analysis set

The FAS is the subset of subjects in the SES for whom any efficacy variable is available (i.e., all subjects who have a baseline and at least one post-baseline value of any efficacy variable).

12.3 Variables for analysis

12.3.1 Efficacy variables

12.3.1.1 Primary efficacy variable

Duration of effect as defined by time between treatment and relapse to baseline status. Effect is defined as improvement at maximum frown as assessed by the investigator on the FWS.

If no improvement is observed on the FWS at any point after treatment, the time will be set to 0.

12.3.1.2 Secondary efficacy variables

- Duration of effect whereby effect is defined by a score of none (0) or mild (1) at maximum frown as assessed by the investigator according to FWS

  This variable is defined as the time between treatment and the first point in time when the score is moderate (2) or severe (3) again. If no improvement is observed on the FWS at any point after treatment, the time will be set to 0

- Duration of effect whereby effect is defined by 2-point improvement from baseline at maximum frown as assessed by the investigator according to FWS

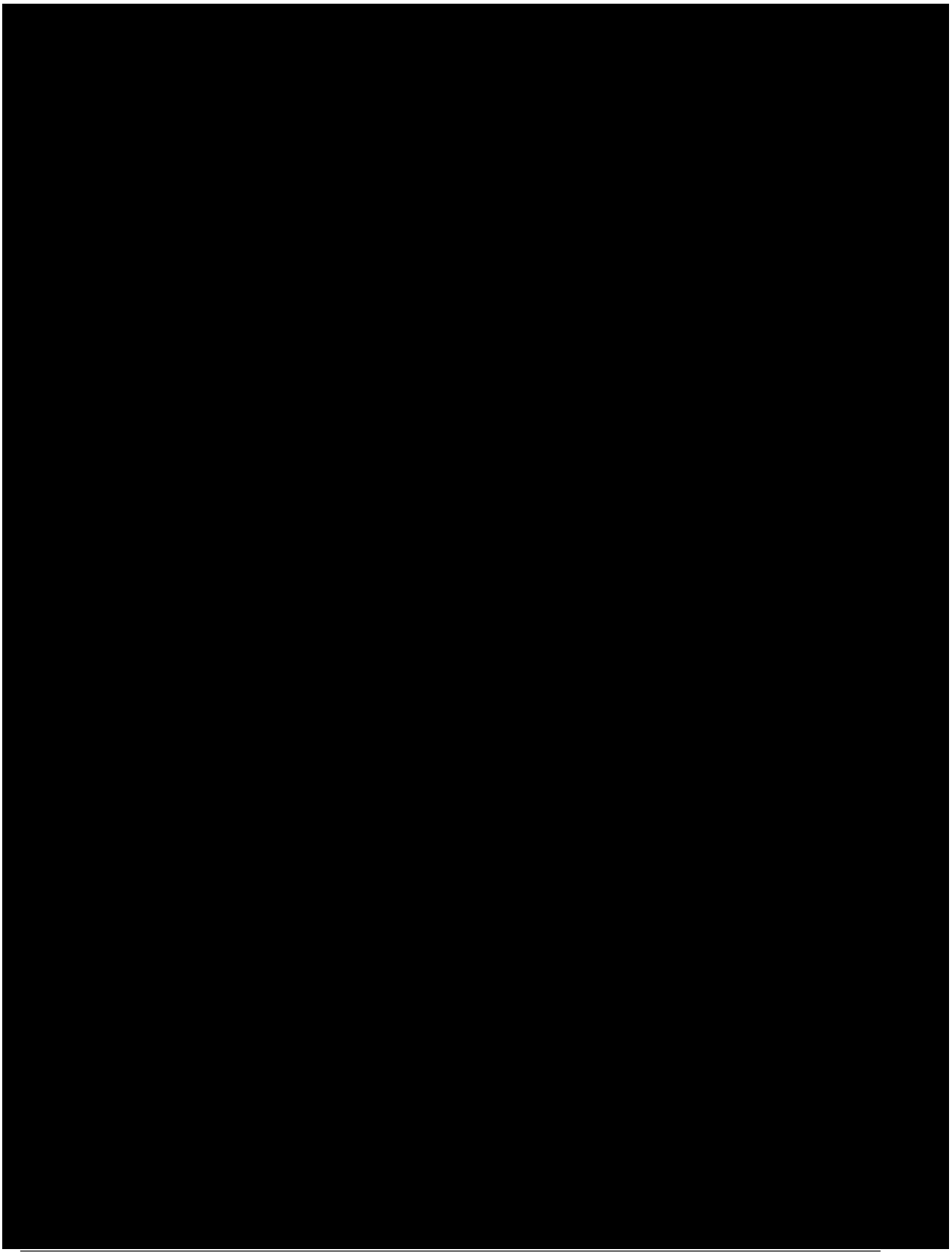
  This variable is defined as the time between treatment and the first point in time when the improvement is less than 2 points again. If no improvement is observed on the FWS at any point after treatment, the time will be set to 0

