Prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of children and adolescents (2–17 years) with chronic troublesome sialorrhea associated with neurological disorders, and/or intellectual disability

Development phase:	Phase 3
Study identifier **EudraCT Number** **IND Number** **Acronym**	MRZ60201_3091_1 2013-004532-30 112,731 SIPEXI **Si**alorrhea **Pe**diatric **X**eomin **I**nvestigation
Date of original clinical study protocol and all previous amendments:	Final protocol version 1.0 (17-JUL-2014) Previous amendment 1 version 1.0 (24-APR-2015) was erroneous and not submitted. Previous amendment 1 version 2.0 (04-MAY-2015) approved and executed.
Indication:	Chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury), and/or intellectual disability in children and adolescents aged 2–17 years
Planned study period:	1st quarter 2015 to 2nd quarter 2019
Investigational product:	NT 201 100 units, powder for solution for injection (active ingredient: NT 101, *Botulinum* neurotoxin type A free from complexing proteins; USAN 'incobotulinumtoxin A')
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:	Medical expert: Biostatistician: Clinical study manager: [redacted]

SIGNATURE PAGE

The study will be conducted in compliance with the clinical study protocol, ICH–GCP principles, the Declaration of Helsinki, a high standard of ethical integrity, and regulatory authority requirements.

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

[redacted]
Medical expert

16-JUN-2016
Date

[redacted]
Signature

[redacted]
Biostatistician

16-Jun-2016
Date

[redacted]
Signature

[redacted]
Clinical study manager

16 Jun 2016
Date

[redacted]
Signature

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

[redacted]
Co-ordinating investigator

20.6.2016
Date

[redacted]
Signature

Statement of Compliance

Investigational Sites

I have thoroughly read and reviewed this clinical study protocol. I understand the requirements and conditions of the clinical study protocol, I agree to perform the clinical study with accuracy and integrity according to this clinical study protocol, the case report form, ICH-GCP principles, the Declaration of Helsinki, regulatory authority requirements and those listed in the ethics section of this protocol (Section 3.2).

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

- Sign and date this clinical study protocol before the study formally starts.
- Wait until I have received written approval from the appropriate IEC/IRB before enrolling any subject (child participant) in this study.
- Obtain written informed consent from the parent(s) / legal guardian(s) before any study-related action is performed, and to obtain written and/or oral assent from the children wherever possible. (This will depend on their mental capacity to understand about the study requirements and whether or not they can clearly express their wish to participate or not.)
- 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.
- Notify study sponsor as soon as possible after notification of potential Food and Drug Administration [FDA], European Medicines Agency [EMA] or other audit.
- Notify the appropriate IEC/IRB on serious adverse events [SAEs] in a timely manner according to local requirements (if applicable).
- Use the investigational product and all study materials only as specified in the clinical study protocol.
- Report to the responsible drug safety officer, within 24 hours, any adverse event [AE] that is serious, and of any AE of special interest [AESI], whether considered treatment-related or not.
- Before initiating the study, I will provide the sponsor with a written disclosure of any financial interest in accordance with 21 CRF Part 54 and a signed 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 strictly confidential, and both the protocol and all study-related materials are proprietary to Merz.
- Any deviation from the clinical study protocol may lead to early termination of the study site.

I confirm that:

- I have the experience and up-to-date training in ICH/GCP, ethical issues and study-related procedures necessary to ensure the safety and well-being of vulnerable children and their families.

Principal investigator	Date	Signature
		Print Name
Investigator	Date	Signature
		Print Name

Stamp of investigation site:

List of Abbreviations and Definitions of Terms

AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
BMI	Body mass index
BoNT	*Botulinum* neurotoxin
BP	Blood pressure
BW	Body weight
CP	Cerebral palsy
CRO	Contract research organization
[redacted]	
C-CASA	Columbia-Classification Algorithm for Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
[redacted]	
DSFS	Drooling Severity and Frequency Scale
eCRF	Electronic case report form
EDTA	Ethylene diamine tetra-acetic acid
EMA	European Medicines Agency
EudraCT	European clinical trial database
FAS	Full analysis set
FDA	Food and Drug Administration, USA
GCP	Good Clinical Practice
GICS	Global Impression of Change Scale
FIA	Fluorescence immunoassay
FIA-AB	Fluorescence immunoassay detecting antibodies
GMFCS	Gross Motor Function Classification System
HDA	Hemidiaphragm assay
HR	Heart rate
IB	Investigator's brochure
ICH	International Conference on Harmonization
ID	Intellectual disability
IEC	Independent ethics committee
IND number	Investigational new drug number (issued by the FDA)

IP	Investigational Product
IRB	Institutional review board
ISF	Investigator's site file
IU	International unit(s)
IWRS	Interactive Web Response System
LDU/kg	Lethal dose units per kilogram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurement
MRZ	Merz
mTDS	Modified Teacher's Drooling Scale
N	Number
OLEX	Open-label extension
PIP	Pediatric Investigation Plan
PPS	Per protocol set
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SES	Safety evaluation set
SOP	Standard operating procedure
TBV	Total blood volume
[redacted]	
TEAE	Treatment emergent adverse event
TEAESI	Treatment emergent adverse event of special interest
TESAE	Treatment emergent serious adverse event
U	Unit(s)
USAN	United States Adopted Name
uSFR	Unstimulated Salivary Flow Rate
V	Visit (number)

Parent(s) In this protocol, the term parent(s) is used for any legally acceptable representative(s) including guardian(s), as defined in the ICH guideline E6 (R1) as individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. Guardian(s) may replace parent(s) in the performance of study procedures. Note that where both parents have responsibility for the subject, both will be required to sign all documents where the parent's/parents' signature(s) is/are needed.

Carer In this protocol, the term “carer” designates the person who spends the greatest amount of time with the subject and is in a responsible position for attending to and caring for the subject. This will often be a parent, but in some situations it may alternatively be a nurse, a day-care attendant or a day-care-center staff member with special responsibility for the subject.

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1 SYNOPSIS

Study title

Prospective, randomized, double-blind, placebo-controlled, parallel-group, multi-center study with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of children and adolescents (2–17 years) with chronic troublesome sialorrhea associated with neurological disorders, and/or intellectual disability.

Study phase

Phase 3

Indication

Chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury), and/or intellectual disability in children and adolescents aged 2–17 years.

Study objectives

The objective of this study is to investigate the efficacy and safety of NT 201 compared with placebo for the treatment of chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury) and/or intellectual disability in children and adolescents naïve to *Botulinum* neurotoxin treatment and aged 2–17 years. The total dose of NT 201 ranges from minimum 20 U to maximum 75 U or approximately 2 U/kg body weight depending on body weight classes. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. In this study, treatment-naïve subjects are defined as those who have not received BoNT treatment for this indication within the last 12 months.

Study population, diagnosis, and main criteria for inclusion and exclusion

Male and female children and adolescents will be recruited who are suffering from troublesome sialorrhea due to neurological disorders, and/or intellectual disability.

Main inclusion criteria:

- Male or female child/adolescent age 2–17 years.
- Any neurological disorder (e.g. cerebral palsy or traumatic brain injury) and/or intellectual disability associated with chronic troublesome sialorrhea for at least 3 months up to the screening. In subjects with intellectual disability (ID) without neurological disorders, a diagnosis of ID by a specialist, e.g. pediatrician or by a center for developmental medicine is required for inclusion.

- Severe drooling (modified Teacher´s Drooling Scale [mTDS] ≥ 6; clothing occasionally becomes damp) as rated by the investigator.
- Parental consent and the subject's oral or written assent as the subject is able to provide.

Main exclusion criteria:

- Chronic troublesome sialorrhea not related to neurological disorders and/or intellectual disability.
- Body weight < 12 kg.
- Pharmacological treatment for sialorrhea or concomitant medication known to influence sialorrhea strongly (e.g. anticholinergics with exception of locally applied or short acting drugs used under general anesthesia) within 45 days before baseline and during the entire study period.
- Any previous known or suspected hypersensitivity to *Botulinum* toxin.
- Aspiration pneumonia within 6 month before screening.
- Any previous treatment with *Botulinum* toxin for any body region during the year before screening or within the screening period
- Prior, concomitant or planned surgery or irradiation to head and neck to control sialorrhea (including salivary gland surgery or salivary gland irradiation) within one year before screening or planned for any part of the entire study period.
- Concurrent diseases, including hematological, hepatic, renal, gastrointestinal, endocrine, pulmonary, musculoskeletal, or psychiatric diseases or conditions, which in the judgment of the investigator would put the subject at risk while in the study, could influence the results of the study, or negatively impact the subject's ability to participate in the study.
- Extremely poor dental and/or oral condition that might preclude safe study participation by the judgment of the investigator.
- Nursing mother or pregnant female subject.

Study design

Main study period: The main period of the study, comprising the screening period and one injection cycle (single treatment followed by 16 weeks for assessment in several visits to the study site) will take place for subjects aged 6–17 years according to a prospective, randomized, double-blind, placebo-controlled, parallel-group design, with active or placebo treatment (randomization ratio 2:1). Subjects aged 2–5 years will not be treated with placebo, but only with active treatment (NT 201) during the main period. The treatment will comprise four injections of NT 201 (parotid and submandibular glands, bilaterally); the dose is defined according to body weight (approximately 2 U/kg). At the end of the main period, subjects will be assessed for eligibility to enter the extension period.

Extension period: The main period will be followed by a 48-week, three-cycle extension period in which all subjects eligible for extension treatment will receive NT 201 ("open-label" treatment) according to the same per-body-weight formula. Dose reduction will be permitted in the third and fourth cycle if relevant adverse events occur. Treatment and observation will be similar to that of the main study period and will be concluded with an end-of-study examination at the end of the fourth cycle.

Data monitoring committee [DMC] and progressive reduction of lower age limit for subjects: Data will be subjected to continual review by an unblinded DMC. The first 30 subjects (age group 10 to 17 years) will be subjected to safety review when four weeks elapsed since the randomization of the last subject. This will be repeated after the recruitment of the next 30 subjects in this age group and then of the first 30 subjects in the age group 6–9 years. If in the above analyses no significant risk is identified by the DMC, then a next cohort can be opened and finally 30 children representing the youngest age group (2–5 years) will be enrolled. In parallel with this, recruitment and treatment of subjects in the age group 10–17 years and 6–9 years will continue. Children in the youngest age group will not be treated with placebo, but only with active treatment (NT 201) during all four injection cycles.

Planned study period

1st quarter 2015 to 2nd quarter 2019

Duration of treatment per subject

Each treatment is to be followed by an observation period of 16 weeks ± 2 weeks. Therefore, for all subjects, the total duration of all injection cycles will be 64 weeks (with permitted variation, 56–72 weeks).

Variables for analysis

Primary efficacy variables

For subjects aged 6–17 years the primary and co-primary variables are:

- Change in unstimulated salivary flow rate [uSFR] from baseline to Week 4.
- Global Impression of Change Scale [GICS] at Week 4 representing the functional improvement in drooling since baseline as assessed by the carer/parent(s).

Secondary efficacy variables

For subjects aged 6–17 years:

- Change in uSFR from baseline to Week 8 and 12.
- GICS at Week 8 and 12.

[redacted]

For the extension period the following efficacy variables will be analyzed

[redacted]

Safety variables

Primary safety variable:

Occurrence of treatment emergent AEs [TEAEs] overall and by injection cycle.

Secondary safety variables:

- Occurrence of treatment emergent AESIs [TEAESIs] overall and by injection cycle.
- Occurrence of treatment emergent SAEs [TESAEs] overall and by injection cycle.
- Occurrence of TEAEs related to treatment as assessed by the investigator overall and by injection cycle.
- Occurrence of TEAEs leading to discontinuation overall and by injection cycle.

Other variables:

- Vital signs (blood pressure, heart rate, body temperature) at screening, baseline, Visits weeks 4 and 16, during the main period and at each injection visit in the extension period and at the end-of-study visit Week 64.
- Body height and weight at screening, final visit of the main period Week 16, and the end-of-study visit Week 64.
- BMI, calculated from body weight and height, at screening, final visit of the main period Week 16 and the end-of-study visit Week 64.
- Clinical chemistry and hematology at screening, final visit of the main period Week 16, and the end-of-study visit Week 64.
- Severity of CP will be assessed by the Gross Motor Function Classification System (GMFCS) at baseline
- Results of dental and oral examination by a dentist at screening (considered as baseline value), in Week 4, at the final visit of the main period (week 16), at the final visit of the second injection cycle (week 32) and the end-of-study visit (week 64), in terms of adverse events: findings indicating a worsening of the subject's condition since screening are to be recorded as adverse events.
- Occurrence of antibodies against *Botulinum* toxin A in subjects' ≥30 kg body weight.
- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during treatment based on the Columbia-Suicide Severity Rating Scale [C-SSRS]. This scale is used to assess suicidality prospectively in this clinical study at baseline and at each post-baseline site visit.

Total number of subjects and number of countries

A total of 249 subjects is planned to be enrolled. Of these, at least 219 are planned to be enrolled in the age group of 6–17 years, who will form the analysis set for the primary efficacy analysis. At least 30 children in the youngest age group of 2–5 years are planned to be enrolled and treated on an open-label basis with active treatment only. The group of older children will be randomized with a randomization ratio of 2:1, i.e., 146 subjects will receive NT 201 and 73 will receive placebo in the main period. (Note that in the extension period no placebo will be administered.)

This international study is planned to be performed in eligible investigational sites in European Union (EU) and outside of the EU (e.g. Poland, Hungary, Romania, Georgia, Turkey, Serbia, Ukraine and Russia).

Number of study sites

This study will be conducted in approximately 8 countries and 40 centers. The selection of countries and centers will be performed on the basis of the outcome of a feasibility survey.

Number of visits

Twenty-one study visits are planned. These will comprise:

Screening	
Baseline (beginning of cycle 1):	7–28 days after screening
Main period (cycle 1):	Three assessment visits and end-of-cycle visit (final visit of the main period).
Extension period (cycles 2–4):	A total of 15 visits; cycles 2 and 3 to end with an end-of-cycle visit and cycle 4 with an end-of-study visit.

The end-of-cycle and the respective subsequent injection visits can be combined where appropriate.

Investigational product, dose, and route of administration

NT 201 (active ingredient: NT 101, *Botulinum* neurotoxin type A, free from complexing proteins, US Adopted Name incobotulinumtoxin A) or matching placebo will be provided in vials as a powder to be dissolved before injection. Quantities in the vials will allow randomized treatment with (i) NT 201 approximately 2 U/kg body weight, according to body weight class, or (ii) placebo, as described under “Study design” (above), under double-blind conditions. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. Note that in the extension period no placebo will be administered.

NT 201 will be prepared for administration by mixing with physiological saline solution. The vials and the volumes used will be selected in such a way that the blinding is not compromised.

The investigational product will be injected bilaterally into the parotid and submandibular glands.

The dose to be administered will be decided on a body-weight basis according to a pre-determined scheme. A single reduction due to AEs at the third and/or fourth administration is allowed, again according to a pre-determined scheme, if adverse events make this desirable.

Statistical analysis methods

Efficacy variables

Efficacy analyses will be based primarily on the full analysis set [FAS] and where deemed sensible additionally, for sensitivity purposes, on the per-protocol set [PPS]. 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 and descriptive *p* values will be given where appropriate.

Primary efficacy variables

The primary efficacy analysis will be performed on the group of subjects within the FAS (age 6–17 years). A mixed model repeated measurement analysis (MMRM, 2-sided, significance level alpha=0.05) with comparison of least square means between NT 201 and placebo will be used for the confirmatory analysis of the co-primary efficacy variables. The dependent variables will be the change in uSFR from baseline (V2) to V3 [Week 4] and the carer's/parent's GICS at V3 [Week 4], respectively. The independent variables are defined as treatment group, pooled investigation sites and age groups as fixed factors, visit*treatment as interaction term, and visit as repeated factor. To adjust for the baseline status, the MMRM of the uSFR change additionally includes the baseline score of the uSFR as covariate. Since no baseline assessment of the GICS is available, the baseline mTDS rated by the parent(s)/carer is used as covariate in the MMRM model for the GICS. Only if both co-primary efficacy variables show a statistically significant difference compared to placebo the superiority of NT 201 will be considered to be proven. Therefore, no α-adjustment for multiple testing is necessary. Sensitivity analyses will be performed using the same approach on the PPS. A non-parametric Wilcoxon rank-sum test will be performed as sensitivity analysis of the co-primary variables to investigate the impact of potential deviations from the assumption of normal distribution.

Secondary efficacy variables

Analyses of secondary efficacy variables are also based on the FAS (subjects aged 6–17 years further specified above). The changes in uSFR from baseline to Week 8 and 12 and the GICS at Week 8 and 12 are analyzed analogously to the primary efficacy variables by means of MMRM.

[redacted]

Safety variables

Two separate safety analyses will be conducted: (i) a comparative analysis of the randomized and treated subjects aged 6–17 years, by treatment (NT 201 or placebo), and (ii) an analysis of all subjects who received NT 201.

The safety variables will be analyzed for the safety evaluation set [SES] by using descriptive summary statistics, frequency tables, and shift tables where appropriate.

Only TEAEs will be analyzed, which are defined as AEs with onset or worsening after the first administration of study medication up to and including the end-of-study visit or, for subjects leaving the study prematurely, up to last documented contact within 64 weeks after first injection with the subject. Incidences will be calculated by system organ class and preferred term level and will be presented by treatment. Listings and, if appropriate, tables displaying incidences for TEAEs leading to discontinuation, serious TEAEs, TEAEs of special interest, and deaths will also be provided.

