TITLE PAGE

Prospective, multicenter, randomized, double-blind, parallel-group, dose-response study of three doses Xeomin® (incobotulinumtoxinA, NT 201) for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy

Development phase:	Phase 3
Study identifier **EudraCT Number** **IND Number**	MRZ60201_3072_1 2012-005496-14 110,686
Acronym:	**XARA** – Incobotulinumto**X**in**A** in a**R**m treatment in Cerebral P**A**lsy
Indication:	Upper limb spasticity or combined upper and lower limb spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy
Planned study period:	Start of recruitment: Jan-2014 End of study: Jan-2019
Investigational product(s):	NT 201, 100 Units, powder for solution for injection (active ingredient: NT 101, Botulinum neurotoxin type A free from complexing proteins, USAN: incobotulinumtoxinA)
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: [redacted] Biostatistician: [redacted] Clinical Project Manager: [redacted]

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SIGNATURE PAGE

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

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

[redacted]	May 17, 2016	[redacted]	
Clinical Project manager	Date	Signature	
[redacted]	April 22ND, 2016	[redacted]	
Medical expert	Date	Signature	
[redacted]	17 May 2016	[redacted]	
Biostatistician	Date	Signature	

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

[redacted]	5/9/16	[redacted]
Coordinating investigator	Date	Signature

STATEMENT OF COMPLIANCE

Investigational Site(s)

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

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

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate independent ethics committees/institutional review boards [IEC/IRB] before enrolling any subject in this study.
- Obtain informed consent [IC] for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements have been fulfilled.
- Permit study-related monitoring, audits, IEC/IRB review, regulatory inspections and cooperate with corresponding functions.
- Notify Study Sponsor as soon as possible after notification of potential Food and Drug Administration [FDA] audit.
- Notify the appropriate IEC/IRB on serious adverse events [SAE]s according to local requirements.
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
- Use the IP and all study materials only as specified in the clinical study protocol.
- Report to the responsible drug safety officer, within 24 hours, any adverse that is serious [SAE], whether considered treatment-related or not as well as any adverse event of special interest [AESI] (see Section 10.3 for definition).
- For US sites: Prior to initiating the study, I will provide the sponsor with a written disclosure information including a written disclosure of any financial interest in accordance with 21 CFR Part 54 and a signed FDA 1572 form according to 21 CFR Part 312.

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 Pharmaceuticals GmbH and – as applicable – of the appropriate IEC/IRB and regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to Merz Pharmaceuticals GmbH.
- Any deviation from the clinical study protocol may lead to early termination of the study site.

Principal investigator	Date	Signature
		Print Name
Investigator	Date	Signature
		Print Name

Investigational site stamp (if applicable):

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AS	Ashworth Scale
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BDRM	Blind data review meeting
BMI	Body mass index
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin type A
BW	Body weight
C	Celsius
[redacted]	[redacted]
CP	Cerebral palsy
CRF	Case report form
CRO	Contract research organization
Ctrl.	Control
DMC	Data monitoring committee
DVP	Data validation plan
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EMG	Electromyography
EOC	End of cycle
EOS	End of study
e-stim	Electrical stimulation
EudraCT	European clinical trial database
F	Fahrenheit
FAS	Full analysis set
FDA	Food and Drug Administration, US
FIA	Fluorescence immunoassay

FIA-AB	Fluorescence immunoassay detecting antibodies
GCP	Good clinical practice
GICS	Global Impression of Change Scales
GMFCS	Gross Motor Function Classification System
Guardian	Person different from parent(s) who legally represents the child/adolescent
HDA	Hemidiaphragm assay
IB	Investigator's brochure
IC	Informed consent
ICH	International Conference on Harmonization
IEC	Independent ethics committee
i m.	Intramuscular
IND	Investigational new drug
IP	Investigational product
IRB	Institutional review board
ISF	Investigator's site file
IV/WRS	Interactive voice (web) response system
LD_{50}U	Lethal Dose 50 (LD_{50}) Units in animal studies
LL	Lower limb
LOCF	Last observation carried forward principle
MAS	modified Ashworth Score
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMRM	Mixed model repeated measurement
MP	Main period
MRZ	Merz
N	Number of non-missing observations
OC	Observed case
OLEX	Open-label-extension period
PBO	Placebo
PI	Principal investigator
PMC	Post Marketing Commitment (US FDA)
PPS	Per protocol set
QPS	Questionnaire on Pain caused by Spasticity
s	Second
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SES	Safety evaluation set
SOP	Standard operating procedure
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
SV	Safety Visit
TBV	Total blood volume
TEAE	Treatment emergent adverse event
TEAESI	Treatment emergent adverse event if special interest
TESAE	Treatment emergent serious adverse event
U	Unit
UL	Upper limb
UMNS	Upper motor neuron syndrome
US	United States
USAN	United States Adopted Name
V	Visit
WHO	World Health Organization
Wk	Week

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1 SYNOPSIS

Study title

Prospective, multicenter, randomized, double-blind, parallel-group, dose-response study of three doses Xeomin® (incobotulinumtoxinA, NT 201) for the treatment of upper limb spasticity alone or combined upper and lower limb spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy.