- Percentage of subjects rated as none (0) or mild (1) at maximum frown by investigator's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as none (0) or mild (1) at maximum frown by subject's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by investigator's rating on FWS at Day 180 (V9)

- Percentage of subjects rated as at least 1-point improvement compared to baseline at maximum frown by subject's rating on FWS Subject at Day 180 (V9)



12.3.2 Pharmacodynamic variables

Not applicable.

12.3.3 Pharmacokinetic variables

Not applicable.

12.3.4 Pharmacogenetic variables

Not applicable.

12.3.5 Safety variables

12.3.5.1 Primary safety variables

Occurrences of TEAEs, TESAEs, TEAESIs, related TEAEs and related TESAEs by dose group for the entire study period.

An AE is considered treatment-emergent with onset or worsening on or after date of the first administration of IP.

12.3.5.2 Secondary safety variables

Not applicable.

[redacted]

12.4 Statistical analysis methods

Analyses will be performed after all subjects of stage 1 have had their Day 180 assessments (interim analysis) and after all subjects of stage 1 and stage 2 (if applicable) have had their last visit (End of MP or OLEX Follow-Up Visit V16, as applicable). If not otherwise specified the data from stage 1 and stage 2 in the 20 U groups will be pooled in case stage 2 is started. Otherwise, the dose groups will be presented as randomized for stage 1 only.

[redacted]

To get early insights, into duration of effect of NT 201 based on the primary efficacy parameter and the occurrence of treatment emergent adverse events (TEAEs) over the entire Main Period of 360 days, it is planned to perform an interim analysis of complete MP data from Stage 1, where doses up to 75 U were administered.

12.4.1 Efficacy variables

The efficacy analyses will be based on the FAS (see Section 12.2).

Statistical tests will be two-sided hypothesis tests for between-treatment differences in general. Continuous variables (values and changes from baseline) will be summarized by N, mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (N, %) and, if applicable, shift tables will be displayed. Confidence limits [redacted] will be given, where appropriate.

12.4.1.1 Primary efficacy variable

The primary endpoint is the duration of effect defined in Section 12.3.1.1. This will be described by Kaplan-Meier Curves per group and the respective medians of times.

[redacted] pairwise log-rank tests will be applied to compare differences between high dose groups and the 20 U group to explore statistical significance. The 20 U group data will be pooled from stage 1 and 2, if applicable.

For the primary endpoint a Cox proportional hazards regression will be applied with covariates dose group (20, 50, 75, 100 U), center, and baseline FWS score at maximum frown as assessed by the investigator. Here, the pooled 20 U group will be used as reference group. To explore potential stage effects, a sensitivity analysis will use dose groups 20 (stage 1), 20 (stage 2), 50, 75 and 100 U with 20 (stage 1) as reference group. Depending on the outcome further exploration might be needed [redacted]

12.4.1.2 Secondary efficacy variables

The secondary duration of effect variables will be analyzed in analogy to the primary variable. However, the Cox proportional hazards regression analysis will be limited to pooling the 20 U groups of both stages.

For the percentages of subjects fulfilling the criteria as described in the secondary efficacy variables two-sided 95% Pearson-Clopper confidence intervals will be computed for responder rates in each dose group.

[redacted]

[redacted]

12.4.2 Pharmacodynamic variables

Not applicable.

12.4.3 Pharmacokinetic variables

Not applicable.

12.4.4 Pharmacogenetic variables

Not applicable.

12.4.5 Safety variables

All safety analyses will be conducted on the SES. Continuous safety variables will be analyzed using summary statistics. Categorical variables will be analyzed using absolute and relative frequencies.

No inferential statistical methods will be applied.