Laboratory evaluations and vital signs (values and changes from baseline) will be analyzed descriptively by treatment and screened for individual notable values and changes.

The number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during treatment based on the C-SSRS will be calculated and presented as proposed in the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0.

In addition, for all subjects the electronic text-string search as described in the article by Posner at al., section “Pharmaceutical company identification of possibly suicidal events” will be used to identify adverse events that could represent “possibly suicidal” events. Findings will be listed.

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]	Medical expert	Telephone: [redacted]9 Telefax: [redacted]5 E-mail: [redacted]
[redacted]	Clinical project manager	Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]
[redacted]	Biostatistician	Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]
[redacted]	Drug safety officer	Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]
[redacted]	Clinical data manager	Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]
[redacted]	Head of production for the investigational product	Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]

2.2 External responsibilities

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

Name	Function	Address
[redacted]	Co-ordinating investigator	[redacted] Germany Telephone: [redacted] Telefax: Email: [redacted]
[redacted]	Clinical research organisation	[redacted] United Kingdom Telephone: [redacted] Fax: [redacted]
[redacted]	Construction and maintenance of the electronic case report form	[redacted] United Kingdom Telephone [redacted] Telefax: [redacted]
[redacted]	Central depot and distribution of study medication	[redacted] UK
[redacted]	Emergency unblinding service	[redacted] Germany Telephone: [redacted] Telefax: [redacted] 414 E-mail: [redacted]
[redacted]	Central laboratory	[redacted] Germany Telephone: [redacted] Telefax: [redacted]
[redacted]	Laboratory for Fluorescence Immunoassay (FIA) to detect antibodies against BoNT-A	[redacted] Germany Telephone: [redacted] Telefax: [redacted]

Name	Function	Address
[redacted]	Laboratory for Hemidiaphragm assay [HDA] detecting of neutralizing antibodies against BoNT-A	[redacted], Germany Telephone: [redacted] Telefax: [redacted]
[redacted]	Contract research organization (responsibility for IWRS)	[redacted] Belgium Telephone: [redacted] Telefax: [redacted] E-mail: [redacted]
(Various)	Data monitoring committee (Section 2.3)	Members' names and affiliations are provided in a separate list (DMC charter).

2.3 Committees

To ensure the well-being of subjects (i.e. child/adolescent participants), safety data from the study will be evaluated by an independent Data Monitoring Committee [DMC] at predetermined points in time, and also after each recruitment step, as detailed in Section 6.3. These reviews will help to ensure:

- The protection of subjects.
- The early detection of safety signals.
- That any safety-related recommendations necessary are made to the sponsor in a timely manner, for implementation as appropriate.
- That the proposed continuation of the study is likely to be safe, ethical and appropriate.

The DMC will consist of permanent members who are not associated with the sponsor or with the operative conduct of the study. A description of the scope of work and operating procedures for the DMC is provided in Section 12.4.7.3. The composition and charter of the DMC are provided separately.

3 ETHICS

3.1 Independent Ethics Committee / Institutional Review Board

The following documents must be submitted to the responsible IEC/IRB and favorable opinion obtained prior to study start:

- The clinical study protocol.
- Any amendment to the clinical study protocol that is not solely of an administrative nature.
- The IB and all updates.
- Subject information and informed consent forms, as well as questionnaires and updates (as 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, some of the above documents will also be submitted to the respective regulatory authority(ies) for separate approval.

3.2 Ethical conduct of the study – general issues

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

This pivotal study aims to fulfill the requirements defined in the pediatric investigational plan [PIP] for Xeomin in sialorrhea in accordance with pediatric drug regulation 1901/2006/EC. The currently agreed key binding elements for this protocol can be found on the homepage of the European Medicines Agency [EMA].

3.3 Subject information and informed consent, assent and dissent

3.3.1 Subject information

The term “subject” used throughout this document includes child and adolescent research subjects (total age span: 2–17 years inclusive). Prior to study enrollment, the subject (if

applicable) and/or the legally acceptable representative[1] (e.g., parent(s), guardian) will be given full verbal and written information on the nature, objective, significance, expected benefits, potential risks, and expected consequences of the study. This verbal and written information will be provided by the investigator (or authorized designee) according to the provisions set forth in the Declaration of Helsinki. The obligations of the investigator are set forth in the clinical study protocol, the ICH-GCP principles (effective as of 17-JAN-1997), and the respective national regulations governing medical research and experimentation on humans.

Each subject and/or the parent will have ample opportunity to question the investigator (or authorized designee) about the study before giving consent, assent or dissent to study participation. **Participation of subjects living in children's homes and/or subjects that are under state custody can only be enrolled if acceptable by local legislation and after written approval of the respective ethics committee.**

3.3.2 Informed consent/assent

As a rule, a pediatric subject is unable to provide IC. Therefore, pediatric subjects are dependent on their parent(s) to assume responsibility for their participation in clinical studies. Full IC should be obtained from the parent(s) in accordance with regional laws or regulations.

IC for subjects will be obtained:

- In writing from the subject's parent(s), or
- Verbally from the parent(s), if the consent is confirmed in writing by an impartial witness.*

* If the subject's parent(s) is/are unable to write, the subject can enter the study by verbal consent of the parent(s). The verbal consent must be documented in writing by at least one impartial 3rd party who witnesses the entire consent process, and signs and dates the consent document. The witness must NOT be a person who is an employee from or a member of the study site (or its institution), CRO, or Merz.

All subjects should be informed to the fullest extent possible about the study in language and terms they are able to understand. Depending on the extent of the subject's level of understanding and decision-making capacity, the subject should assent to the IC given by the subject's parent(s). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, age-conform written assent or the written IC if the adolescent's maturity ensures understanding of the wording in the IC.

[1] The term parent(s) is used for any legally acceptable representative including guardian(s) in this study protocol as defined in the ICH guideline E6 (R1) as individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. Guardian(s) may replace parent(s) in the performance of study procedures.

Assent, like consent, is a continuous process and will be sought during the trial as well. Objections raised by a child at any time during a trial will be considered. The child's will should be respected.[2]

The consent must be confirmed and personally signed and dated by the person who conducted the IC briefings. This person may be the investigator or an authorized designee if in accordance with local legal requirements. In case the IC briefing has been performed by a person different from the investigator, the investigator has to countersign the IC.

The IC process must be traceable from the available documentation, i.e., the subject's medical file (see Section 11.2). At a minimum, this documentation should include information about when the subject (if applicable) and the parent(s) were 1st informed about the study and who supplied the information. The parent(s) will be given a copy of the signed and dated written IC form as well as all consent form updates (if applicable). Subjects will be given a copy of the signed and dated, separately designed and age-conform written informed assent form (if applicable).

During the course of the study, the subject and/or the parent(s) will be informed in a timely manner if information becomes available that may be relevant to the subject's (if applicable) and/or the parent's willingness to continue participation in the study. In case of AEs, or poor tolerability to the IP, the subject and/or the parent(s) should inform the investigator, who then will make a judgment whether continuing in the study serves the subject's best interests. The subject and/or the parent(s), however, are free to withdraw consent at any time and for any reason, whether expressed or not. All subjects and/or their parent(s) should be made aware of their rights to decline to participate or to withdraw from the study at any time. Therefore, attention should be paid to signs of undue distress in subjects who are unable to clearly articulate their distress.

3.3.3 Subject card

A subject card will be given to all subjects (if the subject is able to keep the card) and the parent(s). They 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 and institution, as the main contact for product information and emergency unblinding.

- Information that the subject is taking part in a clinical study conducted with *Botulinum* toxin type A [BoNT-A] with the randomization number of the assigned medication.

[2] Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population; Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, February 2008

- A 24-hour hotline number for emergency unblinding service.

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.

The subject or his/her parents may consult his/her physician for treatment options, and receive medication to reduce sialorrhea, e.g. anticholinergics or any other rehabilitation measure, at the investigator's discretion. This also applies to subjects who discontinue the study prematurely.

3.3.5 Subject privacy

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

3.3.6 Contact point

If required by local regulations subjects (if applicable), and/or the parent(s) will be provided with a contact address where they may obtain further information regarding clinical studies.

3.4 Insurance

From the enrolment into the study by signature of the IC 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 respective country in which the study is performed.

The subject (if applicable) or parent(s) will be informed by the investigator and through the subject's informed consent form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the parent(s), if requested or if required by local law.

Any medical deviation from the clinical study protocol that is deemed to have occurred through the fault of the subject or parent(s) is not 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 agreed 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 agreed clinical study protocol.

For country-specific requirements, see Section 16.1.

3.5 Financing

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

4 INTRODUCTION

4.1 Study background

4.1.1 Disease background

Sialorrhea (or drooling) is an excess spillage of saliva over the lip margin. This is considered normal in infants but usually stops by 18 months of age. After three years of age (according to some authors four years) this is generally considered to be pathological.

In healthy individuals a mean of 1.0–1.5 liters of saliva are secreted and swallowed each day. Children before puberty produce significantly less (750–900 ml per day). It is produced continuously, predominantly by the three pairs of major salivary glands: parotid, sublingual, and submandibular, and it is conducted by salivary ducts to the oral cavity. In an unstimulated, “resting” state, the submandibular gland contributes about 70% to the overall salivary flow. Upon visual, mechanical or olfactory stimulation salivation is increased about fivefold, with the ratio varying between the three gland pairs. The parotid produces approximately 70% of the total stimulated salivary volume. Dry foods and sour (acidic) juices mechanically induce copious salivary secretion.

Sialorrhea is usually caused by neuromuscular dysfunction (e.g., Parkinson's disease, stroke, cerebral palsy), hypersecretion (e.g., medication side effects, gastro-esophageal reflux disease) or anatomic abnormalities (e.g., macroglossia, oral incompetence, dental malocclusion).The etiology of sialorrhea is multifactorial. In most individuals who drool, intra-oral saliva management is disturbed to some extent. These individuals may demonstrate a variety of symptoms because of sensorimotor impairments or there may be anatomical abnormalities. Inadequate lip closure, habitual open-mouth posture, ineffective or limited tongue movements, poor co-ordination between the oral and the pharyngeal states of swallowing, malocclusion, flexed posture, gingivitis and dental caries may contribute to the origin of drooling. Additionally sialorrhea may be due to excessive saliva production or excessive pooling of saliva in the anterior oral cavity secondary to poor swallowing.

Overall, it is estimated that in the general population up to 0.6% of children show clinically relevant chronic drooling [Fairhurst 2011].

Pediatric sialorrhea can be associated with general physical disability such as infantile cerebral palsy, with other neurodevelopmental disorders and/or intellectual disability [ID], metabolic and neurodegenerative diseases. It can also be an unspecific symptom of disturbed oral-motor control. The majority of children with severe drooling suffer from impaired tongue or bulbar control rather than from insufficient closure of the mouth or from hypersalivation.

Cerebral palsy is one of the most important causes of severe drooling in children. The most prevalent disease in pediatric droolers, however, is quadriplegic infantile cerebral

palsy [CP]. In previous CP studies about 10% of a Swedish population of children with CP showed "embarrassing drooling" [Ekedahl 1974]. In another study moderate to severe drooling occurred in 10–37% of pediatric CP individuals [Van De Heyning 1980]. Furthermore, the prevalence of drooling was investigated in a population of children with CP across dental age and of the total population 33% had severe drooling and 58% some degree of drooling. The authors concluded that the degree of drooling decreased as the dental age increased [Tahmassebi 2003]. A Spanish research group evaluated 50 individuals with CP, both children and adults and 58% of those had drooling [Morales Chavez 2008].

In conclusion, approximately every third or fourth patient with CP develops some kind of drooling. On the other hand, for CP as the most relevant cause of sialorrhea in children, the overall incidence is estimated to around 2 - 2.5 per 1,000 live births in the developed countries [Sätilä 2007]. In Europe, the CP incidence for the period 1980–1990 was found to be 2.08 per 1000 live births, ranging from 1.49–2.63 among 11 centers (post-natal cases excluded) [Surveillance of Cerebral Palsy in Europe 2000]. There are important adverse consequences of sialorrhea. These range from quality-of-life issues (such as social isolation) and unintelligible speech to facial skin maceration and even increased morbidity and mortality (dehydration, choking, aspiration, and pneumonia). The negative impact of sialorrhea e.g. on speaking, eating and social interaction was recently confirmed in a survey study with 240 patients [Daniel 2012].

4.1.2 *Botulinum toxin in sialorrhea*

The flow of saliva is enhanced by both sympathetic and parasympathetic innervation, in both cases involving the neurotransmitter acetylcholine. *Botulinum* toxins in general block acetylcholinergic transmission at the neuromuscular junction and cholinergic synapses by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings, and can thus suppress salivation.

Numerous studies have demonstrated that BoNT-A and BoNT-B are effective and safe for the reduction of sialorrhea in children and adult patients [Alrefai 2009, Costa 2008, Intiso 2012, Jackson 2009, Lagalla 2009, Lin 2008, Lipp 2003, Nordgarden 2012, Reddihough 2010, Reid 2008, Schroeder 2012, Wilken 2008, Wu 2011]. The treated salivary glands (parotid and submandibular glands) and the doses injected into salivary glands are variable, depending on the type and the preparation of BoNT used. The mean global doses injected into salivary glands in adult patients ranged from 55 U to 200 U (Botox®) [Lagalla 2006, Porta 2001] and from 250 U to 450 U (Dysport®) [Mancini 2003, Nobrega 2007] for BoNT-A and from 2500 U to 4000 U for BoNT-B [Jackson 2009, Lagalla 2009, Ondo 2004]. A recent research study comparing the two toxins in controlling sialorrhea of ALS and Parkinson patients reported that either 250 U BoNT-A (Dysport®) or 2500 U BoNT-B (Neurobloc®) have similar effectiveness and safety [Guidubaldi 2011].

In children with cerebral palsy, seven studies [Alrefai 2009, Lin 2008, Nordgarden 2012, Reid 2008, Schroeder 2012, Wilken 2008, Wu 2011] examined the efficacy and safety of

BoNT-A or BoNT-B in a randomized, controlled design. Control groups were treated either with placebo [Alrefai 2009, Lin 2008, Nordgarden 2012, Wu 2011] or remained untreated [Reid 2008], or received BoNT-B [Schroeder 2012, Wilken 2008]. The mean doses injected in children's parotid and submandibular glands ranged from 30 U to 100 U with Botox® (on average ranging 2–4 U/kg body weight) and 140 U with Dysport®. In two studies BoNT-B was used as comparator with the total dose of 2383 U [Schroeder 2012] and an average dose of 120 U/kg body weight [Wilken 2008].

Several uncontrolled, retrospective, or controlled but open-label studies have also been performed [Banerjee 2006, Basciani 2011, Bothwell 2002, Ciftci 2013, Erasmus 2012, Erasmus 2010, García Ron 2012, Hassin-Baer 2005, Jeung 2012, Jongerius 2004a, Kaufman 1995, Khan 2011, Lee 2011, Ong 2009, Reid 2013, Savarese 2004, Scheffer 2010, Suskind 2002]. In these, a wider range of total doses was used (10 U to 300 U Botox®) than in the controlled studies, making the comparison of efficacy and safety results more difficult.

Across published trials, intraglandular injections were administered using a wide spectrum of strategies according to the clinician's experience: single versus multiple injection points, both glands treated versus only one, same dose for both the parotid and submandibular glands versus different doses, and anatomic landmarks versus ultrasound guidance.

The efficacy analyses of these studies reflect the various objective measures (e.g. saliva collection by a cap, cotton rolls, gauze pads, bibs) and/or subjective measures (e.g. Visual analogue scale, Drooling Severity and Frequency Scale, Drooling Impact Scale, [redacted].

Overall, the majority of children responded positively to BoNT-A. With higher doses (above 2.5U /kg body weight) reduction of sialorrhea could be achieved two weeks after injection, and maximum response was observed one month after treatment [Reid 2008], with a positive effect lasting about three to four months in most children. In one study, 83% of the children treated showed a good response to BoNT-A after the first injection [Wilken 2008]. In subjects treated with moderate doses (1.3–2.5 U/kg body weight) the salivary flow rate could be decreased significantly in comparison with control [Wu 2011], and DQs were substantially reduced [Erasmus 2010]. Others report 53% marked improvement – as seen by visual analogue scale [VAS], number of bibs used per day, and weight of dental rolls – and in 11% no response [Savarese 2004]. Subjects treated with rather lower doses (1.3 U/kg body weight or less) showed either no significant reduction or around 40% response rate within one month after treatment [Ciftci 2013, Hassin-Baer 2005].

The long-term effect of BoNT was not tested in the above-mentioned studies, and the maximum duration covered only two injection cycles. None of the studies were sufficiently powered to show significant and clinically relevant treatment effects or measurable difference compared with placebo-treated subjects, and therefore the information gathered from these trials did not reach the evidence level necessary for the market approval of BoNT-A for the indication sialorrhea in children or adults.

4.1.3 Toxicological information

Several studies have investigated the potential clinical improvement in drooling after the injection of *Botulinum* toxin type A (BoNT-A). In contrast, only some studies have investigated histological changes of the salivary glands caused by BoNT-A injection. In one study, BoNT-A was injected into rat submandibular salivary glands and the resulting change in structure and function was monitored. Atrophy of glandular cells, decreased size of acinar cells, and reduced granules in acinar cells were observed on histological examination [Teymoortash 2007]. Another study reported salivary gland shrinkage following the injection of BoNT-A into rat salivary glands without histopathological changes [Coskun 2007]. Animal studies in rabbits did not reveal any histological changes three months after 8 U of BoNT-A administration [Gerlinger 2007].