Study phase

Phase 3

Indication

Upper limb [UL] or combined UL and lower limb [LL] spasticity in children and adolescents (age 2 - 17 years) with cerebral palsy [CP].

Study objectives

To investigate efficacy and safety of Xeomin® (incobotulinumtoxinA, NT 201) in subjects[1] with UL spasticity alone or with combined UL and LL spasticity due to CP with a 1st double-blind cycle, the main period [MP], and three subsequent treatment cycles, the open-label extension period [OLEX]. Injection treatments in MP and OLEX will be followed by 12-16 weeks observation each.

During MP, in a three arm, parallel-group double-blind design subjects will receive one of three fixed doses of Xeomin® per treated UL.

- In the high dose group 8 Units [U] per kg body weight [BW] NT 201 (maximum dose per UL: 200 Units for subjects ≥25kg BW).
- In the mid dose group 6 U/kg BW (maximum of 150 U) per UL.
- In the low dose group 2 U/kg BW (maximum of 50 U) per UL.

As clinically needed, UL treatment can be administered uni- or bilaterally with doses as outlined above for each treated UL.

Subjects may receive additional BoNT injections in one out of five predefined treatment combinations up to the maximum total dose applicable for their GMFCS level (I-III: 20 U/kg BW NT 201, maximum of 500 U; IV and V: 16 U/kg BW NT 201, maximum of 400 U).

After completion of MP, all eligible subjects will continue treatment in OLEX with NT 201 doses as in the high dose group of MP.

[1] Subjects eligible for this study are children (age 2-11 years) and adolescents (age 12-17 years inclusive).

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

Subjects who meet the following main inclusion criteria:

- Female or male subject of 2 to 17 years of age (inclusive).
- Uni- or bilateral CP with clinical need for injections with NT 201 for the treatment of UL spasticity at least unilaterally.
- Ashworth Scale [AS] score in the main clinical target patterns in this study:
  - Flexed elbow: AS≥2 in elbow flexors (at least unilaterally).

  and/or

  - Flexed Wrist: AS≥2 in wrist flexors (at least unilaterally).
- Clinical need according to the judgment of the investigator in one out of five treatment combinations (A-E, as shown below).
  AS score must be ≥2 for each target pattern chosen for injection at the Baseline Injection Visit V2.

A. UL(s) treatment **only** (GMFCS I-V):

Unilateral treatment of UL spasticity with

8 U/kg BW NT 201 (maximum of 200 U) for[2]:

1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW).

and

2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

or

Bilateral treatment of UL spasticity with

Equal doses of **8** U/kg BW NT 201 (maximum of 200 U) **to each UL.**

Dose per UL must be distributed between:

1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW).

and

[2] Maximum total body doses in this study protocol refer to subjects with BW ≥ 25kg. In subjects < 25kg doses will be adjusted to BW (see Appendix 16.4).

2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

B. Unilateral UL and unilateral LL treatment (GMFCS I-V):

Unilateral treatment of UL spasticity with

8 U/kg BW NT 201 (maximum of 200 U) for[2]:

1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW).

and

2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

plus

Ipsilateral unilateral treatment of LL spasticity with

8 U/kg BW NT 201 (maximum of 200 U). Dose to LL must be distributed to at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe as clinically needed.

C. Unilateral UL and bilateral LL treatment (GMFCS I-III)

Unilateral treatment of UL spasticity with

8 U/kg BW NT 201 (maximum of 200 U) for[2]:

1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW).

and

2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

plus

Bilateral treatment of LL spasticity with

12 U/kg BW (maximum of 300 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

D. Unilateral UL and bilateral LL treatment (GMFCS IV and V)

Unilateral treatment of UL spasticity with

8 U/kg BW NT 201 (maximum of 200 U) for[2]:

1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW).

and

2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

plus

Bilateral treatment of LL spasticity with

8 U/kg BW (maximum of 200 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

E. Bilateral UL treatment and bilateral LL treatment (GMFCS I-III)

Bilateral treatment of UL spasticity with

Equal doses of **8** U/kg BW NT 201 (maximum of 200 U) **to each UL**

Dose per UL must be distributed between

1. at least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW)

and

2. additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

plus

Bilateral treatment of LL spasticity with

4 U/kg BW (maximum of 100 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

Treatment-naïve subjects or pre-treated (non-naïve) subjects may enter the study. Treatment-naïve subjects will be defined as individuals who have not received any BoNT treatment within the last 12 months before study injections for treatment of limb spasticity.