12.4.5.1 Primary safety variable

Incidences (absolute and percentage) of TEAEs, TEAESIs, TESAEs, and related TEAEs will be calculated on the level of SOC and PT.

In addition, incidences for TEAE will also be presented by worst intensity and by worst causal relationship.

[redacted]

All incidences will be presented by dose group and overall.

Related TESAEs, deaths and TEAEs leading to premature discontinuation will be listed only.

For details on the safety evaluation for the DEM, see Section 12.4.7.2.1.

For details on the safety analyses for the interim analysis (after Day 180 of stage 1), see Section 12.4.7.2.2.

12.4.5.2 Secondary safety variables

Not applicable.

12.4.7 Special statistical/analytical issues

12.4.7.1 Discontinuations and missing data

With relevance to efficacy objectives treatment will be applied only once and hence cannot be discontinued. Therefore, no premature discontinuation from treatment can occur. Missing values likewise occur at random or because the subject completes the study early due to relapse to baseline. The latter will not impact the primary analysis of duration of effect since this was completely captured. Hence, for any Kaplan-Meier analysis and inferential statistics intermittent missing data will be ignored and monotone missingness be considered as censored.

Due to the COVID-19 pandemic, a considerable amount of missing data is expected for subjects from Stage 2. Restrictions related to COVID-19 in both the US and in Germany (temporarily closed sites, stay-at-home orders, quarantines imposed to subjects suspected to be infected) may make it impossible for many subjects to attend all planned on-site visits. Since live assessments by investigators cannot be performed remotely, this will inevitably lead to missing data.

Handling of missing data due to the COVID-19 pandemic in the final statistical analysis will depend on the number and pattern of missing values, which will be thoroughly described in the clinical study report. Decisions on any additional analyses to account for missingness due to COVID-19 will be made at the latest during the BDRM for the final analysis and described in an amendment to the SAP, which will be finalized prior to database close for the final analysis (see also section 12.4.7.6).

12.4.7.2 Interim analyses

12.4.7.2.1 Dose Escalation Meeting

A blinded evaluation of safety data will be performed in a DEM when all enrolled subjects for stage 1 have had their Day 30±7 Follow-up Observational Visit V4. Based on the stage 1 data, a decision to proceed with stage 2 of the study with a dose group of 100 U NT 201 will be made. The evaluation includes blinded safety data of stage 1 subjects of the 20 U, 50 U, and 75 U NT 201 dose group up to Follow-up Observational Visit V4, Day 30±7.

For more details, see Section 12.4.7.3.

For this DEM the following data will be presented overall for the pooled blinded data:

- Subject disposition and demographic data
- Listings of medical history, concomitant diseases, previous and concomitant treatments
- Incidences of TEAEs, TEAESIs, TESAEs, and related TEAEs by SOC and PT
- Listings of TEAE, TEAESIs, TESAEs, Deaths and AEs leading to premature discontinuation

12.4.7.2.2 Interim analysis after Day 180 of stage 1

An interim analysis of complete 180-day data (V9) of stage 1 will be performed. This interim analysis will serve to get early insights regarding the benefit-risk assessment and duration of effect of the dose groups investigated in the stage 1. However, it is not the aim of this analysis to decide on premature termination of the study.

Data will be unblinded for sponsor staff and vendor data management and biostatistics staff only as required for the sake of the interim analysis.

For data of Stage 1 until Day 180, the blind will not be broken until a BDRM focusing on the interim analysis has convened, the first version of the SAP has been finalized, and a database snapshot has been saved. After the blind is broken, the statistical analysis of Stage 1 Day 180 results will proceed.

The study will be continued and investigators, subjects, site staff and monitors (except the unblinded monitor responsible for IWRS compliance) will be kept blinded with regard to stage 1 subject's assignment to treatment groups. Stage 2 subjects, if applicable, will not be included in the 180-day interim analysis. The blind for subjects in stage 2 will be maintained. Moreover, the blindness of investigators and subjects, site staff and blinded monitor will be maintained throughout for both stages until final unblinding.

For the remaining data, the blind will not be broken until the final BDRM has convened, the final version of the SAP has been finalized, and the database has been closed. After the blind is broken, the overall statistical analysis of results will proceed. The SAP might be amended to stage 2 specific aspects before unblinding of stage 2.