To support the injection of NT 201 into the salivary glands in humans, a chronic toxicity study has been performed in the Sprague-Dawley rat to determine the toxicity of NT 201 following four intra-glandular administrations to the left submandibular salivary gland at eight week intervals at doses of 0, 2, 10 and 40 LDU/kg and to evaluate the possible regression of any toxic signs during an eight week treatment-free period.

Treatment-related mortality occurred at the dose level of 40 LDU/kg in ten males and five females which were found dead or killed moribund a few days after the second, third or fourth injection. Severe clinical signs (noisy/labored breathing, subdued behavior/decreased activity, pilo-erection, slight hypersalivation and red-stained fur) were noted before death or sacrifice. After the histopathological examination, the cause of death or moribund status was considered to be acute bronchopneumonia with presence of alveolar foreign materials. This was probably a consequence of muscular dysfunction in the region surrounding the pharynx/larynx, resulting in inhalation of material from the oral cavity.

Clinical signs such as noisy breathing and red-stained fur were noted mainly during the two weeks following the second to fourth injections in a few surviving animals treated at 40 LDU/kg by the intraglandular route. No relevant clinical signs were seen in animals treated at a level of 2 or 10 LDU/kg.

A severely reduced food consumption and marked body weight loss were noted in the week following each injection in animals at 40 LDU/kg, leading to a reduced body weight gain throughout the treatment period, partially reversible at the end of the treatment-free period. Similar, but by far less marked, changes in body weight and food consumption were noted in animals given 10 LDU/kg; these recovered by the next injection. Body weight development at 2 LDU/kg was comparable to that in controls.

Changes in clinical pathology variables were observed throughout the study period; these changes were considered to be associated with the reduced food consumption and low body weight of the animals, and the changes resolved by the end of the treatment-free period.

Mean amylase serum activity was slightly lower than controls at all dose levels from the second injection; this was considered to be associated with the pharmacological effect of the test item.

Mean weights of the left (injected) mandibular salivary gland were lower than controls and also lower compared with the weights of the respective contralateral gland in all treated groups. Histopathologically, a treatment-related multifocal acinar atrophy was observed in the left mandibular salivary gland in some animals receiving 40 LDU/kg, accounting for the slightly lower weight of the gland. These treatment-related changes in mandibular glands were probably related to the pharmacological action of NT 201. At the end of the eight week treatment-free period, the mean weight of the left mandibular gland was still slightly lower than that of controls and the right mandibular gland.

Consequently, under the experimental conditions of this study, the 'no observed adverse effect' level was concluded to be 10 LDU/kg. This is around four times the maximum intended clinical dose in the indication with children (2.5 U/kg) or five times the average intended dose in children in this study (2.0 U/kg).

4.2 Study rationale

Merz has initiated a clinical development program for bilateral intraglandular injection of incobotulinumtoxin A (NT 201; Xeomin®) into the parotid and submandibular salivary glands for the treatment of chronic troublesome sialorrhea in adult and pediatric patients.

This pivotal phase 3 study will serve to investigate the efficacy and safety of NT 201 in children and adolescents with chronic troublesome sialorrhea. The study has been discussed and acknowledged by the EMA's Pediatric Committee as the pivotal study of the Xeomin PIP for sialorrhea and aims to fulfill the requirements of the pediatric drug regulation of the EU (see Section 16.1). The results of this study will enlarge the data base of clinical studies with BoNT-A treatment for sialorrhea of neurological origin and improve the low-level evidence [Vashishta 2013] for efficacy and safety of repeat-dose treatment of BoNT-A. This monitored, placebo-controlled, randomized clinical study will observe the treated subjects following the PIP and in accordance with a high scientific standard, with ICH GCP, and with all local laws and regulations.

Troublesome sialorrhea can have several different causes, including being a chronic symptom of neurological diseases (e.g. cerebral palsy). Sialorrhea may require continuous treatment to improve functioning and quality of life for patients. Symptomatic therapies for sialorrhea include long-term repeated treatment with BoNT-A or BoNT-B as an established off-label therapy [Reddihough 2010]. Therefore, this study is planned to investigate repeated treatments over a 12-month period.

The repeat treatments will be injected at intervals of 16 weeks. This is oriented toward the EU-approved interval for NT 201 in spasticity, i.e., every 12 weeks [Merz Pharmaceuticals GmbH 2013] and the effect maintained in a recently published study with BoNT-B of 12 weeks [Chinnapongse 2012]; however, the interval is extended in the present study to minimize any possible overlapping of dose effects.

This study will investigate the treatment of sialorrhea with an average per-body-weight dose of 2 U per kg (corresponding e.g. to 30 U in a 15-kg child at each injection session. (In practice this will be done by using fixed doses determined by weight classes; see Section 8.2.3.) Repeated injections with doses in line with the upper dose limit of NT 201 used in the off-label treatment of sialorrhea are expected to allow a systematic evaluation of safety and efficacy within the protected frame of a monitored study.

Each subject in the age group 6–17 years will receive active treatment at some point (at the latest with the second treatment) during the study. Each child aged 2–5 years will only receive active treatment.

Subjects with chronic troublesome sialorrhea who are treatment-naïve will be enrolled. In this study, treatment-naïve subjects are defined as those who have not received BoNT treatment for this indication within the last 12 months. This regulatory definition aims to avoid bias by comparison of treatment effects in subjects' assessments.

At present, no data from a controlled clinical study are available regarding treatment of chronic troublesome sialorrhea with a per-body-weight dose of 2 U NT 201 administered at fixed 16-week intervals. The performance of this study will contribute to the clinical development program of NT 201 in the indication chronic troublesome sialorrhea.

Currently, no pharmacological agents have FDA or EU approval for treatment of sialorrhea even in adults. However, many trials have been reported since the first description of the treatment of sialorrhea with *Botulinum* toxin formulations [Bhatia 1999, Jost 1999] over the years, only some consensus has been established among specialists on the treatment of sialorrhea with *Botulinum* toxins [Miller 2009, Naumann 2008, Reddihough 2010]. Nevertheless the appropriate dosing and the advantages of ultrasound guided injections versus anatomic landmarks guided application are not evidence-based recommendations.

Ultrasound guidance for the intraglandular injections is recommended by current consensus papers [Reddihough 2010] although there is no further evidence for better efficacy or safety of ultrasound-guided compared with landmark-guided injections. To be compliant with the agreed PIP in the EU the use of ultrasound guidance is mandatory in this study.

Periodontal and dental diseases are known adverse reactions caused by iatrogenic xerostomia following salivary gland irradiation. Injections with *Botulinum* toxins into the salivary glands result in less severe and only temporary changes of periodontal or dental tissues. Thickened saliva resulting from salivary gland injection with *Botulinum* toxin was described for children, as causing worsening of swallowing, breathing or speaking [Erasmus 2010]. Human saliva serves multiple functions in the oral cavity, including moistening of food, facilitation of mastication and swallowing, and cleaning and lubrication of the oral mucosa.

Additionally, secretory immunoglobulin A (sIgA) content within the saliva protects the oral cavity, including dental structures, from bacterial growth and plaque formation (part

of the immune system), preventing dental decay and erosion. With reduced salivary flow rates resulting from the BoNT treatment, the concentration of sIgA increases in the saliva probably as a result of reduced saliva volume [Ellies 2002]. The lack of detrimental effect upon dental and oral health with long-term treatment of sialorrhea with BoNT has not been demonstrated, and, furthermore, both adults with Parkinson's disease and children with cerebral palsy are known to be at increased risk of dental and periodontal disease due to their disabilities in regular oral hygiene. Therefore, the FDA has recommended that a qualified dental health provider need to perform several oral examinations on study subjects during the trial.

4.3 Risk-benefit assessment

In the main period of this study, approximately 176 subjects will be treated with NT 201 (all age groups) and 73 with placebo (age groups 10–17 years, 6–9 years). Combined, bilateral injections of NT 201 (or placebo) into both the parotid and the submandibular glands will be given; because of the minor contribution and anatomical location of the sublingual glands, these will not be treated. Provided the proven therapeutic equivalence of NT 201 and Botox® [Benecke 2012, Roggenkamper 2012], the chosen average dose level of 2 U NT 201 /kg body weight can be expected to be safe and efficacious, as the same average dose level of Botox® has been shown to be safe and efficacious in a similar trial in CP patients [Banerjee 2006]. Additionally, this dose level is within the dose recommendations of a recent consensus paper [Reddihough 2010]. The mean doses injected in children's parotid and submandibular glands ranged from 30 U to 100 U with Botox® (average dose ranging 2–4 U/kg body weight).

Further, Rodriguez and Abarca [Rodríguez Abarca 2012] reported on administration of total 60 units NT 201 in 9 children (4–15 year of age) suffering from sialorrhea due to CP and progressive encephalopathy. One subject reported a transitory nasopharyngeal reflux after the administration of NT 201.

Because previous studies have shown a variability of the effective dose [Reddihough 2010] and because of treatment limitations due to potential worsening of dysphagia by local side effects of *Botulinum* toxin, the treatment will be investigated in an extension period where all subjects will receive active treatment.

Because of the need to proceed with particular caution in a pediatric population, frequent safety reviews will take place and the three age groups 10–17 years, 6–9 years, and 2–5 years will begin treatment in a staggered manner. The first two age groups are required to have safety assessments by a data monitoring committee [DMC] after every 30 subjects has been treated, and the results of these analyses will determine the continuation of the study. In addition, the DMC will monitor safety data on a regular basis, and any adverse events of special interest will be elicited by specific questioning. Thus, the risks of study participation are considered to be at least outweighed by its potential benefits.

As this is the first placebo-controlled, randomized pediatric study with NT 201 in this indication, no clear information regarding its expected side effects is available. However,

on the basis of the literature [Reddihough 2010] the following risks of intraglandular *Botulinum* toxin injections could be identified:

Adverse effects relating to trauma at the site of the injection

- Pain (not severe) at the injection site either during the procedure, or because of gland swelling (hours) or hematoma formation (days) following the procedure.
- Hematoma in the peri-glandular region caused by bleeding from the skin or subcutaneous tissue.
- Intra-oral blood caused by intraglandular/transductal bleeding.
- Swelling of the gland caused by bleeding or injection of too large a volume of solution.
- Swallowing problems, caused by swelling of the gland, which usually resolves within two hours.
- Infection.
- Theoretical possibility of trauma to the facial nerve when injecting the parotid gland.

Adverse effects relating to BoNT-A and BoNT-B

- Increased dryness of the mouth leading to problems such as manipulation of solid food.
- Thickening of saliva because the water component is influenced by cholinergic blockade, leading to an increase in the concentrations of mucins and proteins.
- Chewing and swallowing problems because of diffusion of BoNT into the surrounding muscular tissue.
- Loss of BoNT because of intravascular injection (without systemic consequences because of the low dosages used; however, iatrogenic botulism has been reported in a single case).

When BoNT is injected into the parotid, diffusion of BoNT into the masseter muscle is possible, causing weakness in chewing.

Currently no large, randomized, double-blind, placebo controlled clinical trial has been performed on the use of NT 201 in the management of sialorrhea in adult or pediatric patients. Only small case series and clinical trials with significant design limitations have been performed.

Kossmehl [Kossmehl 2007] found in a case series ($N = 6$) of patients suffering from Parkinson's disease, multiple system atrophy or stroke a clear reduction in saliva production (greater than 50% reduction in saliva production by objective measurement of saliva weight collected with dental rolls before and after placement), and drooling severity and frequency scale [DSFS] score improvements in all patients after ultrasound-guided injections of 50 U NT 201 in both parotid glands (total dose 100 U).

South [South 2011] performed a double-blind, placebo-controlled, cross-over study of NT 201 for sialorrhea in eight subjects with Parkinson‘s disease. Participants received in total 80 U of NT 201 (40 U each in the right and left parotids, distributed evenly) or

saline injected at 0 and 16 weeks. There was a trend toward progressive reduction in saliva weight measures after the injection of NT 201. In the placebo arm, there was an initial improvement of drooling and then a decline by 12 weeks after injection. This trend was also present in the subjective measures [DSFS] and was similar in the active-treatment and placebo arm of the trial. There was significant variation in results of both objective and subjective measures of sialorrhea among individual participants. There was a mild increase in impairment in subjective rating of swallowing function at four weeks after injection with NT 201; this was not seen in the placebo arm. However, no participants reported significant worsening of their swallowing function such that diet modification or formal assessment was required.

Castelnovo [Castelnovo 2013] performed an open-label study of NT 201 for the treatment of sialorrhea in subjects with Parkinson's disease ($N = 17$), amyotrophic lateral sclerosis ($N = 7$) and cerebral palsy ($N = 1$). In total, 25 patients were treated. In group A, comprising 12 patients, only one injection was given into the parotid glands. In group B, comprising 13 patients, single injections were given in both parotid and submandibular glands. The amount of neurotoxin injected was 35 U NT 201 in each parotid gland and 25 U in each submandibular gland. The efficacy of the BoNT treatment was evaluated 4–12 weeks after the injection, measured with the drooling rating scale [DRS] and the clinical global impression scale. Intraglandular injection of NT 201 was safe, well tolerated, and effective in treating sialorrhea. Both injection protocols, i.e. in the parotid glands only or injection of both the submandibular and parotid glands, showed similar effectiveness in controlling sialorrhea. No adverse events were recorded in either of the two groups.

Huß [Huß 2009] published a case report of sialorrhea caused by a swallowing impairment in a 24-year-old female patient with CP, who was treated with intraglandular NT 201 injected at 3.25 U/kg body weight after decreasing responsiveness to BoNT-B. The salivary production was reduced noticeably, without adverse systemic or local effects; constipation was a distant effect.

Rodriguez [Rodríguez Abarca 2012] performed a prospective, longitudinal, controlled study ($N = 9$; CP and progressive encephalopathy) of NT 201, testing efficacy in sialorrhea in children (4–15 years of age). Efficacy was analyzed after four months. In eight patients a decrease in the intensity and frequency of sialorrhea (60–80%) was observed.

With respect to the recommendations of the FDA concerning prospective suicidality monitoring [Food and Drug Administration (FDA) 2012] in clinical studies with NT 201 the risk of suicidality was assessed retrospectively before implementing the C-SSRS. Cumulatively, 794,297 patients have been exposed to Xeomin® in the context of post-marketing experience overall (3,177,186 vials) during the reporting period 31-MAY-2005 until 31-Dec-2014. Until now, approximately 4,206 subjects received NT 201 during the clinical development program. Additionally, a literature and internet research was performed to identify scientific publications covering the incidence of suicide related events in patients treated with any botulinum toxin. Overall, no relevant publications

could be identified, which reported about suicide in relation with botulinum toxin treatment.

In summary no evidence of a causal relationship of suicide and suicide related events in patients treated with NT 201/Xeomin® could be revealed.

For further information, see the current investigator's brochure [IB] for NT 201.

5 STUDY OBJECTIVES

The objective of this study is to investigate the efficacy and safety of NT 201 compared with placebo for the treatment of chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury) and/or intellectual disability in children and adolescents aged 2–17 years, naïve to *Botulinum* neurotoxin treatment. The total dose of NT 201 ranges from minimum 20 U to maximum 75 U or approximately 2 U/kg body weight depending on body weight classes. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. In this study, treatment-naïve subjects are defined as those who have not received BoNT treatment for this indication within the last 12 months.

6 INVESTIGATIONAL PLAN

6.1 Overall study design

6.1.1 Summary of design

This is a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a screening period, a main period [MP] followed by an open-label extension [OLEX] period.

Subjects (adolescents and children) will be recruited in a staggered manner in consecutive age groups: 10–17 years (inclusive), 6–9 years (inclusive) and 2–5 years (inclusive). In the main period the subjects in the age groups from 6 to 17 years will be randomized to receive double-blind, placebo-controlled treatment. Subjects aged 2–5 years at screening will not be randomized, but will be treated with NT 201 in an open-label fashion. In the extension period all subjects will be treated with NT 201 in an open-label fashion.

The study will consist of four injection cycles. The first injection cycle is the main period. The total duration of the main period is 15–22 weeks (comprising the screening period of up to 4 weeks before the first injection and the main treatment period of 16 ± 2 weeks). This first injection cycle will be followed by three subsequent open-label injection cycles (16 ± 2 weeks each) for all subjects. The total treatment period will thus last for 56–72 weeks after the first injection for those completing all four injection cycles. For the safety of subjects, a DMC will assess adverse events [AEs], including adverse events of special interest [AESIs] and serious adverse events [SAEs] at regular intervals and after each group of 30 subjects has been fully recruited.

It is planned that a total of 249 subjects will be enrolled and that, of these, at least 219 in the age group 6–17 years (inclusive) will form the set of subjects for the primary analysis. At least 30 children in the youngest age group of 2–5 years inclusive are planned to be enrolled; these will be treated with active treatment only. The group of older subjects will be randomized at a randomization ratio of 2:1, i.e., 146 subjects will be treated with NT 201 and 73 with placebo.

6.1.2 Number and time points of scheduled visits

Screening

- Screening visit [V1] (Day –28 to –7).

Placebo-controlled main period (first injection cycle)

- Baseline injection visit [V2] (Day 1 of first injection cycle; randomization).
- Assessment visit [V3] (Week 4 ± 3 days).

- Assessment visit [V4] (Week 8 ± 7 days).
- Assessment visit [V5] (Week 12 ± 7 days).
- Final visit of main period [V6] (Week 16 ± 2 weeks).