Main exclusion criterion:

Pre-treated (non-naïve) subjects must not have received BoNT treatment within the last 14 weeks prior to the Screening Visit (V1) in any indication.

Study design

Prospective, multicenter, multi-national phase 3 study including a double-blind, parallel-group dose-response MP and a subsequent OLEX.

MP: Randomized, double-blind, parallel-group, three arm, dose-response design. Subjects will receive uni- or bilateral UL injections alone or additional uni- or bilateral LL injection treatment as clinically needed and as allowed up to the maximum total body dose (for details see below). Judgment on clinical need will be based on treatment doses in the high dose group. In the mid dose and in the low dose group dose(s) to UL(s) and LL(s) will uniformly be reduced to 75% (mid dose) and 25% (low dose) of doses administered in the high-dose group.

OLEX: Open-label, non-controlled, repeated-dose design.

All subjects will receive doses for uni- or bilateral UL injection treatment alone or additional uni- or bilateral LL injection treatment as clinically needed and as allowed up to the maximum total body dose of the high dose group of MP (for details see below).

All subjects in this study will receive at least uni- or bilateral treatment of UL(s) spasticity with fixed doses per limb:

The double-blind treatment period will consist of one injection session in three dose groups with a subsequent 14 ± 2 weeks observation period. The treatment dose per UL will be fixed per dose group.

In the high dose group 8 U/kg BW NT 201 (maximum of 200 U) will be injected per treated UL.

In the mid dose group 6 U/kg BW NT 201 (maximum of 150 U) will be injected per treated UL.

In the low dose group 2 U/kg BW NT 201 (maximum of 50 U) will be injected per treated UL.

Treatment of additional limbs up to maximum total body dose:

Depending on the individual distribution of spasticity, subjects may have an additional clinical need for injections to LL(s). Thus, even with fixed doses per UL, the total body

dose may vary from 8 U/kg BW NT 201 (maximum of 200 U for subjects ≥ 25kg BW) in subjects with unilateral UL injections only to 20 U/kg BW NT 201 (maximum of 500 U for subjects with BW ≥ 25 kg), e.g. in subjects with unilateral UL plus bilateral LL injections in GMFCS level I-III. For details on the five allowed treatment combinations (A-E) in this study and the distribution of total body dose in each of the treatment combination see also Section 8.1.1.2).

Subjects showing clinical need for reinjection with IP between 12 to 16 weeks after the baseline injection visit in MP will continue treatment in OLEX with three injection sessions with injection intervals of 14±2 weeks in the same treatment combination chosen in MP but in injection doses of the high dose group of MP. The maximum total dose per injection session in OLEX is 500 U of NT 201 for subjects ≥25kg BW and of GMFCS level I-III (see details on dose below and in Section 8.1.1.2).

A data monitoring committee [DMC] for the safeguard of subjects will monitor and assess adverse events [AEs], AEs of special interest [AESIs] and SAEs occurring after the injection treatment.

Planned study period

Start of recruitment: Jan-2014

End of study (last subject last visit): Jan-2019

Duration of treatment per subject

The regular duration of study participation for subjects will be 50 to 66 weeks consisting of a screening period of 2 weeks followed by an observation period with 4 treatment cycles of 12 to 16 weeks each (total treatment period of 48 to 64 weeks).
Subjects not showing a clinical need for reinjection until 16 weeks after the baseline visit will end study participation after the final visit of MP without reinjection.

Variables for analysis

Primary efficacy variable (MP only):

- Change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4) of MP.
  An IV/WRS will be used for selection and randomization to treatment groups in MP, if two main clinical target patterns would qualify for primary efficacy analysis based on (for further details see Section 8.2.1)
  (a) clinical need for IP injection in combination with
  (b) an AS score of ≥2.
  The other main clinical target pattern (if treated) will be analyzed as key secondary variable (see below). For subjects with bilateral UL treatment, the body side for analysis will be decided by the investigator at screening (for details see Section 8.2.1).

Co-primary efficacy variable (MP only):

- Investigator's Global Impression of Change Scale [GICS] at Day 29 (Week 4) of MP.