As the blind of the subjects of Stage 2 will be maintained and procedures for Stage 2 will be very advanced when results are disseminated there is no impact on validity of stage 2 data and the credibility of study results.

For this interim analysis the following data will be presented based on the data up to Day 180 of stage 1:

- Subject disposition and demographic data
- Primary and secondary duration of effect variables
  - Kaplan-Meier estimates
  - Pairwise log-rank test vs. 20 U group
  - Cox proportional hazards regression with dose group and center as fixed effects
- Investigator's FWS and subject's FWS at maximum frown [redacted]: Percentages of subjects fulfilling criteria as defined for secondary [redacted] variables including 95% confidence intervals

[redacted]

- Listings of medical history, concomitant diseases, previous and concomitant treatments
- Incidences of TEAE, TEAESIs, TESAEs, and related TEAEs by SOC and PT
- Listings of SAEs, Deaths and AEs leading to premature discontinuation

12.4.7.2.3 Interim analysis after End of Main Period of stage 1

An interim analysis of complete Stage 1 MP data will be performed as soon as data until and including the End of MP visit V15 from Stage 1 subjects are completely available (except for missingness due to premature study discontinuation or intermittently missing visits). The analysis of Stage 1 MP data will serve to get further insights regarding duration of effect and occurrence of TEAEs over the entire Main Period of up to 360 days. As outlined and substantiated in more detail in the newly added section 12.4.7.6, this will allow for better-informed decision making during the further conduct of the study in Stage 2 under the specific circumstances of the COVID-19 pandemic and related restrictions that might make it difficult or impossible for subjects to further attend on-site visits for a certain period of time.

Prior to the interim analysis of Stage 1 at Day 180 (see previous section), the blind has already been broken for sponsor staff and vendor data management and biostatistics staff with regards to all subjects randomized in Stage 1. Thus, no new subjects will need to be unblinded for this additional interim analysis at End of MP of Stage 1.

Data as needed for the analyses below will be cleaned and the analyses will be described

in an update to the SAP. After a database snapshot has been saved, the statistical analysis of the entire MP of Stage 1 will be carried out.

The study will be continued and investigators, subjects, site staff and monitors (except the unblinded monitor responsible for IWRS compliance) will be kept blinded with regards to Stage 1 subject's assignment to treatment groups. Stage 2 subjects will not be included in the interim analysis of Stage 1 MP data. The blind for subjects in Stage 2 will be maintained. Moreover, the blindness of investigators and subjects, site staff and blinded monitor will be maintained throughout for both stages until final unblinding.

For Stage 2 subjects, the blind will not be broken until the final BDRM has convened, the final version of the SAP has been finalized, and the database has been closed. After the blind is broken, the overall statistical analysis of results will proceed. The SAP might be amended to Stage 2 specific aspects before unblinding of Stage 2.
As the blind of the subjects of Stage 2 will be maintained and procedures for Stage 2 will be very advanced when results of Stage 1 MP are disseminated, there is no impact on validity of Stage 2 data and the credibility of study results.

For this interim analysis the following data will be presented based on at least the following data up to End of MP of Stage 1:

- Subject disposition and demographic data
- Primary duration of effect variables
    - Kaplan-Meier estimates
    - Pairwise log-rank test vs. 20 U group
    - Cox proportional hazards regression with dose group, center and baseline FWS score at maximum frown as assessed by the investigator as fixed effects
- Incidences of TEAE, TEAESIs, TESAEs, and related TEAEs by SOCand PT

12.4.7.3 Committees

[redacted]he DEM will receive complete blinded safety data of stage 1 subjects of the 20 U, 50 U, and 75 U NT 201 dose group up to Follow-up Observational Visit V4, Day 30±7 (see Section 12.4.7.2). Based on the stage 1 data a decision to proceed with stage 2 of the study with a dose group of 100 U NT 201 will be made.

[redacted]

[redacted]

12.4.7.4 Multiple comparisons/multiplicity

[redacted]
no multiplicity adjustment is foreseen.

12.4.7.5 Examination of subgroups

Subgroup analyses will be specified in the SAP.