Open-label extension period (second, third and fourth injection cycle)

Second injection cycle (16 ± 2 weeks after 1st injection):

- Injection visit [V6a] (Day 1 of second injection cycle).
- Assessment visits [V7] (4 weeks ± 3 days after the 2nd injection) and [V8, V9] (8, 12 weeks ± 7 days after the 2nd injection).
- End of cycle visit [V10] (16 weeks ± 2 weeks after 2nd injection).

Third injection cycle (16 ± 2 weeks after 2nd injection):

- Injection visit [V10a] (Day 1 of third injection cycle).
- Assessment visits [V11] (4 weeks ± 3 days after 3rd injection) and [V12, V13] (8, 12 weeks ± 7 days after 3rd injection).
- End of cycle visit [V14] (16 weeks ± 2 weeks after 3rd injection).

Fourth injection cycle (16 ± 2 weeks after 3rd injection):

- Injection visit [V14a] (Day 1 of fourth injection cycle).
- Assessment visits [V15] (4 weeks ± 3 days after 4th injection) and V16, V17] (8, 12 weeks ± 7 days after 4th injection).
- End of cycle/study visit [V18] (16 weeks ± 2 weeks after 4th injection).

End-of-study visit

This will be the same as the end-of-cycle visit for the fourth injection cycle (above). Subjects who withdraw, or are withdrawn, prematurely from the study will be requested to attend for this final examination.

6.1.3 End of study

The end of the study as a whole will be defined as the date of the last study visit by the last subject.

6.1.4 Study flow chart

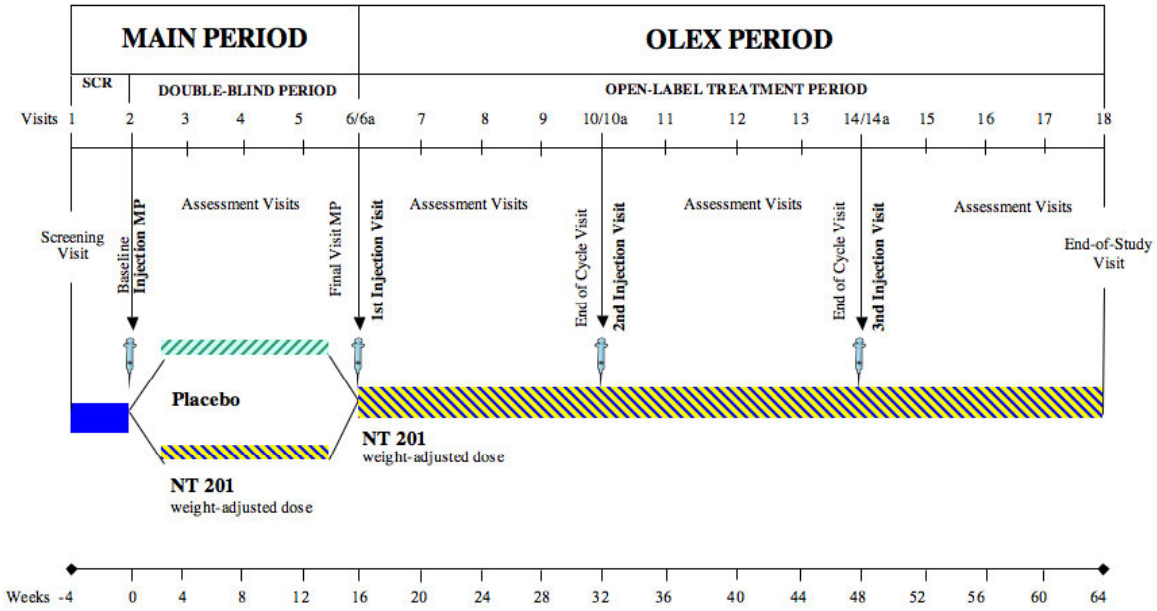


Figure 1: Study Flow Chart

Note: For children age 2–5 years only the NT 201 arm is applicable.

6.2 Discussion of study design, including choice of control groups

Important design features of this study are discussed in turn below.

Randomization and blinding

The use of 2:1 randomization (NT 201 or placebo) in the main period and the migration to all-active treatment in the extension period has been chosen in order to keep the number of subjects treated with placebo as small as possible.

The double-blind, placebo-controlled, randomized, multi-center design of the main period has been chosen to allow the acquisition of scientifically robust efficacy and safety data on NT 201 in children and adolescents with chronic troublesome sialorrhea due to neurological disorders – data that will not be biased by the subject or the investigator. A superiority study with a placebo control allows valid conclusions about efficacy and safety and represents the state of the art in this kind of clinical research.

Currently, no pharmacological agents have FDA or EU approval for treatment of sialorrhea in adults. For pediatric patients, there is currently only one pharmacological agent approved by the FDA for chronic severe sialorrhea (Cuvposa (glycopyrrolate) Oral Solution [NDA 022571]). This is an anticholinergic indicated to reduce chronic troublesome drooling in patients aged 3–16 years with neurological conditions associated

with problem drooling (e.g., cerebral palsy). The use of this agent is compromised by the occurrence of dose-limiting constipation and drowsiness, both of which already can be problematic in CP. Additionally, Cuvposa has other anticholinergic drug effects which may limit its use in patients with coronary heart disease, congestive heart failure, and cardiac tachycardia. Cuvposa is administered as an oral solution. Therefore using it as a comparator in this study would compromise the blinding and it could only be implemented by a double-dummy design, meaning that both the NT 201-treated group and the control group would need to receive the oral solution (placebo or active treatment) and the injection (active treatment or placebo, respectively) at the same time. This would lead to higher risks for subjects than the pure placebo control.

As no substance has yet received marketing approval for the treatment of chronic troublesome sialorrhea for minors in the EU, and to date no appropriately powered pivotal study data on *Botulinum* toxin in this indication are available, therefore placebo treatment in about 33% of all enrolled and randomized subjects (age 6–17 years) for one single injection cycle during the main period out of a total of four injection cycles is justified. All children age 2–5 years will receive NT 201 in the main period. However, it was also considered to be important not to withhold treatment from subjects needing it in this burdensome indication. Therefore, the placebo group in the main period was kept small, and the extension period (required by the need for long-term safety data) was designed without placebo treatment. All subjects will receive active treatment during the extension period. All subjects are expected to benefit from treatment with NT 201 (subjects in the placebo group three times, subjects in the active treatment group four times).

Following discussions with the relevant regulatory authorities, it was considered necessary to follow at least 100 children treated with clinically relevant doses of NT 201 continuously for one year. At least 50 of these patients must have received the high dose (at least 2 U/kg body weight) consistently for one year (series of four injections). The safety database requirement in children for cumulative exposure at six months is also at least 100 subjects treated consistently with clinically relevant dosages for two injections.

Duration of treatment and assessment

The length of each injection cycle was chosen on the basis of reported observations that the effect of *Botulinum* toxin builds up over approximately two weeks after treatment and decays after 8–12 weeks [Chinnapongse 2012, ClinicalTrials.gov 2011]. Therefore, in order to avoid any unwanted reinforcement of consecutive doses, a separation of 16 weeks (at least 14 weeks) between doses was incorporated into the design.

Sialorrhea manifesting itself as a consequence of neurological disease is a chronic health problem and requires long-term treatment. Therefore, the extension period of this study investigates the efficacy and safety of repeated administration of NT 201, given at fixed intervals. Following the placebo-controlled main period of 16±2 weeks' duration, all subjects complying with the eligibility criteria will receive active treatment in the extension period. Each subject will receive at least three injections with NT 201 within an overall treatment period of 64 weeks.

Recruitment strategy based on safety monitoring

The staggered recruitment described in the following section will give early warning if any unexpected safety issues arise. Depending on the results of the (numerous) safety reviews, the design of the study may be modified by discontinuing recruitment, either for the next younger age group or completely. Details are set out in the following section.

6.3 Recruitment strategy

This international study is planned to be performed in eligible investigational sites in about 40 centers in European Union (EU) and outside of the EU (e.g. Poland, Hungary, Romania, Georgia, Turkey, Serbia, Ukraine and Russia). The selection of countries and centers was performed on the basis of the outcome of a feasibility survey. A conservative staggered recruitment procedure will be applied in order to minimize potential age-related risks for the participating children and adolescents. This comprises the steps set out below, in which reference is made to the age groups defined in Table 1.

Table 1: Overview of age groups and recruitment steps

Step	Age 10–17 inclusive	Age 6–9 inclusive	Age 2–5 inclusive	Cohort number for initial DMC review
1	30 subjects	–	–	1
2	30 subjects	–	–	2
3	Continuous recruitment	30 subjects	–	3
4	Continuous recruitment	Continuous recruitment	30 subjects	4
Random-ization?	Yes	Yes	No	
Treatment in main period	Double-blind, placebo-controlled		Open, active treatment only	

Step 1

In the first recruitment period, 30 children/adolescents (10–17 years of age) will be recruited (cohort 1). These subjects will be randomized and treated with either NT 201 (active treatment) or placebo (randomization ratio 2:1) during the double-blind main period.

Safety data acquired from this cohort will be reviewed by the DMC when 4 weeks elapsed after the last subject of the cohort was randomized.

Step 2

If in the above analysis no significant risk is identified by the DMC, then a second set of 30 children/adolescents (10–17 years of age) will be recruited, randomized and treated in the same manner as the first 30 subjects (cohort 2).

Safety data acquired from cohorts 1 and 2 will be reviewed by the DMC when 4 weeks elapsed after the last subject of cohort 2 was randomized.

Step 3

If in the above analyses no significant risk is identified by the DMC, then a further group of 30 younger children (6–9 years of age) will be recruited, randomized and treated (cohort 3).

In parallel with this, recruitment and treatment of subjects in the age group 10–17 years will continue.

Safety data acquired from all subjects randomized hitherto ($N \geq 90$) will be reviewed by the DMC when 4 weeks elapsed after the last subject of cohort 3 was randomized.

Step 4

If in the above analyses no significant risk is identified by the DMC, then a further 30 children representing the youngest age group (2–5 years of age) will be enrolled (cohort 4). Children in this youngest age group will not be treated with placebo, but only with active treatment (NT 201) during all four injection cycles.

In parallel with this, recruitment and treatment of subjects in the older two age groups will continue.

Termination of recruitment

Recruitment will continue in the age groups covering the age range from 6 to 17 years inclusive until the target number of 219 subjects randomized and treated is reached. Recruitment in these age groups will then stop.

Recruitment will continue in the age group 2–5 years inclusive until the target number of 30 subjects treated is reached. Recruitment in this age group will then stop.

If recruitment in one or another group is unexpectedly or disproportionately slow, then the sponsor has the right to terminate recruitment before the respective target number is reached. The sponsor also has the right to terminate recruitment, overall or in a given age group, by recommendation of the DMC for safety-related reasons.

With the recruitment strategy described above, and assuming that no premature termination of recruitment takes place as outlined above, a total of 249 subjects will be enrolled and treated; of these, 30 will have received active treatment without randomization, 219 will have been randomized to receive either active treatment (146 subjects) or placebo (73 subjects) in the main period. All study subjects will have received NT 201 in the extension period.

Period of recruitment

It is estimated that recruitment will commence in the first quarter of 2015 and will be completed during the first quarter of 2018. The end of the study (final study visit by the last subject) would then be in the second quarter of 2019.

7 STUDY POPULATION

7.1 Selection of study population

Study subjects (male and female children and adolescents in the respective age groups) will be recruited according to criteria determined by having a relevant medical condition of chronic troublesome sialorrhea associated with neurological disorders and/or intellectual disability requiring study treatment, and by having no medical condition or other circumstance that might interfere with the conduct or result of the study or endanger a subject's safety.

Distribution of gender

As the study indications are not gender-specific, no stratification or selective recruitment of male/female subjects will be performed. It is assumed that the accrual of male and female subjects without distinction at all investigation sites will in itself lead to a balance of the genders that will be adequate for the study analysis.

7.2 Inclusion criteria

Only individuals meeting all of the following inclusion criteria, at screening and/or at baseline as indicated, will be considered for study enrollment:

Inclusion Criteria	Ratio-nale	Scr	BL
1. Written informed consent obtained from the child's/adolescent's parent(s) and oral or written assent by the child/adolescent (following information to the extent compatible with the subject's understanding if applicable).	Adm	X	
2. Male or female child/adolescent aged 2 to 17 years (i.e., second birthday reached, and eighteenth birthday not yet reached, on the date of first administration of study medication).	Adm	X	X
3. Understanding of study procedures and willingness to abide by all procedures during the course of the study by the parent(s) and/or the child/adolescent (if applicable).	Adm	X	
[redacted]			

Inclusion Criteria	Ratio-nale	Scr	BL
5. Any neurological disorder (e.g. cerebral palsy or traumatic brain injury) and/or intellectual disability associated with chronic troublesome sialorrhea for at least 3 months up to the screening. In subjects with intellectual disability (ID) without neurological disorders, a diagnosis of ID by a specialist, e.g. pediatrician or by a center for developmental medicine is required for inclusion.	Ind	X	
6. mTDS of ≥ 6 (= severe drooling to the extent that clothing becomes damp occasionally) rated by the investigator.	Ind	X	X
7. Female subjects of child-bearing potential[a] must be using a highly effective method of birth control[b].	Safety	X	X

a Any female who has experienced menarche and is not permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).

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

Screening [Scr]; baseline [BL]; administrative [Adm]; definition of the study indication [Ind].

Note: The technical prerequisite for inclusion of subjects is the confirmation through the IWRS [interactive web response system] that the study is currently recruiting in the age group of the child/adolescent.

7.3 Exclusion criteria

Individuals meeting any of the following criteria, at screening or at baseline as indicated, will not be included in the study:

Exclusion Criteria	Ratio-nale	Scr	BL
1. Diagnosis of chronic troublesome sialorrhea not related to a neurological disorder and/or intellectual disability, e.g. malformation of the salivary ducts or glands.	Int	X	
2. Subject with body weight < 12 kg.	Safety	X	X
[redacted]			

Exclusion Criteria	Ratio-nale	Scr	BL
4. Aspiration pneumonia within 6 months before screening.	Safety	X	X
[redacted]			
7. Prior, concomitant or planned surgery or irradiation to head and neck to control sialorrhea (including salivary gland surgery or salivary gland irradiation) within one year before screening or planned for any part of the entire study period.	Int	X	X
[redacted]			
9. Any previous treatment with *Botulinum* toxin for any body region during the year before screening or within the screening period.	Int	X	X
[redacted]			
11. Known or suspected hypersensitivity to either *Botulinum* toxin (any serotype) or any ingredient of the formulation or analgesics or sedatives (used for premedication for analgosedation or anesthesia).	Safety	X	X
12. Extremely poor dental and/or oral condition that might preclude safe study participation by the judgment of the investigator.	Int	X[#]	X
[redacted]			

Exclusion Criteria	Ratio-nale	Scr	BL
16. Pharmacological treatment for sialorrhea or concomitant medication known to influence sialorrhea strongly (e.g. anticholinergics with exception of locally applied or short acting drugs used under general anesthesia) within 45 days before baseline and during the entire study period.	Int	X	X
[redacted]			
18. Concurrent diseases, including hematological, hepatic, renal, gastrointestinal, endocrine, pulmonary, musculoskeletal, or psychiatric diseases or conditions, which in the judgment of the investigator would put the subject at risk while in the study, could influence the results of the study, or negatively impact the subject's ability to participate in the study	Safety	X	X
19. Nursing mother or pregnant female subject.	Safety	X	X
[redacted]			

Exclusion Criteria	Ratio-nale	Scr	BL
[redacted]			

Screening [Scr]; baseline [BL]; risk of interference with study objectives [Int]; administrative [Adm]; (*) to avoid unnecessary distress to the subject; #dental examination by dentist needs to be performed until baseline visit.

7.4 Eligibility criteria for continued treatment in the extension period

Criteria for the transition to the extension period (V6/6a) and for continued treatment within the extension period (V10/10a and V14/14a) are listed below. (Note that the pairs of visits 6/6a, 10/10a and 14/14a will normally take place on the same respective day.)

If these eligibility criteria are not fulfilled at the end-of-cycle visit postponement of study treatment may take place at the beginning of the following injection cycle of the extension period. The re-injection visit can be postponed for up to a maximum of two weeks (but no longer than 18 weeks after the preceding treatment visit). For subjects who still do not fulfill the eligibility criteria at the revisit, study participation will be ended.

Eligibility Criteria for Extension Treatment	Ratio-nale	Visits 6, 6a, 10, 10a, 14, 14a
1. Clinical need for re-injection.	Ind	X
2. Absence of medically-relevant severe adverse events of special interest that are judged to have a causal relationship to the study treatment (indicative of toxin spread in the area of injection), especially respiratory arrest/distress/failure and dysphagia necessitating diet changes occurred during any period of the study.	Safety	X
3. No concomitant infection or inflammation in the head and neck region.	Safety	X

Eligibility Criteria for Extension Treatment	Ratio-nale	Visits 6, 6a, 10, 10a, 14, 14a
4. Negative result of pregnancy test (testing only performed for female with history of menarche, i.e. the first menstrual bleeding).	Safety	X
5. No significant risk of suicidality since last injection based on • the Investigator's judgment, and • if appropriate, as indicated by a response of "no" to questions 4 or 5 in the suicidal ideation section of the C-SSRS • and no non suicidal self-injurious behavior • and no suicidal behavior.	Safety	X

Definition of indication for continued study treatment [Ind]; administrative [Adm].