Key-secondary efficacy variables (MP only):

- Change from baseline in AS score of the **other treated main clinical target pattern** (i.e. of elbow flexors or wrist flexors, if treated) at Day 29 (Week 4) of MP. This analysis will be performed in case two target patterns would qualify as main clinical target pattern for the main clinical target pattern not analyzed as primary efficacy variable. For subjects with bilateral UL treatment body side to be analyzed is decided by investigator at screening (for details on definition see 8.2.1).

- Change from baseline in AS score of treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Day 29 (Week 4) of MP. For subjects with bilateral UL treatment body side to be analyzed is decided by investigator at screening (for details on definition and on selection of variables to assess treatment of target patterns flexed wrist and clenched fist see Sections 8.2.1, 12.4.1.1 and 12.4.1.3).

Secondary efficacy variables (MP only):

- Change from baseline in AS score for each treated clinical pattern (e.g., flexed elbow, flexed wrist, clenched fist, etc.) of the UL at all other post baseline visits of MP. For subjects with bilateral UL treatment body side to be analyzed will be decided by investigator at screening.

- Change from baseline in scores of pain intensity (from subjects) and pain frequency (from parent/caregiver) assessed with 'Questionnaire on Pain caused by Spasticity [QPS]' to all post baseline visits of MP.

- Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) of MP.

Safety variables:

Primary safety variables:

Not applicable

Secondary safety variables:

- Occurrence of treatment emergent adverse events [TEAEs] overall and per treatment cycle.

- Occurrence of TEAEs of Special Interest [TEAESIs] overall and per treatment cycle.

- Occurrence of serious TEAEs [TESAEs] overall and per treatment cycle.
- Occurrence of TEAEs related to treatment as assessed by the investigator overall and per treatment cycle.
- Occurrence of TEAEs by worst intensity overall and per treatment cycle.
- Occurrence of TEAEs by worst causal relationship overall and per treatment cycle.
- Occurrence of TEAEs by final outcome overall and per treatment cycle.
- Occurrence of TEAEs leading to discontinuation overall and per treatment cycle.

Other safety variables:

- Investigator's Global Assessment of Tolerability at Day 99 (Week 14) of MP and all OLEX cycles.
- Vital signs (blood pressure, heart rate) at all visits of MP and all OLEX cycles.
- BMI, weight, height at Screening V1, Baseline Injection Visit V2, at the Final Visit of MP V5, at all Injection Visits of OLEX (V6[3], V10 and V14) and at the End of Study Visit (V17).
- Clinical chemistry and hematology at Screening (V1), the Injection Visit V6 of OLEX and the End of Study Visit (V17).
- Occurrence of antibodies against BoNT-A in subjects ≥21 kg BW.

Total number of subjects and number of countries

At least 344 subjects (ratio 2 : 1 : 1) will be randomized:
at least 172 subjects will be randomized to the high dose group,
at least 86 subjects to the mid dose group and
at least 86 subjects to the low dose group.
Overall and in each of the treatment groups, there will be 50% of subjects with flexed wrist and 50% with flexed elbow as primary clinical target pattern.

This international study is planned to be performed in eligible investigational sites worldwide.

Number of study sites

[3] If V5 and V6 will be performed at the same day, BW and height can be transferred from V5 to V6.

It is planned to conduct the study in approximately 45 sites.

Number of visits

Each subject will participate in a total of 14 regular visits and four telephone contacts. The number of visits may increase to a maximum of 17, if the Injection Visits of OLEX will be scheduled to revisits. To assess the length of treatment effects one optional telephone contact [TC] can be scheduled at week 12 of MP, to inquire the need for reinjection with IP before week 16.
The injection visit of each OLEX cycle may be performed on the same day as the Final Visit of MP or the End of Cycle Visits of the preceding treatment cycle.[4] If eligibility for reinjection is not reached on the day of the Final Visit of MP or on the End of Cycle Visits, injection visits can be rescheduled up to 16 weeks after the injection visit of the preceding cycle. If possible, all visits should be performed at similar day time.

Screening:

Screening Visit (V1):	Day -14 (Week –2) ± 5 days
Main Period (MP)**:**	
Baseline Injection Visit (V2):	Day 1, randomization
Telephone Contact (TC1):	Day 8 (Week 1) ± 3 days of MP
Ctrl. Visit (V3):	Day 29 (Week 4) ± 3 days of MP
Ctrl. Visit (V4):	Day 57 (Week 8) ± 3 days of MP
Optional Telephone Contact Wk12:	Day 85 (Week 12) ± 3 days of MP
Final Visit of MP (V5)	Day 99 (Week 14) ± 14 days of MP

Open-Label Extension Period (OLEX)

Injection Visit (V6, V10, V14):	Day 1 of the 2nd to 4th treatment cycle.
Telephone Contact (TC2, TC3, TC4):	Day 8 (Week 1) ± 3 days of 2nd to 4th treatment cycle

[4] At each injection visit eligibility criteria have to be assessed prior to injection. If all of the eligibility criteria are fulfilled, the Injection Visit will be on the same day as the End of Cycle Visit. In case an eligibility criterion is not met and the investigator assumes that the respective eligibility criterion is likely to be fulfilled within the upper time limit for reinjection of 16 weeks after the last injection, the injection visit may be scheduled. Otherwise the subject will be withdrawn from the study.