12.4.7.6 Additional analyses due to outbreak of COVID-19 pandemic

Due to the COVID-19 pandemic, a considerable amount of missing data is expected for subjects from Stage 2 (see also section 12.4.7.1). This especially applies to efficacy variables that are based on live assessments by investigators, which cannot be performed remotely. The primary as well as several secondary [redacted] efficacy parameters will be affected. It should be noted that under specific circumstances, subsequently missing live ratings on the FWS by the investigator are likely to introduce bias to the assessment of the primary and secondaryduration of effect variables. If relapse to baseline status is first assessed only after several intermittently missing follow-up visits due to canceled on-site visits, the time to relapse will be overestimated.

Data from Main Period of Stage 1 are in contrast not affected by this or any other kind of bias caused by COVID-19 pandemic because Stage 1 subjects did not miss any MP visits due to COVID-19 outbreak. Therefore, conduct of separate analyses of data from Stage 1 and Stage 2 subjects will likely be necessary in addition to pooled analyses as planned for the final analysis of the study; this decision will be taken at the latest during the BDRM for the final analysis (see below). However, for reasons outlined in the following, it appears reasonable to perform an interim analysis of Main Period data from Stage 1 as soon as MP data from all Stage 1 subjects are available and cleaned.

As described in the newly added section 12.4.7.2.3 above, the additional interim analysis of complete MP data from Stage 1 will focus on the assessment of duration of effect of NT 201 according to the primary efficacy parameter and on occurrence of treatment emergent ~~adverse events (TEAEs), especially treatment-related TEAEs, over the 360 Day follow-up~~

period. Efficacy and safety data from Stage 1, where doses up to 75 U were applied, can give further insights into the efficacy and safety profile of NT 201. Depending on the future development of the COVID-19 pandemic and related restrictions in both countries this can be very valuable to decide whether resumption of on-site visits for Stage 2 subjects with intermittently missing on-site visits still appears meaningful and might outweigh the specific efforts and risks associated with travelling during the COVID-19 pandemic. Insights from the interim analysis at End of MP of Stage 1 might be valuable to decide whether affected Stage 2 subjects should be motivated to re-assume on-site visits after a certain time period with missing efficacy data according to investigator's assessments.

Any further additional statistical analyses planned to analyze the impact of missingness (see also section 12.4.7.1) and/or potential bias on data assessment due to COVID-19 pandemic (e.g. heterogeneity of Stage 1 and Stage 2 subjects due to COVID-19 related restrictions) will be decided upon at the latest during the BDRM for the final analysis.

Depending on the amount of missing data and pattern of missingness, this might include separate analyses of Stage 2 subjects only. Any additionally planned analyses will be thoroughly described in an updated version of the statistical analysis plan, which will be finalized prior to database close for the final analysis.

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, questionnaires and scales) to the eCRF.

If corrections are necessary, an authorized member of the investigator's site staff will enter the correct data into the web-based eCRF. The audit trail in the EDC system documents all changes. Edit checks issue automatic queries during data entry when a field is not populated 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.

The data management / biostatistics vendor [redacted] will be responsible for data processing. Final database close will occur only after quality assurance procedures have been completed.

13.2 Record-keeping

Upon closure of the study, the investigator must maintain all study-site records in a safe and secure location. The investigator is responsible for the integrity, retention, and security of all study-related records. The investigator must ensure that any reproductions of the original records are legible and provide a true and accurate copy of the original. Accurate, complete, and current records must be stored in such a way as to permit easy and timely retrieval for the sponsor or any applicable regulatory authorities.

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. However, these documents are to be retained for a longer period, if required by applicable regulatory requirements or by agreement with the sponsor.

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

- Source documentation (e.g. subject file, questionnaires and scales).
- Subject identification code list (respective template provided to the investigator along with the Investigator's site file, at the beginning of the study), which identifies the subject by number, name, and date of birth.
- A signed copy of the final clinical study protocol and any amendment.
- 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/IRB and with the regulatory authority(ies).
- Copies of laboratory normal ranges and methods
- Copies of study supply receipt forms and drug inventory forms.
- Copies of all correspondence between the investigator and the monitor, and between the investigator and the sponsor.
- Copies of safety information reported during the study and submitted by the sponsor.

The investigator must notify the sponsor in the event of any changes to archival arrangements due to withdrawal of the investigator's responsibility for keeping study

records to ensure that suitable arrangements for the retention of study records are made.

13.3 Destruction of study documents

Study documents may not be destroyed by study site personnel before end of the retention period specified above without the prior written consent of the sponsor. The principal investigator must inform the sponsor in due time if the principal investigator 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, 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