7.5 Removal of subjects from treatment or assessment

7.5.1 Discontinuation of subject's study participation

In accordance with the Declaration of Helsinki and the informed consent form, the subject or his/her parent(s) may discontinue the subject's participation in the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled (see Section 7.5.3). Both the premature withdrawal from the study and the reason(s) for this are to be recorded in the subject's file and the eCRF. The date and circumstances of the discontinuation should be stated.

Subjects are to be withdrawn from the study by the investigator at any time if any of the following occurs:

- Withdrawal of informed consent.
- Pregnancy (no further administration of NT 201, blood sampling, or any other interventional or invasive procedure will be performed).
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.
- Any eligibility criteria for reinjection are not met within 18 weeks after the previous injection of IP in the respective injection cycle (MP or OLEX).

- AESIs of severe intensity that represent respiratory function disorders or swallowing disorders will trigger the premature termination of a subject without reexposition to IP. The terms for these severe AESIs are:

  - AESI terms related to respiratory function disorders are aspiration, diaphragmatic paralysis, dyspnoea, pneumonia aspiration, respiratory arrest, respiratory depression, and respiratory failure.

  - AESI terms related to swallowing disorders are bulbar palsy, multiple cranial nerve palsies, dysphagia, hypoglossal nerve paresis, cranial nerve paresis, cranial nerve paralysis.

- Positive report on suicidality of subject (C-SSRS answer „yes“ to questions 4 or 5 or any suicidal behavior) or non-suicidal self-injurious behavior.

Deviations from this clinical study protocol, or conditions arising from the exclusion criteria as set out in Section 7.3, may (but will not necessarily) lead to the subject's withdrawal. All such conditions are to be properly documented. In such cases, the decision on whether or not to withdraw the subject will be made by the investigator in consultation with the sponsor, taking principally the safety of the subject into account.

Subjects who are withdrawn from the study because of AEs will be treated by standard clinical methods and will be followed up until (and including) the last scheduled visit of the injection cycle in which they were withdrawn or until 28 days after the onset of the adverse event, whichever date is the later. All pertinent information concerning the AE will be documented in the subject's hospital medical file as well as in the eCRF AE report form.

Following a subject's withdrawal, a final examination should be performed for safety reasons if parents/carers are willing to bring the child for the visit. 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 subject's hospital medical file (e.g., times and dates of telephone contact, copies of letters).

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

The study or a study site can be terminated prematurely, 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 NT 201 do not justify a continuation of the study.

- The investigator or study site exhibit serious and/or persistent non-adherence to the clinical study protocol, the Declaration of Helsinki, ICH–GCP, and/or applicable regulatory or clinical requirements.

- The sponsor decides to terminate the study at any time for any other reason (e.g. based on the recommendation of the DMC).

- AESIs of severe intensity that represent respiratory function disorders or swallowing disorders, that are deemed to be related to IP administration, and that last >1 week will trigger premature termination of the study. The threshold for premature study termination is set to at least five of the severe AESIs described above for the first 50 subjects injected. Once 50 or more subjects have been treated in this study the threshold is set to at least 10% of all treated subjects.

- AESI terms related to respiratory function disorders are aspiration, diaphragmatic paralysis, dyspnoea, pneumonia aspiration, respiratory arrest, respiratory depression, and respiratory failure.

- AESI terms related to swallowing disorders are bulbar palsy, multiple cranial nerve palsies, dysphagia, hypoglossal nerve paresis, cranial nerve paresis, cranial nerve paralysis.

Furthermore, the study (or the participation of a study site) may be ended prematurely if the regulatory authority or the IEC/IRB decides to terminate 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/or their legally acceptable representatives and ensure appropriate follow-up treatment. Within the time-frames stipulated in the applicable regulations, the sponsor will promptly inform the investigators, study sites, IEC/IRB and regulatory authorities of the termination or suspension of the study, and will provide reasons for this action.

7.5.3 Provision of care for subjects after leaving the study

After leaving the study (following regular completion or premature discontinuation), the subjects will be treated by their physician according to their medical condition and standard treatments in the country concerned. For further information, see Section 3.3.4.

8 TREATMENTS

8.1 Investigational products

8.1.1 Description of investigational products

NT 201 will be provided in quantities of 100 units (active ingredient: NT 101, *Botulinum* neurotoxin type A, free from complexing proteins, US Adopted Name incobotulinumtoxin A) or placebo, both as powder for dissolution before injection. The excipients of the final formulation of NT 101 (that is the active neurotoxin molecule in the preparation of NT 201) are sucrose for stabilization and human serum albumin to prevent adsorption of the neurotoxin on container, syringe, and needle. NT 201 contains no hemagglutinins. The same ingredients are used for placebo. The vials with the powder for solution for injection will be reconstituted with 4.0 mL sterile physiological (0.9%) sodium chloride solution per vial respectively. For NT 201, dilution of a vial containing 100 U NT 201 with 4.0 mL saline results in the concentration of 25 U per mL solution. The reconstitution volume is fixed.

NT 201 and placebo are manufactured and released by Merz Pharmaceuticals GmbH, Eckenheimer Landstr. 100, D–60318 Frankfurt/Main, Germany.

8.1.1.1 Instructions for preparation

[redacted]

Dose regimens in the main period

For the NT 201 group dosages will be given according to the predefined volumes of fixed total doses defined for each of the six body-weight classes (see Table 2 in Section 8.2.3 below).

In general for subjects with a body weight of 12–30 kg the total dose is approximately 2 U/kg. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. Due to the unitary concentration of the NT 201 solution the dose adjustment will be performed by adapting the injection volumes for each dose group (see Table 2).

In the placebo group, subjects will receive the respective volume of placebo solution (0.9% sodium chloride, sucrose and human serum albumin) as in the NT 201 treatment group according to their bodyweight classification.

Dose regimens in the extension period

There will be no placebo group in the extension period. The regimen for the administration of NT 201 will be the same body weight-adjusted dosing scheme as for the main period. Dosages will be adapted to actual body weight of subjects at each injection visit according to the dosage instructions.

The subject's body weight will be re-determined at each injection visit, and if the body weight has increased (or decreased) over the limit of the class then the subject will be treated in the next higher (or lower) dosage group accordingly.

Dose reduction in the extension period (3rd or 4th injection cycles only)

In the third or fourth injection cycles, the quantities of NT 201 administered can be reduced if there are treatment emergent adverse events that the investigator considers as demanding a reduction in dose level in order to avoid a repetition of the adverse event or the withdrawal of the subject from the study. This reduction will take place at the discretion of the investigator to minimize the risk of further occurrence of such AEs or the discontinuation of the study for the subject. The quantities to be administered in the reduced-dose treatment are defined in Section 8.2.3. Quantities other than those given in Section 8.2.3 (with corresponding adaptation to body weight and possible dose reduction following relevant adverse events) are not allowed.

If the dose has been reduced in the third injection cycle, then in the fourth cycle the reduced dose will also be given.

8.1.1.2 Instructions for administration

The technique of injection is described in Appendix 16.5.

Treatment will be administered via intraparenchymal/intraglandular injections (percutaneously) into the parotid and submandibular glands bilaterally with a single

injection site per gland per side. To avoid swallowing problems caused by thickened saliva and in order to safeguard against excessive reduction of salivary flow during mastication and eating, the ratio of toxin dosages injected into the parotid and submandibular gland is set to be 3:2.

Injection of both salivary glands at each side will be performed at each injection visit using mandatory ultrasound guidance (see Appendix 16.5 for injection technique). Investigators will receive specific training on ultrasound guidance technique and on the anatomical localization of the target injection points.

Quantities to be administered (one injection into each gland, four injections per treatment) are shown below in Section 8.2.3. Note especially the normal and reduced dose levels in Table 2 and Table 3 respectively; the reduced amounts in Table 3 apply only to the third and fourth study treatments if a treatment emergent adverse event occurs that the investigator considers as demanding a reduction in dose level.

Investigators will be trained in the administration of study medication before the inception of the study at their respective centers.

The injections will be performed with ultrasound guidance at each gland and on each occasion. The salivary glands are to be examined sonographically by using a commercially available ultrasound system equipped with a high-resolution, 7.5-MHz small-parts transducer. The transducer is to be positioned in such a way that injection with the needle is possible along the longitudinal axis of the transducer, providing a quick and easy-to-perform visualization of the needle in the gland. Furthermore, ultrasound is to be used to monitor and guide the spreading of the fluid throughout the gland accordingly [Jongerius 2004a].

General anesthesia, medication for analgesia and analgosedation will be offered to all subjects unless contraindicated and in line with international guidelines on sedation in children. It is to be administered by (or under direct supervision of) trained and qualified anesthesiologists with adequate experience, monitoring equipment and support personnel.

In case the child has an anaphylactic reaction or unexpected airway problems, easy access to a pediatric intensive care bed and extensive monitoring and emergency equipment and support personnel is required.

The investigator will use the NT 201 and placebo vials provided and all other study materials only within the framework of this clinical study and in accordance with this protocol.

8.1.2 Packaging and labeling

Boxes for each injection visit, containing one vial of investigational product (IP; vials containing NT 201 or placebo), will be sent to the study sites. Sites are supported in purchasing vials with 10 ml sterile saline for reconstitution, syringes and needles for the reconstitution, and syringes and needles for the injections. Boxes and vials will be labeled

appropriately; printed labels will contain the information set out below. To maintain the blind, medication (NT 201 and placebo) for use in both periods of the study will have the same printed label information on the outer packaging (box) and the immediate containers (vials). See Section 8.5 for further details on the blinding procedures planned for this study.

The study medication will be labeled according to the regulatory requirements of the participating countries. The labels will include, as minimum information, the name and address of the sponsor, the study reference number, EudraCT/IND number, expiry date, medication kit number, dosage form, route of administration, quantity of dosage units, batch number, directions for use, storage conditions, period of use and 'For clinical trial use only'.

If exchange of IP due to the expiry date becomes necessary, the IP will be replaced in due time.

8.1.3 Storage of investigational product

Study medication should be stored at +2 to +25 °C (36–77 °F). It is recommended not to freeze the study medication.

Storage temperature will be monitored once daily on working days, and the minimum/maximum temperature for each day (or shorter monitoring interval) will be recorded in a temperature log.

The IP should be reconstituted shortly before use. However, reconstituted IP can be stored in the original vial for up to 24 hours at +2 to +8°C (36–46°F) in a drug refrigerator if the injection needs to be postponed to the day following that on which the reconstitution was performed. Any deviation from this will be documented on the drug accountability log. Reconstituted study medication is not to be stored in syringes.

8.1.4 Accountability for investigational product

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

Supply and receipt of IP will be managed with the help of the IWRS-system. Upon receipt of the IPs, the investigator or pharmacist or other qualified staff according to local law will visually inspect the shipment and verify the number and condition of the IPs. The investigator or authorized site staff or pharmacist will electronically acknowledge the

receipt of IP and also the temperature log (Section 8.1.3). An IP supply and return form will be completed and signed by the investigator or authorized site staff or pharmacist according to local law. The original signed form is to be filed with the inventory / drug accountability records. Prescription and Return of IP will be tracked in the IWRS-system according to data input from the investigator or authorized site staff. Drug Accountability forms will be signed by the investigator and filed in the investigator site file and trial master file.

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

For subject drug accountability and treatment compliance, see Section 8.2.5.

8.1.5 Destruction of investigational product

All used vials including residual fluid content are to be neutralized by adding a denaturing solution (i.e. alcohol) to the active substance according to local standard practice. The IP inactivation has to be done immediately after each injection session. Upon the completion or termination of the study, all unused and used and denaturated empty vials of IP(s) have to be shipped to an authorized warehouse for destruction of the IP. More detailed information is given in the Trial Medication Handling Manual and in the IWRS Manual.

8.2 Treatments administered

Subjects aged 6–17 years will receive NT 201 or placebo in the main period and NT 201 in the extension period. In the main period the treatment will be randomized and double-blinded; in the extension period all patients will receive open-label active treatment. Subjects aged 2–5 years will receive NT 201 in the main period and in the extension period. For details, see Sections 8.2.1 to 8.2.4.

8.2.1 Methods of assigning subjects to treatment groups

Each subject screened will be given a screening number through the IWRS. Rescreened subjects will receive a new screening number. Only the subjects who are randomized will receive a randomization number at baseline visit (V2).

Randomization to NT 201 and placebo in a ratio of 2:1 will be applied during the main period, for the subjects aged 6–17 years. Subjects aged 2–5 years will not be randomized.

Randomization will include staggering of the age groups as described in Section 6.3.

The randomization officer responsible will perform the random allocation of treatments to subjects using the computerized randomization program [redacted]

[redacted], Germany) by preparing a randomization list for each age group including – for each subject – a randomization number and the allocation to treatment for the main period. The IWRS will allocate the randomization number to a subject and will determine a medication kit with a unique medication number for each injection visit of the subject. The randomization number and the medication numbers for each subject will be recorded in the eCRF.

Recruitment in each age group will be closed when the requisite number of subjects has been recruited; for details see Section 6.3. Slight over-recruitment (up to 10%) may occur in consequence of technical factors. After the end of recruitment, subjects leaving the study prematurely will not be replaced.

The randomization list will be sealed and locked in the sponsor's quality management department and will not be accessible before database closure.

8.2.2 Selection of doses in the study

The mean doses injected in children's parotid and submandibular glands ranged from 30 U to 100 U with Botox® (on average ranging 2–4 U/kg body weight) and are within the dose recommendations of a recent consensus paper [Reddihough 2010].

Rodriguez and Abarca [Rodríguez Abarca 2012] reported on administration of total 60 units NT 201 in 9 children (4–15 years of age) suffering from sialorrhea due to CP and progressive encephalopathy. One subject reported a transitory nasopharyngeal reflux after the administration of NT 201.

Two randomized, double-blind, active-controlled, parallel-group Phase 3 studies in the indications cervical dystonia and blepharospasm in adults demonstrated that NT 201 and Botox® show good and similar efficacy for both primary and secondary endpoints. Not only statistical non-inferiority of NT 201 versus Botox® was shown by these studies but also therapeutic equivalence of NT 201 and Botox® was proven [Benecke 2012, Roggenkamper 2012].

Based on these facts and that in a similar trial with onabotulinumtoxin A in CP patients the average dose level of 2 U/kg body weight has been shown to be safe and efficacious [Banerjee 2006] the average dose of 2 U NT 201/kg body weight was chosen. Body weight classes and dose ranges were defined accordingly.

Dose regimens for main period

All subjects aged 6–17 years inclusive will receive a dose of NT 201 or matching placebo (randomization ratio 2:1).

For subjects with a body weight of 12–30 kg the total dose on each treatment day will be approximately 2 U/kg. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. As NT 201 is supplied at a fixed concentration, the dose adjustment will be

performed by adapting the injection volumes for each dose group (see Table 2 in Section 8.2.3 below).

All subjects in the age range 2–5 years inclusive will receive a body-weight-based dose of approximately 2 U/kg NT 201, and none will receive placebo.

Dose regimens for the extension period

There will be no placebo group in the extension period. The regimen for the administration of NT 201 will be the same body weight-adjusted dosing scheme as for the main period. Dosages will be adapted to actual body weight of subjects at each injection visit according to the dosage instructions.

The subject's body weight will be re-determined at each injection visit, and if the body weight has increased (or decreased) over the limit of the class then the subject will be treated in the next higher (or lower) dosage group accordingly. For details see Section 8.2.3.

No dose reduction due to AE is allowed for the second injection cycle (V6). If, in the opinion of the investigator, a dose reduction is advised, the dose can be reduced for the third injection cycle (V10) at the earliest. Only one dose reduction due to AE is allowed during the entire study period.

8.2.3 Selection and timing of doses for each subject

For selection of doses, see Section 8.2.2; for timing of doses see Sections 6.1.2 and 9.2. No other dose levels and no other timing will be permitted.

The principle of by-weight dosing set out in Section 8.2.2 leads to the following table of doses for guidance of the investigator (Table 2).

Table 2 shows the amount of IP to be administered for each subject at each visit, according to the subject's body weight as determined at that visit.

Therefore:

– The subject's body weight will be determined immediately before each injection session, and if the body weight has increased (or decreased) then the subject will be treated in the next higher (or lower) dosage group.
– At each injection session (V2, V6, V10 and V14), a total of four injections will be administered, one in each gland (left and right parotid, left and right submandibular).

Table 2: Dosing scheme

If a treatment-emergent adverse event occurs that the investigator considers as demanding a reduction in dose level, this reduction can only be implemented at the following injection visit of the extension period (V10 or V14) if the dose was not reduced because of weight loss at the same visit.

For reduced dose at the third and fourth administration of study medication (following a relevant adverse event; see Section 8.1.1.2 for details), each subject will be treated at the dose level set out in Table 2. For subjects in the smallest weight group (12 to 15 kg) dose reduction to a reduced level is not allowed; the only option is reduction to zero, i.e., discontinuation of the subject's participation in this study.

Table 3: Dosing scheme with dose reduction in the third or fourth injection cycle

(following an adverse event; see text)

If in the third cycle the dose is reduced, then in the fourth cycle the dose will likewise be determined by reference to Table 3, using the subject's current body weight.

In the event of a subject's gaining weight such that he/she would progress from one dose level to a higher dose level according to Table 2, while at the same time requiring dose reduction because of a relevant adverse event (as described above and in Section 8.1.1.2), the subject will remain at the previous dose level.

In the event of a subject's losing weight and the occurrence of a relevant AE, only one dose reduction is allowed at the next injection session.

8.2.4 Duration of treatment per subject

Each subject who completes the study will have received the total of four treatments, each comprising four intraglandular injections administered on a single day. The fourth treatment day is scheduled to be 48 weeks after the first treatment day, with a permitted variation of up to ±6 weeks. For details see Section 6.1.2.

Each treatment is to be followed by an observation period of 16 weeks ± 2 weeks. Therefore, for all subjects, the total duration of all injection cycles will be 64 weeks (with the permitted variation as specified in Table 6, 56–72 weeks).

8.2.5 Treatment compliance

At the beginning of the study, the site will receive drug accountability forms to document how and when IP is dispensed to subjects or returned unused. These forms will be made available to the authorized individuals (e.g. monitor, auditor) and will include the following information: study number, dates, quantities, and the code number assigned to the IP and study subjects.

All injections will be administered by study-site staff, so deviations from compliance with the treatment schedule (apart from discontinuation) are not anticipated.

The vials will be checked to ensure that the IP assigned by the IWRS was administered.

8.2.6 Treatment of overdose

As study treatment will be administered exclusively in a clinical setting by study-site medical personnel, the risk of overdose (e.g. due to reconstitution or application error) in this study is considered to be low. Nevertheless, any deviation from the planned dosing scheme (excluding dose adjustment due to body weight changes or AEs) is to be reported as an AE and treated accordingly. The investigator is advised to use best clinical judgment in the unlikely event of an overdose with the IP.

There is no significant information regarding overdose from clinical studies in adults in upper limb spasticity, cervical dystonia, and blepharospasm.

Excessive doses of NT 201 may be expected to produce neuromuscular weakness with a variety of symptoms. Signs include acute symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysphonia, and dysphagia, which would typically occur 12 to 72 hours after exposure [Arnon 2001]. Furthermore, signs and symptoms of overdose can result in ptosis, generalized muscle weakness and paralysis of respiratory muscle leading to aspiration pneumonia. Clinical cases of iatrogenic botulism after BoNT injection were reported in 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 (if applicable) and parent(s) should be advised to seek immediate medical care if symptoms such as swallowing difficulties, speech or breathing problems occur. Subjects (if applicable) and parent(s) will receive a subject card with contact information in case of emergency (see Section 3.3.3) should additional information on the scope of the study be required.

In case of an overdose the subject must be medically monitored for several days. If signs of intoxication appear, hospitalization with general supportive measures is necessary. Intubation and assisted ventilation may become necessary 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 is to be recorded. It is to include a detailed list of all medications (including rescue medication) that the subject took during at least the four weeks (for *Botulinum* toxin preparations, one year) up to the date of screening. The record is to 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, and it must later be completed to show whether 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 impact on study results, e.g. salivary-gland surgery.

For details of medications prohibited at/before screening, see the exclusion criteria (Section 7.3).

The following medications are forbidden, or their intake is restricted, during the study:

- *Botulinum* toxin during the screening period and the entire year before screening.
- *Botulinum* toxin (other than the study treatment) at (or planned for) any time during the entire study period.
- Concomitant medication known to cause strong hypersalivation (e.g. clozapine).
- Concomitant use of aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function and of anticoagulants (however aspirin and platelet aggregation inhibitors are allowed)
- Pharmacological treatment for sialorrhea or concomitant medication known to influence sialorrhea strongly (e.g. anticholinergics; with exception of locally applied or short acting drugs used under general anesthesia) within 45 days before baseline and during the entire study period.

The following non-drug therapies are forbidden to be planned during the study:

- Salivary gland surgery or irradiation during the entire study period (including the screening period).
- Surgery (except minor surgeries not affecting the head-neck region) in any indication in the three months before screening, during the screening period or planned for any time during the main study period.

Hyposalivation or dry mouth – as a possible temporary consequence of the study treatment – can be eased by sialogogues such as ice chips or cold water. The use of sugar-free chewing gums or sour sugar-free sweets is also considered suitable for reducing a sensation of dry mouth. Furthermore, for a purely symptomatic treatment of hyposalivation a wide range of saliva substitutes are available on market, including sprays, gels and mouth rinses. It is recommended to use those agents to diminish symptoms of dry mouth temporarily. Saliva substitutes mostly contain carboxymethylcellulose, xanthan gum or mucins. Oxygenated glyceroltriester-based saliva substitute sprays seem to be also effective improving symptoms of xerostomia. The dental association of Baden-Württemberg, Germany, recommends two saliva substitutes: Glandosane® (Cell Pharm GmbH, Bad Vilbel, Germany) for edentulous patients (it is based on carboxymethylcellulose) and Dry Mouth Gel® (GC Europe, Leuven, Belgium) for dentulous patients (as it has a neutral pH value and is based on diglycerine). Subjects with dry mouth should be advised to try some saliva substitutes and should choose one agent according to their preference and to avoid the use of such substances before or during saliva collection as specified in Appendix 16.3.1.

Therapy changes (including changes of regimen) during the study are to be documented in the subject's file and in the eCRF. All concomitant medications administered in connection with adverse events are to be recorded.

8.4 Restrictions during the study

The following life-style behavior patterns are forbidden during the study:

– All recreational drugs (i.e., the use of any illegal drugs, or the use of legal drugs for recreational purposes).
– Smoking and the consumption of alcoholic drinks are prohibited during the study.

For restrictions on concomitant medications and other forms of treatment, see Section 8.3.

8.5 Blinding

The main period of the study will be conducted in a double-blind fashion. All vials containing study medication (active or placebo) will have the same appearance. The identity of individual IP will remain unknown to the investigator, medical staff, all subjects, their caregivers and other study staff (excluding the external unblinded biostatistician). All other individuals involved in the study (e.g. clinical study manager, medical expert, study biostatistician) will remain blinded.

An independent DMC will assess subject safety data throughout the study (see Section 12.4.7.3). Special care will be exercised in the selection of DMC members in order to safeguard the study team from unblinding. Procedures for the evaluation of safety data and unblinding will be documented in writing. Details of DMC members and the committee's charter are provided separately.

8.5.1 Emergency envelopes

The [redacted] computer randomization program (see Section 8.2.1) also will be used to prepare a complete set of sealed emergency envelopes. In an emergency, these envelopes will allow unblinding of the treatment received by an individual subject while maintaining the overall study blind. The set of envelopes will be sent to [redacted], Germany) to be kept there for emergency unblinding if necessary.

At the end of the study, all emergency envelopes are to be returned to the sponsor's quality management department. Any opened emergency envelope must be returned bearing the date and reason for opening.

Any other emergency unblinding will be done through the IWRS.

8.5.2 Unblinding procedures

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

The DMC will be semi-blinded with respect to treatment group comparisons based on frequency tables ("semi-blinded" means here that tables will only contain labeled treatment-group information such as "Treatment A" and "Treatment B"). Subject data

listings will not contain any treatment-group information; thus, the DMC will remain blinded in respect of the treatment administered to individual subjects. To ensure blinding of the sponsor's study-team members and of the staff at the sites, these persons will not participate in the closed sessions of the DMC meetings and will not have access to the semi-blinded data prepared for the DMC. An electronic version of the semi-blinded treatment allocation ("Treatment A" and "Treatment B") will be transferred from the randomization officer to the DMC biostatistician, who will be responsible for the preparation of the tables and listings for the DMC meetings and will not be part of the study team. The DMC may require knowing the actual treatment for single subjects in order to evaluate the safety information of AESIs and SAEs received from the study to early identify signals and to give advice. The biostatistician of the DMC will also receive IWRS access and a password enabling him/her to break the blinding code of subjects via this system. The DMC biostatistician is responsible for the safekeeping of the password. If safety concerns arise that require the unblinding of a subject by the DMC, then the DMC should confer with Merz before performing unblinding of the subject by IWRS. Detailed procedures for unblinding in any case of safety concern are laid down in the DMC charter.

The investigator will remain blinded throughout the study except in cases where unblinding is required: In the event of an SAE that requires further therapeutic decisions depending on the knowledge of the treatment group, the investigator will use the IWRS for unblinding. The sponsor will be notified through the IWRS. Additionally, the Corporate Product Safety department will be able to unblind subjects by means of the IWRS.

Furthermore, PharmOlam will also receive IWRS access and a password for regulatory unblinding for reporting suspected unexpected serious adverse reactions to regulatory authorities and IEC(s)/IRB(s).

9 STUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 Assessments

9.1.1 Clinical evaluations

9.1.1.1 General assessments and screening

After consent and assent has been obtained, at the screening visit the subject's demographic data, medical history and all previous (i.e., administered within the past year for BoNT products or 45 days for all other medications), current and concomitant medications and treatments planned during the study will be recorded (see Section 8.3). A review of this information will aid the investigator in assessing whether the subject should be enrolled. Other data will be collected as required, including information obtained from a physical examination (which must include the chest, to ensure there is no previous evidence of aspiration), a neurological examination and vital signs (see below). For children suffering of cerebral palsy (CP) the severity of CP will be assessed by the Gross Motor Function Classification System (GMFCS) at baseline. Dental examination by a dentist needs to be performed during the screening period (allowing the investigator to review the dental examination report and dental exclusion criteria at baseline visit the latest). Counseling of parents and subjects may take place according to need and mental capacity, at the investigator's discretion. In case if the subject is not eligible (due to any temporarily limited condition e.g. short term infection of airways) at the baseline visit he/she will be considered to fail screening. Rescreening of this particular subject is allowed to be performed subsequently to the resolution of the temporary condition. In this case a new screening number needs to be generated and all screening assessments need to be he repeated.

The following vital signs will be examined as scheduled in the overview of study activities (Table 6): heart rate and systolic and diastolic blood pressure (after 5 min. in a recumbent position); temperature. Body height will be measured with a stadiometer, and body weight (with the subject in underwear and not wearing shoes) will also be measured.

9.1.1.2 Efficacy assessments

The following efficacy assessments will be used to compare the efficacy of the active treatment (NT 201) with that of placebo. Details of these assessments are given in the appendices to this protocol Appendix 16.3.

- Unstimulated salivary flow rate [uSFR] (weighing of two absorptive swabs soaked with saliva over five minutes; procedure repeated once after 30 minutes [±5 minutes]) for all randomized subjects.

- Global Impression of Change Scale [GICS] of functioning as a result of treatment from last injection on a 7-point scale by carer/parent(s) and subject in a combined rating.
- [redacted]
- [redacted]
- [redacted]

9.1.1.3 Safety assessments

The following assessments will be used to assess the safety of the study treatment:

- Adverse events [AEs] including e.g. adverse events of special interest [AESIs] (see also Section 10.3.) and serious adverse events [SAEs].
- Vital signs (blood pressure, heart rate, body temperature).
- Body weight, height.
- Clinical chemistry and hematology as possible for the age group of the child/adolescent (for details see Section 9.1.2).
- Urinary pregnancy test (in female subjects >12 years of age or with a history of menarche, i.e. the first menstrual bleeding only) prior to every injection session and at the end-of-study visit.
- Dental and oral examination by a dentist during the screening period until baseline, in Week 4, at the final visit of the main period V6 (Week 16), at V10 and the end-of-study visit, in terms of adverse events: findings indicating a worsening of the subject's dental / oral condition since screening/baseline are to be recorded as adverse events (Appendix 16.4).

Each subject will be observed at the investigation site by the site personal and supervised by a physician for at least two hours after administration of the injections, to detect and control any bleeding, pain, swelling or other adverse events resulting from the injections into the salivary glands and any side effects of the applied analgesia or sedation.

- Emergency pediatric equipment and fast access to pediatric intensive-care facilities must be available in the event of an adverse reaction related to study drug administration, sedation or general anesthetic. Latently developing iatrogenic botulism due to toxin spread needs to be treated in a pediatric intensive-care facility.

To monitor potential spread of toxin, subjects, carer and parent(s) (as appropriate) will be actively questioned about the occurrence of AESIs at every visit after every injection session of investigational product (for details see Section 10.3). AESIs are to be reported to the responsible CRO within 24 hours (see reporting procedure in Section 10.2). Any adult responsible for the child's care will be given (a) contact card(s) with emergency instructions for the prompt reporting of adverse events.

All subjects for whom AEs are reported, whether these are considered related to the use of investigational product or not, will be monitored carefully until the AE has resolved or stabilized, or until the final visit of this study (i.e. 16 weeks after the last injection of the IP).

9.1.2 Laboratory evaluations

9.1.2.1 Clinical and research laboratory evaluations

Blood and urine will be sampled for standard laboratory assessments and for antibodies against BoNT according to the schedule set out in Table 6. For hematological measurements 1.2 mL blood will be drawn into an EDTA tube, for clinico-chemical assessments 1.2 mL blood will be drawn into a serum tube and for antibodies against BoNT testing 19.9 mL blood will be drawn into 3 serum tubes for subjects ≥30 kg BW. The total blood volume required for this study will be 47.0 mL over 72 weeks (details in Table 5 and Section 9.1.6).

In order to minimize distress and bruising, only qualified staff, experienced in pediatric venipuncture, will perform the blood draw as follows:

- All children will be offered local anesthesia (e.g., using lidocaine plaster such as EMLA or lidocaine or Ametop cream).
- Children will always have a loved one present to comfort them (if they want) and be distracted during the blood sampling as necessary.
- Depending on IEC/IRB advice and local rules, we suggest that only two attempts should be made for research-only sampling. Should the participant become acutely and inconsolably distressed during or before the blood draw the procedure must stop immediately and the subject must be withdrawn from the sampling.
- Blood samples will be kept to a minimum, particularly for the younger children.

9.1.2.2 Clinical chemistry, hematology and pregnancy tests

Safety laboratory assessments will include the values listed in Table 4 below.

Table 4: Standard safety laboratory values

Clinical Chemistry:	Alanine aminotransferase	Glucose
	Albumin	γ-Glutamyltransferase
	Alkaline phosphatase	Lipase
	Amylase, total *	Potassium
	Aspartate aminotransferase	Protein total
	Bilirubin, total †	Sodium
	Calcium	Triglycerides
	Chloride	Thyroid-stimulating hormone
	Cholesterol, total	Urea / Blood urea nitrogen
	Creatine kinase	Uric acid
	Creatinine	
Hematology:	Hematocrit, hemoglobin, red blood cell count and derived parameter (MCH, MCV, MCHC)	
	White blood cell count	
	Differential count (automated count, percentage and absolute; manual count, percentage)	
	Platelet count	
Pregnancy test:	β-HCG Human chorionic gonadotropin, beta form (in females of child-bearing potential only) in urine (at visits where pregnancy testing is specified).	

* If total amylase is elevated, then pancreatic amylase will also be measured

† If total bilirubin is increased, then indirect bilirubin will also be measured.

9.1.2.3 Antibodies against Botulinum toxin

To detect antibodies against *Botulinum* toxin in study subjects the fluorescence immunoassay [FIA] and the hemidiaphragm assay [HDA] will be used.

Blood will be sampled for analysis of antibodies against BoNT for subjects with ≥30 kg BW. For children with <30 kg BW no blood samples for analysis of antibodies against BoNT will be taken. Blood amounts will be taken according to the weight group of the subject in context of all blood withdrawals during the study (Section 9.1.7). For subjects with ≥30 kg BW first blood samples are taken at baseline (V2). Subsequent antibody tests after repeated IP exposure will be performed for subjects with ≥30 kg BW only at the end-of-study visit (V18; alternatively, if preferred, at V17).

The serum amount necessary for FIA-AB is 1.5 mL and 4.5 mL for HDA. To yield the required serum amount the estimated blood amount is 4.9 mL for FIA-AB and 15 mL (2x7.5 mL) for HDA. Sample work-up at the study site includes preparation of serum by centrifugation at room temperature and transfer into provided tubes. Serum samples should preferably be stored at -20°C (±5°C) but must be within a range of -5°C to -90°C until frozen shipment to the analyzing laboratory.

Blood samples will be screened using the FIA-AB that detects antibodies against BoNT A in human serum. FIA-AB detects binding to specific BoNT epitopes and allows the identification of sera that react with the toxin, but the FIA-AB is not capable to discriminate between neutralizing and non-neutralizing antibodies [Goschel 1997].

Samples that are positive in the FIA-AB will be tested using the validated mouse ex vivo HDA. The HDA is the most sensitive functional assay (sensitivity <0.5 mU/mL) currently available [Sesardic 2004]. To spare animals, the assay is performed only if the FIA-AB is positive.

9.1.3 Pharmacodynamics

Not applicable.

9.1.4 Pharmacokinetics

Not applicable.

9.1.5 Pharmacogenetics

Not applicable.

9.1.6 Table of blood volume

Blood samples will be taken for general safety testing (hematological and clinico-chemical assessments) and also for additional measurements of antibodies against BoNT.

Laboratory evaluations will be performed as possible for the age group of the subject. The bulletin of the World Health Organization published a recent literature review on the blood sample volumes in child health research [Howie 2011]. The author concludes that blood sample volume limits ranging from 1–5% of total blood volume [TBV] within 24 hours and up to 10% of total blood volume over eight weeks were consistent with minimal risk to healthy children as far as limited evidence available may support any risk evaluation. However, lower limits for sick children seem advisable.

Per individual, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80–90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight [European Medicines Agency (EMA) 2008].

In this study, the lower limits mentioned for relevant age groups and weight classes in literature [European Medicines Agency (EMA) 2008] will be applied. Blood sample collection for clinical chemistry and hematology will be restricted in frequency and

volume. Limits will be set by the following assumption on the TBV and restrictions on maximum blood volumes withdrawn per time period:

TBV= 80 mL/kg body weight

Maximum blood volume in any withdrawal: 1% of TBV

Maximum blood volume over 12 weeks: 3% of TBV

A central laboratory capable of handling properly the relatively smaller volumes of samples (as compared to those usually obtained from adult subjects) will perform the analyses.

The following blood volumes are necessary to result in sufficient serum volumes for the respective tests:

- Hematology (EDTA tube): 1.2 mL
- Clinical chemistry (serum tube): 1.2 mL
- Fluorescence immunoassay [FIA]: 4.9 mL blood (1.5 mL serum)
- Hemidiaphragm assay [HDA]: 15.0 mL blood(4.5 mL serum)

Note that for clinical chemistry the same procedure for blood sampling is always to be followed, irrespective of which laboratory values are to be measured at the visit in question. Details of the procedures, including possible local anesthesia, are given in Section 9.1.2

Table 5 shows the maximum amounts of blood that will be required and the calculated maximum total amount of blood to be drawn during the study.

Table 5: Blood volumes required

Visit	Blood volume withdrawn		
	Hematology *	Clinical chemistry †	Antibody tests†#
Screening	1.2 ml	1.2 ml	
Visit 2			19.9 ml
Visit 6	1.2 ml	1.2 ml	
Visit 18	1.2 ml	1.2 ml	19.9 ml
Total volume drawn:	7.2 ml (47.0 ml#)		

* To be collected in an EDTA tube (Section 9.1.2). † To be collected in a serum tube (Section 9.1.2).
# Only for subjects with ≥ 30 kg BW (Section 9.1.2.3).

9.1.7 Specimen preparation, handling, storage, and shipping

This study does not involve the retention of any biological samples. The only samples taken will be blood and urine for safety testing (the latter for on-site pregnancy tests only). These will be analyzed at the central laboratory without retention of material.

9.2 Visit schedule

The purpose of the screening visit is to determine the subject's eligibility for study participation. The subject will be notified of any new diagnosis of an abnormal medical condition during the screening process, and will be referred for appropriate care. The screening evaluation must be completed 7–28 days (Table 6) before the baseline visit.

The baseline visit, at which the final decision on inclusion, the randomization (subjects aged 6–17 years only) of the subject and the administration of the first study treatment are performed, is defined as Day 1.

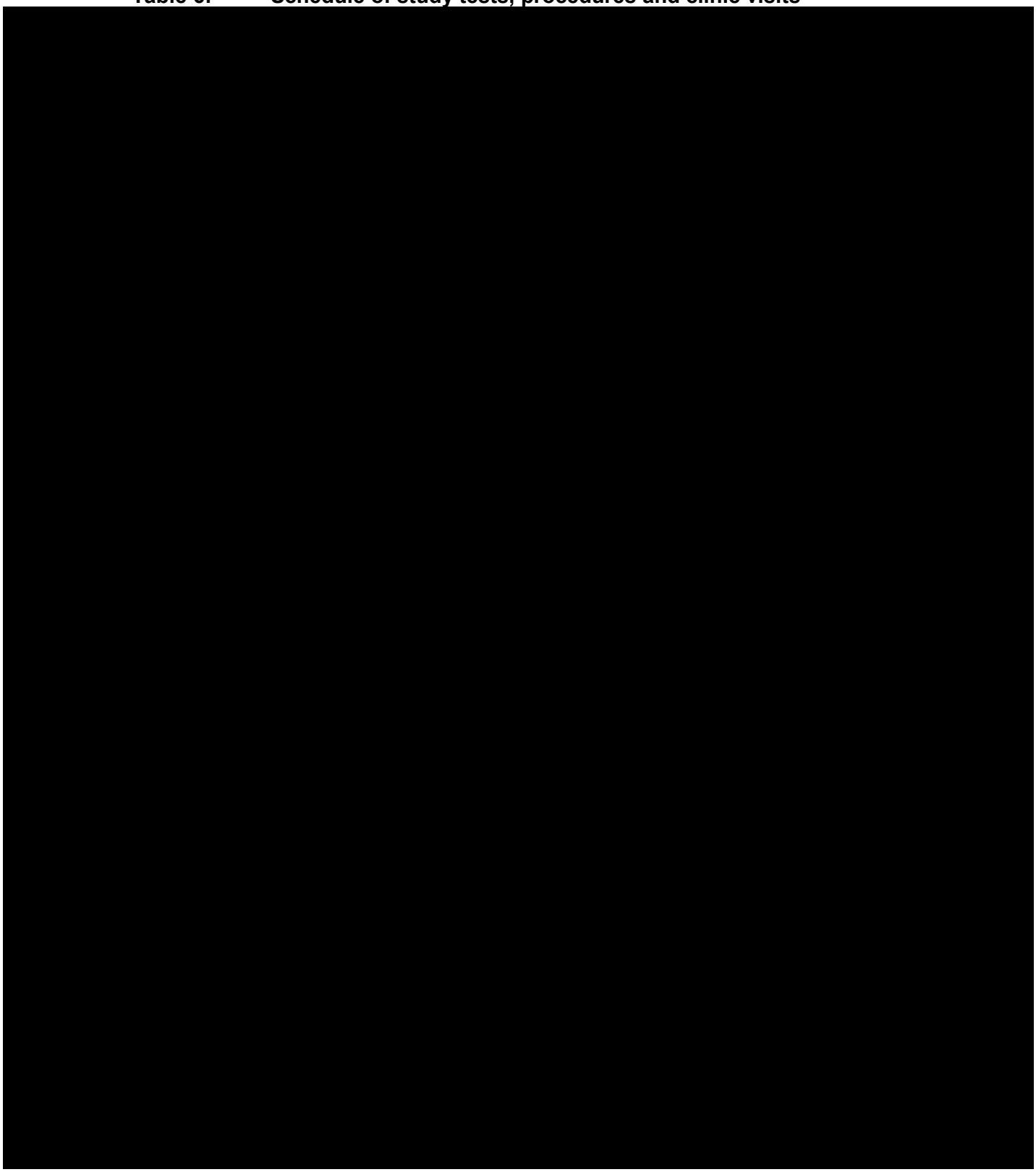
During the study, subjects will receive NT 201 (or, in the main period, matching placebo [subjects aged 6–17 years only]) at the beginning of each 16-week injection cycle. The visit schedules with study activities are shown in Table 6. For each study visit a time window is allowed, as detailed in Table 6 and described in Section 6.1.2.

The final study visit will take place after a total of 64 ± 8 weeks, at the end of the fourth injection cycle. Since this will be as long as 16 ± 2 weeks after the last administration of NT 201, no further visit for safety follow-up is planned.

At the physician's discretion, the final visit of each study injection cycle can be advanced by up to two weeks (e.g., if the physician considers earlier repeated treatment/assessment to be advisable) or postponed by up to two weeks (in the converse situation).

Unscheduled visits may be required in the case of premature discontinuation of study treatment. In this case, a final assessment (the end-of-study visit) will be performed. 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.

Table 6: Schedule of study tests, procedures and clinic visits



[redacted]

10 SAFETY ASSESSMENTS

10.1 Definition of an adverse event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that 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 and/or study treatment.

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 AEs extends from the time when the informed consent form was signed until the subject's final study visit. Any medical occurrence between the time when the informed consent form is signed and the first intake of study medication is an AE and has to be documented in the subject's file and in the eCRF AE report form.

Non-serious AEs will not be followed up after the final study visit (i.e., 16 ± 2 weeks after the last administration of NT 201), which will take place after a total of 64 ± 8 weeks, at the end of the fourth injection cycle. In cases of study participation discontinuation the final visit takes place 16 ± 2 weeks after the last administration of NT 201, after which no further visit for safety follow-up is considered necessary (see Section 9.2).

Pre-existing conditions that do not worsen during the course of the study are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the subject at screening. Abnormal clinically relevant laboratory values obtained during the subject's screening period will only meet AE criteria if newly detected.

Incidental findings of abnormal laboratory values will be reported to the investigator immediately so that the subject can promptly be referred for treatment and care.

Data pertaining to AEs will be collected during each study visit based on the subject's spontaneous description, through investigator inquiry, or discovered in the course of examinations done during the visit. The investigator will assess and record any AE in detail in the subject file and on the eCRF AE report page. 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).
- Action taken with IP (see Section 10.1.3).
- Whether the AE led to discontinuation of the study (yes or no).
- Date of resolution (and time, if applicable).

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

In the case of an SAE or an AESI (alert term, as defined in Section 10.3), the investigator is also to complete an SAE report form or AESI report form and report the event to the sponsor immediately, as described in Section 10.2.

Conduct in the unlikely event of overdose with NT 201 is described in Section 8.2.6.

10.1.1 Definition of intensity

The clinical intensity of an AE will be classified as:

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 page). In such situations, the investigator should make a judgment based on personal experience.

10.1.2 Definition of causal relationship with investigational product

An AE is considered to be "related" to IP if a causal relationship between the IP 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 convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline). Otherwise, the relationship should be considered as "not related."

10.1.3 Categories of actions taken and outcome

Action taken with the IP:

- Drug withdrawn (no further study injections given).
- Dose reduced (at the next injection possible i.e. at V10a [injection cycle 3] or V14a [injection cycle 4] only, due to weight loss or AEs).
- Dose increased (at next injection visit i.e. at V10a or V14a only, according to weight gain of subject).
- Dose not changed.
- Unknown.
- Not applicable.
- Drug withdrawn temporarily (further study injections delayed).

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 attributed with 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.[3]
- Requires inpatient hospitalization, or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Consists of any other medically important condition.[4]

For this study the following may be considered important medical conditions: suicidal ideation (a response of "yes" to questions 4 or 5) or any suicidal behavior as indicated by the C-SSRS and confirmed by the Investigator or when reported based on other information by the Investigator.

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

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

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

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

The report must be delivered to the report assessing site of the CRO listed below.

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[3] 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.

[4] 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."

The address for SAE reporting is:

Company	[redacted]
Department	[redacted]
Street address	[redacted]
Postal code, city, country	[redacted], Serbia
Telephone:	[redacted]
Telefax:	[redacted]
E-mail:	[redacted]

The investigator must supply further supporting information within 3 days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information. Follow-up reports should 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 has 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 Corporate 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 the IP. These reports generally will not be entered into the study database.

10.3 Adverse events of special interest (alert terms)

All AEs of special interest (alert terms) that occur during the study period, whether considered to be related to IP(s) or not, must be reported by telephone, telefax, or secure e-mail within 24 hours of knowledge of the event (see contact details in Section 10.2.)

At each visit the investigator or a representative authorized by the investigator will ask actively the child/adolescent (if applicable) or his/her parent(s)/carer about the occurrence of AESIs.

For this study, the following AEs are defined as AESIs:

Table 7: List of AESIs

MedDRA Preferred Term (MedDRA version 15.1)		
Accommodation disorder	Eyelid ptosis	Peripheral nerve palsy
Areflexia	Facial paresis	Peripheral paralysis
Aspiration	Hemiparesis	Pelvic floor muscle weakness
Botulism	Hypoglossal nerve paresis	Pneumonia aspiration
Bradycardia	Hyporeflexia	Pupillary reflex impaired
Bulbar palsy	Hypotonia	Quadriparesis
Constipation	Ileus paralytic	Respiratory arrest
Cranial nerve palsies, multiple	Monoparesis	Respiratory depression
Cranial nerve paralysis	Muscular weakness	Respiratory failure
Diaphragmatic paralysis	IIIrd nerve paresis	Speech disorder
Diplopia	IVth nerve paresis	Trigeminal nerve paresis
Dysarthria	VIIth nerve paralysis	Urinary retention
Dysphagia	Paralysis	Vision blurred
Dysphonia	Paralysis flaccid	Vocal cord paralysis
Dyspnea	Paraparesis	Vocal cord paresis
Extraocular muscle paresis	Paresis	
Eyelid function disorder	Paresis cranial nerve	

In addition to the terms listed in Table 7, adverse event ‘dry mouth’ considered to be severe, serious or irreversible are also to be reported as AESIs.

10.4 Expected adverse events

Expected AEs are those listed in the current version of the Investigator’s Brochure [IB] for Xeomin®. It should be noted that intraglandular application of BoNT is not necessarily expected to lead to the same adverse events as application at other sites (e.g. intramuscular injection).

10.5 Unexpected adverse events

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

10.6 Pregnancy

Any pregnancy that starts during the study must be reported by the investigator to the CRO (see contact details in Section 10.2.) within 24 hours of learning of its occurrence. The pregnancy plan will include:

- Ensuring that the young person is treated with respect and confidentiality.
- Measures taken at site to ensure the physical and mental safety and well-being of the mother and baby; the mother will be referred for counseling as appropriate.
- The subject will be withdrawn from the study immediately (apart from end-of-study safety checks and assessments).
- She will receive no further study drug.
- Pregnancies and pregnancy follow-up are to be reported on a pregnancy monitoring form.
- With the explicit consent from the subject's parents or legal representative(s), which must be documented in the subject's medical records, pregnancy follow-up must 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.

Each pregnancy is to be reported as a non-serious AE (drug exposure before or during pregnancy) within 24 hours of knowledge as well.

10.7 Other safety assessments

A dental and oral examination will be performed by a qualified dental health provider (minimum qualification: dentist) at screening (V1), V3 and V6 of the main study period, at V10 and at the-end-of-study visit (V18), or at the subject's last study visit if this is earlier. Results of dental and oral examination will be reported in terms of adverse events: findings indicating a worsening of the subject's condition since screening are to be recorded as adverse events.

Details are given in Appendices 16.4.1.

As part of the physical examination, particular attention will be paid to lungs in order to detect any signs of aspiration, at baseline and every subsequent visit.

C-SSRS

Prospective monitoring of suicidality with the Columbia-Suicide Severity Rating Scale [C-SSRS] should be considered the most important (but not the only) source of information concerning suicidality.

Suicidality will be assessed prospectively in subjects at baseline and every scheduled and unscheduled post-baseline site visit. The appropriate version of this scale ensures the consistent application of this important measure regardless of indication or investigator experience with the subject matter. With C-SSRS in place, administration of this semi-structured clinician-based assessment scale is standardized. The C-SSRS quickly and efficiently identifies those subjects that require additional clinician follow-up.

Following versions of the C-SSRS are to be applied only for newly recruited patients:

1. Children's baseline / screening version

2. Children's since last visit version.

The C-SSRS interview should only be assessed with children of respective age and cognitive state. Clear age cut-offs for the C-SSRS were not defined by the authors, but it has been found that administration is possible in general for children with a developmental age of about 7 years. Otherwise it should be documented in the electronic Case Report Form (eCRF) that a child was not able to assess the C-SSRS at a respective visit.

The C-SSRS is based on the research and development at the Columbia University by Posner et al. [Posner 2007a] supported by Columbia-Classification Algorithm for Suicide Assessment (C-CASA) developed by the same group [Posner 2007b]. It is a semi-structured clinical interview consisting of domains of suicidal ideation, suicidal behavior and non-suicidal self-injurious behavior, and details of actual and potential lethality. It is designed for personal interview administration. Subjects or Parents/Caregivers are asked directly by a trained clinical assessor. Clinical assessment questions are presented, and subjects provide their responses. These responses enable the interviewer to branch to the appropriate follow-up questions, faithfully adhering to C-SSRS probing specifications and potential positive responses. This approach provides consistent assessment and documentation.

At the end of the assessment the subject should not be released from the study center until the results of the C-SSRS (positive or negative) are reviewed and the subject is not considered to be at risk. If there is doubt about whether a subject is at risk, the Investigator should obtain appropriate psychiatric consultation.

11 DATA QUALITY ASSURANCE

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of the 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.

The sponsor is also to be notified immediately of any inspection foreseen at third-party vendors (e.g. inspection of investigation sites or a CRO by national authorities).

11.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including – but not limited to – methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, and validation methods).

This study will be monitored regularly by a qualified monitor from the CRO according to GCP and ethical guidelines and the respective SOPs (see Section 11.4).

11.2 Source documentation requirements

All data collected from a subject during the course of a clinical study are to be entered and/or filed in the respective 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 primary physician being informed). The subject's file must also contain a descriptive statement on the informed consent procedure (see Section 3.3.2). The site will keep a source data location list which will outline for the different data categories (e.g. demographics, medical history, and adverse events etc.), including electronic data, which document serves as source for this data (e.g. subject file, laboratory report).

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

Study sites will use a sponsor-validated, web-based electronic case report form [eCRF], and study data will be entered on a secure on-line basis by authorized study-site personnel.

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 be

overlapping, 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, such as printing by sequential date order. 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 should also sign and date after verifying the source data. The paper print-out should be stored in the ISF. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initialed and dated. The same applies to corrections of any paper-based data.

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

11.3 Data management

Authorized members of the investigator's staff will enter the information required by the protocol into the web-based eCRFs (electronic data-capture [EDC] system [redacted]) provided by Merz Pharmaceuticals/[redacted] and developed by the data manager for the study.

All persons who are to enter data into the eCRF will be trained by using an e-learning tool and support from a member of the CRO if necessary. After the successful completion of the training, all participants will receive a training certificate. Access to the e-learning tool and to the eCRF will be password-controlled. Passwords must be kept securely and be individual to each member of staff, and must not be shared with or used by anyone else.

Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the site via the web-based eCRF; answers to queries or changes to the data will be documented in the eCRF directly by an authorized member of the investigator's staff. The audit trail in [redacted] documents all changes. Edit checks trigger automatic queries during data entry when a field is not populated according to the specifications set out in the data validation plan. Manual queries (to be answered by site staff) can be raised during source data verification or during medical, safety or data management review.

Laboratory data will be received electronically and merged with the eCRF data (but not uploaded into the EDC system). Plausibility checks will be performed to ensure correctness and completeness of these data. Abnormal results will be reported to the investigator in a timely manner for review and treatment if necessary to ensure the subject's well-being during the research.

The sponsor's data management function team will be responsible for data-processing, in accordance with the sponsor's data management procedures and all applicable laws. No identifiable data will be processed. After all data have been entered and all queries solved, the data base will be closed. After database closure, unblinding will take place. If

there are any changes to the data after data-base closure, these changes will be documented according to the relevant SOP.

The results of the semi-structured interview will be documented by using the paper version of the C-SSRS and the data will be entered into the eCRF. Plausibility checks will be performed to ensure correctness and completeness of these data.

11.4 Monitoring

This study will be monitored regularly by a qualified monitor from the CRO according to GCP guidelines and the respective SOPs. Monitoring procedures include one or more visits designed to clarify all prerequisites before the study commences. Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule. During these visits, the monitor will check for completion of the entries on all the eCRFs; for compliance with the clinical study protocol, ICH GCP principles, the Declaration of Helsinki, and regulatory authority requirements; for the integrity of the source data with the eCRF entries; and for subject eligibility. Monitoring also will be aimed at detecting any misconduct or fraud. Risk-based monitoring will not be used for this study because of the vulnerable nature of the study participants.

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 eCRF and subject files before each monitoring visit.
- Have the source documentation available at the monitoring visits.
- Record all IP dispensed in the eCRF and the drug inventory records.

All subjects who are screened, but not entered into the study, will be listed on the subject screening/enrollment log according to local confidentiality requirements – for example by initials and date of birth.

Further details of monitoring activities will be set forth in the monitoring manual.

11.5 Auditing

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance function team may arrange to visit the investigator in order to audit the performance of the study at the study site, as

well as all study documents originating there. Auditors conduct their work independently of the clinical study and its performance.

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

12 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study planning. Further details on the statistical and analytical aspects will be presented in the Statistical Analysis Plan [SAP].

Any deviations from planned analyses, the reasons for such deviation, 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.

Note that the groups of

- subjects in age group 6–17 years treated with active treatment or placebo
  and
- subjects in age group 2–5 years treated with active treatment only

will be analyzed separately.

12.1 Determination of sample size

A total of 249 subjects is planned to be enrolled. Of these, at least 219 children and adolescents are planned to be enrolled in the age group 6–17 years, which will form the population for the primary efficacy analysis. In the main period, this group of children/adolescents will be randomized with a randomization ratio of 2:1, i.e. 146 subjects will receive NT 201 and 73 subjects will receive placebo. At least 30 children in the youngest age group 2–5 years are planned to be enrolled and treated open-label with active treatment only.

[redacted]

12.1.1 Safety

Subjects in age group 6–17 years

To generate a database with long-term safety data large enough to fulfill the requirements set out in the ICH E1 guideline (at least 100 subjects treated over one year) and taking into account an anticipated drop-out rate [redacted] at least 144 subjects have to be included in the NT 201 group.

Subjects in age group 2–5 years

A total of 30 subjects in the youngest age group are assumed to be a sufficiently large database to generate a safety profile for this patient group.

12.1.2 Efficacy

Subjects in age group 6–17 years

The sample size of 219 subjects is sufficient to provide 95% power to detect a statistically significant difference in means of 1.0 point between active treatment-treated and placebo-treated subjects with a standard deviation of 1.93 points (two-sided *t* test, significance level $\alpha = 0.05$).

Subjects in age group 2–5 years

Since the primary efficacy analysis is based on the population of subjects aged 6–17 years, no formal sample size estimation is necessary for the subjects in the youngest age group (2–5 years) who all receive active treatment. Additionally, only the co-primary efficacy variable 'GICS four weeks after injection' is assessed in this population. Power calculations with respect to the GICS four weeks after injection show that the sample size of 30 subjects is sufficient to detect a GICS of ± 2.0 points as a statistically significant difference to a GICS of 0 points (no change) at Week 4 (V3) with a power of 95% by assuming a standard deviation of 2.94 points (two-sided *t* test, significance level $\alpha = 0.05$).

12.2 Analysis sets

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

Safety evaluation set MP

The safety evaluation set [SES] of the main period is the subset of all subjects who received study medication (NT 201 or placebo) during the main period of the study.

Full analysis set

The full analysis set [FAS] is identical to the subset of subjects in the SES (MP).

Per protocol set

The per protocol set [PPS] is the subset of subjects in the FAS aged 6-17 years without major deviations from this protocol. Major protocol deviations will be defined during the blind data review meeting at the end of this study.

For the OLEX period, the following analysis set is defined:

Safety evaluation set OLEX

The safety evaluation set [SES] of the OLEX period is the subset of all subjects who received study medication (NT 201) at least once during the OLEX period of the study.

12.3 Variables for analysis

12.3.1 Efficacy variables

12.3.1.1 Primary efficacy variables

The following variables will be defined as primary and co-primary efficacy variables for the subjects aged 6–17 years:

- Change in mean uSFR from baseline (V2) to V3 [Week 4]. The mean uSFR is calculated by averaging the two assessments at each visit.
- GICS at V3 [Week 4] representing the functional improvement in drooling since baseline as assessed by the carer/parent(s).

12.3.1.2 Secondary efficacy variables

The following secondary efficacy variables will be analyzed for the subjects aged 6–17 years:

- Change in mean uSFR from baseline (V2) to V4 and V5 [Week 8 and 12, respectively].
- GICS at V4 and V5 [Week 8 and 12, respectively].

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 variable

Occurrence of treatment emergent AEs [TEAEs] overall and by injection cycle.

12.3.5.2 Secondary safety variables

- Occurrence of treatment emergent AESIs [TEAESIs] overall and by injection cycle.
- Occurrence of treatment emergent SAEs [TESAEs] overall and by injection cycle.
- Occurrence of TEAEs related to treatment as assessed by the investigator overall and by injection cycle.
- Occurrence of TEAEs leading to discontinuation overall and by injection cycle.

12.3.5.3 Other safety variables

- The number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during treatment based on the C-SSRS.

12.3.6 Other variables

The following additional variables will be analyzed:

- Vital signs (blood pressure, heart rate, body temperature) at screening (V1), baseline (V2), V3 [week 4], V6 [week 16], during the main period and at each injection visit in the extension period and at the end-of-study visit (V18) [Week 64].
- Body height and weight at screening (V1), final visit of the main period (V6) [Week 16], and end-of-study visit (V18) [Week 64].
- BMI, calculated from body weight and height, at screening (V1), final visit of the main period (V6) [Week 16], and end-of-study visit (V18) [Week 64].
- Clinical chemistry (including alkaline phosphatase [AP] and blood glucose [BG]) and hematology at screening (V1), final visit of the main period V6 [Week 16], and end-of-study visit V18 [Week 64].
- GMFCS level at baseline (V2) for CP patients.
- Occurrence of antibodies against BoNT-A in subjects with ≥ 30 kg BW.

12.4 Statistical analysis methods

Full details of all analyses will be given in the SAP.

12.4.1 Efficacy variables

All efficacy analyses on data from the main period will be based primarily on the FAS and where deemed sensible additionally, for sensitivity purposes, on the PPS. Analyses on data from the extension period are based on the SES only. If not stated otherwise, analyses are performed by all age groups and treatments. 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 and descriptive p-values will be given, where appropriate.

12.4.1.1 Primary efficacy variables

The primary efficacy analysis will be performed on the group of subjects within the FAS aged 6–17 years. A mixed model repeated measurement analysis (MMRM, 2-sided, significance level alpha=0.05) with comparison of least square means between NT 201 and placebo will be used for the confirmatory analysis of the co-primary efficacy variables. The dependent variables will be the change in uSFR from baseline (V2) to V3 [Week 4] and the carer's/parent's GICS at V3 [Week 4], respectively. The independent variables are defined as treatment group, pooled investigation sites and age groups as fixed factors, visit*treatment as interaction term, and visit as repeated factor. To adjust for the baseline status, the MMRM of the uSFR change additionally includes the baseline score of the uSFR as covariate. Since no baseline assessment of the GICS is available, the baseline mTDS rated by the parent(s)/carer is used as covariate in the MMRM model for the GICS. Only if both co-primary efficacy variables show a statistically significant difference compared to placebo the superiority of NT 201 over placebo will be considered to be proven. Therefore, no α-adjustment for multiple testing is necessary.

Sensitivity analyses will be performed using the same approach on the PPS.

In order to investigate the impact of missing values and different approaches for handling of missing data, sensitivity analyses will be performed on the FAS (age 6-17 years) and on the PPS using the baseline observation carried forward approach (BOCF, no effect) for uSFR while imputing missing GICS entries at week 4 as “no change” and without missing replacement (observed case analysis). For this purpose the MMRM model as described above will be adapted as an analysis of covariance (ANCOVA) model without visit*treatment as interaction and without visit as repeated factor.

Furthermore, a non-parametric Wilcoxon rank-sum test will be performed as sensitivity analysis of the co-primary efficacy variables to investigate the impact of potential deviations from the assumption of normal distribution. The test will be performed for FAS (age 6-17 years) and PPS using observed cases as well as using BOCF for uSFR and imputing “no change” for GICS.

12.4.1.2 Secondary efficacy variables

Analyses of secondary efficacy variables are also based on the subjects within the FAS aged 6–17 years. The changes in uSFR from baseline (V2) to V4 and V5 [Week 8 and 12, respectively] and the GICS at V4 and V5 [Week 8 and 12, respectively] are analyzed analogously to the primary efficacy variables by means of a MMRM and ANCOVA with the analysis sets and methods to handle missing values as described in Section 12.4.1.1.

[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

The safety variables will be analyzed for the SES by using descriptive summary statistics, frequency tables, and shift tables where appropriate.

AEs will be coded according to the MedDRA version that is in effect when the study is initiated. Only TEAEs will be analyzed, which are defined as AEs with onset or worsening after the first administration of IP up to and including the end-of-study visit (V18 [Week 64]) or, for subjects leaving the study prematurely, up to last recorded contact with the subject within 64 weeks after first injection. Incidences will be calculated for TEAEs at the system organ class level and at the preferred term level and will be presented by treatment, by injection cycle and overall. Additionally, TEAEs will be analyzed by worst intensity and by outcome. Listings and, if appropriate, tables displaying incidences for TEAEs leading to discontinuation, serious TEAEs, TEAEs of special interest, and deaths will also be provided.

Laboratory evaluations and vital signs (values and changes from baseline) will be analyzed descriptively by treatment and screened for individual notable values and/or changes.

The number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during treatment based on the C-SSRS will be calculated and presented as proposed in the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0 (Finalized February 2013) [Mary E. Nilsson 2013], Table 1.

In addition, for all subjects the electronic text-string search as described in the article by Posner at al. [Posner 2007b] , section “Pharmaceutical company identification of possibly suicidal events” will be used to identify adverse events that could represent “possibly suicidal” events. Findings will be listed.

All analyses will be performed by age groups and treatment and additionally for the group of subjects of all ages (2-17) who received NT 201 in the respective treatment period (main or extension period).

12.4.6 Other variables

Subject dispositions, demographic data, and baseline characteristics will be presented by using standard descriptive statistics; no homogeneity tests will be performed. Demographic data will be summarized for all subjects in the SES, the FAS and the PPS. This will be done by age groups and treatment and for the SES additionally for the group of subjects of all ages (2-17) who received NT 201 in the respective treatment period (main or extension period). The remaining baseline data will be summarized descriptively for the FAS and the PPS only.

Frequencies of concomitant treatments will be given based on different ATC [Anatomic Therapeutic Chemical] code levels for the SES. Indications for concomitant therapies will not be coded and will only be listed. Medical history and concomitant diseases will be described on the basis of MedDRA system organ class and preferred term levels for the SES.

Occurrence of antibodies against BoNT-A in subjects with ≥ 30 kg BW will be analyzed descriptively (values and changes from baseline) and screened for individual notable values and/or changes.

12.4.7 Special statistical/analytical issues

12.4.7.1 Discontinuations and missing data

Reasons for premature discontinuation by a subject will be summarized descriptively and listed. Where the discontinuation was due to an adverse event, this will be included in the listing of adverse events, and such events will be included as a category in the summary of adverse events.

The analysis of the primary and secondary efficacy variables will be performed using a MMRM as well as using an ANCOVA based on observed cases and an ANCOVA with missing values replaced by the baseline value or “no change” (‘baseline observation carried forward approach’). By using all values of the dependent efficacy variable available in the timeframe underlying the MMRM, i.e. the main period, the MMRM reduces the influence of single missing values. The use of the ANCOVA model with missing values replaced by the baseline value is considered to be a conservative approach because if a comparable percentage of missing values is expected in both treatment groups (in the placebo group there may be more missing values due to lack of efficacy and in the verum group more due to adverse events) the replacement of missing values by the baseline value of the uSFR – or by ‘no change’ for the GICS – leads to a decrease in the difference of the observed treatment effects (see also Section 12.4.1.1).

If a subject is not able to answer (documented in the eCRF) then the result of the subject's GICS entry will be replaced by the result of the carer's GICS entry. If it is not documented in the eCRF that the subject is not able to answer then the subject's GICS entry will not be replaced by the carer's GICS entry.

12.4.7.2 Interim analyses

No interim analysis is planned for this study except from the analyses providing tables and listings for the DMC meetings.

12.4.7.3 Committees

An independent DMC will be assigned to monitor subjects' safety throughout the clinical course of the study (see Appendix 2, Section 16.2). It will consist of an odd number (e.g., three) of physicians who are suitably qualified and who have experience in analyzing pediatric clinical trial data, to allow majority decisions to be made. The primary purpose of the DMC is to safeguard subjects by monitoring AESIs, SAEs and AEs on a regular basis.

The DMC will meet at regular intervals, either physically or remotely by secure teleconference during the main and extension period to review safety data. They will decide upon and prioritize any safety issues and actions for the attention of the sponsor. The DMC is semi-blinded (see Section 8.5.2) with respect to treatment group comparisons based on frequency tables. Subject data listings will contain no treatment group information such that the DMC remains blinded with respect to individual subjects unless the treatment codes of individual subjects with AESIs, SAEs and AEs are unblinded for the DMC on request, by using the IWRS (see Section 8.5 for information on maintaining the study blind).

If considered necessary, the DMC will make recommendations regarding the timely management of subject withdrawals and/or measures for the study if there are relevant safety findings.

The DMC can make recommendations, if necessary, such as the following:

- Changes in study design (such as lowering the dose, additional telephone contacts etc.).
- Changes in timing of assessments.
- Implementation of additional safety measures.
- Unblinding of subjects if required for safety reasons.
- Prematurely discontinuing dosing in an age group.
- Prematurely discontinuing dosing in all age groups.
- Putting the study on hold.
- Stopping the study, as defined in Section 7.5.2.

For each DMC meeting, minutes will be taken by the responsible DMC coordinator/administrator of the CRO and reviewed by the DMC members before finalization.

Details of responsibilities and procedures to be followed by the DMC will be laid down in the DMC Charter.

A list of members of the committee and a copy of the committee's charter are provided separately and will be reviewed by the IEC/IRB.

12.4.7.4 Multiple comparisons/multiplicity

The overall hypothesis of no differences between treatment groups is only to be rejected if both treatment comparisons – based on the co-primary efficacy variables – yield a significant result, i.e. if for both tests the hypothesis of no difference between treatment groups can be rejected. Thus, no issue with respect to multiplicity arises and no α-adjustment is necessary.

Results of all other tests or confidence intervals are only descriptive; a confirmatory interpretation is not valid in this context.

12.4.7.5 Examination of subgroups

Subgroups analyses by age groups are planned. Further details and the definition of any further subgroup analyses will be provided in the SAP.

13 DATA HANDLING AND RECORD-KEEPING

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

13.1 Corrections to data

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

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

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

Entries in paper-based source documents must be made with a blue or black ballpoint pen and must be legible. Pencils may not be used. It is not allowed to erase or overwrite entries, or to use correction fluid or tape. The monitor is not allowed to make entries. If corrections in paper-based source documents are necessary, an authorized member of the investigator's staff will enter them in the following manner: the wrong entry will be crossed out, although it must remain legible, and the correct entry will be placed next to it. Corrections will be initialed, dated and, if necessary, explained (e.g. for corrections concerning adverse events or a co-primary variable).

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

13.2 Record-keeping

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

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

- Subject files including records of study specific assessments and of the results of dental assessments.

- Subject identification code list (i.e., provided by template to the investigator, along with the ISF, at the beginning of the study), which identifies the subject by number, name, and date of birth.

- A signed copy of the final clinical study protocol and any amendment.

- A DVD with eCRF data and any associated subject-related source data (or, where applicable, authorized copies of source data).

- Signed informed consent and assent 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 and most recent inspection accreditation.

- Copies of study supply receipt forms and drug inventory forms.

- Copies of all correspondence between the investigator and the monitor, and between the investigator and the sponsor.

- Copies of safety information reported during the study and submitted by the sponsor.

13.3 Destruction of study documents

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

14 PUBLICATION POLICY

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

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

The study will be registered and study results will be disclosed by the sponsor (or delegate) in one or more public clinical study registry(ies), according to national/international regulations and commitments of pharmaceutical industry associations. Study registration may include a list of the investigational sites, as applicable.

No publications of results will reveal the identity of any subject.

Note: A summary of the results may be required to be placed in the public domain, e.g., on the web sites of regulatory authorities.

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