Ctrl. Visit (V7, V11, V15):	Day 29 (Week 4) ± 3 days of 2nd to 4th treatment cycle
Ctrl. Visit (V8, V12, V16):	Day 57 (Week 8) ± 3 days of 2nd to 4th treatment cycle
End of Cycle Visit (V9, V13)	Day 99 (Week 14) ± 14 days of 2nd and 3rd treatment cycle
End of Study Visit (V17):	Day 99 (Week 14) ± 14 days of 4th treatment cycle.

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

NT 201, 100 U, powder for solution for injection (active ingredient: NT 101, Botulinum neurotoxin type A free from complexing proteins; USAN: incobotulinumtoxinA) and placebo [PBO] will be used for reconstitution. PBO will be only used as part of the IP to achieve the lower concentrations in the mid and low dose group with an equal injection volume for all three dose groups.

Each medication kit consists of four vials of IP. Each vial will be reconstituted with 2 mL sterile physiological (0.9%) sodium chloride solution. Based on the selection of one out of five treatment combinations (A-E, for details see section below) in combination with the subjects BW either one (for total injection volume up to 8 mL) or two (for total injection volume up to 10 mL) medication kits will be assigned to a subject via IV/WRS in MP and OLEX. In MP the medication kit (blinded mixture of NT 201 only or NT 201 and PBO vials) will consist of 4 vials which must be pooled to achieve the target concentration of NT 201 in the respective study arm. In OLEX two different medications kits are provided. They either contain 4 or 1 vials with 100 U NT 201.

MP:

For subjects randomized to the high dose group each medication kit of MP consists of four vials with 100 U NT 201 (dilution strength of IP: 5 U per 0.1 mL).

For subjects randomized to the mid dose group each medication kit of MP consists of three vials with 100 U NT 201 and one PBO vial (dilution strength of IP: 3.8 U per 0.1 mL[5]).

For subjects randomized to the low dose group each medication kits of MP consist of one vial with 100 U NT 201 and three PBO vials (dilution strength of IP: 1.3 U per 0.1 mL[5]).

OLEX: For subjects in OLEX who will need total injection volumes of NT 201 of up to 8ml each medication kit consists of four vials with 100 U NT 201 (dilution strength of IP: 5 U per 0.1 mL).

[5] Values rounded to the 1st decimal place.

Subjects with a total injection volume from >8ml to 10ml will need an additional medication kit (OLEX only) with 1 vial NT 201 (100 U).

The IP will be injected as intramuscular [i.m.] injection into spastic muscles.

Fixed total doses will be used for the main clinical target patterns flexed elbow (e.g. 4 U/kg BW NT 201 in the high dose group in MP and for all subjects in OLEX) and flexed wrist (e.g. 2 U/kg in the high dose group in MP and for all subjects in OLEX) with pre-defined dose ranges and ranges for injection sites per muscle. In the target pattern flexed elbow treatment of biceps is mandatory. The investigator has to choose at the Baseline Injection Visit V2 to either inject brachialis or brachioradialis, as clinically appropriate.

In the optional clinical target pattern clenched fist fixed dosing (e.g. 2 U/kg BW NT 201 in the high dose group in MP and in OLEX) will be applied. In the remaining optional target patterns thumb in palm and pronated forearm muscles can be chosen by the investigator as clinically appropriate within dose ranges specified for individual muscles in this study (see also Table 14).

Selection of clinical patterns for LL treatment is up to the discretion of the investigator based on her/his clinical judgment. As in the UL(s), in LL(s) only target patterns with an AS score ≥2 at the Baseline Injection Visit of MP are eligible for treatment. The dose ranges per muscle and number of injection sites given in Table 15 should be adhered. Clinical patterns for treatment are pes equinus, flexed knee, adducted thigh, and extended great toe. The specified maximum dose limits per muscle and the total dose limits for LL treatment must be respected.

Investigators must be experienced and/or trained in technically guided BoNT treatment of children/adolescents with CP. Technically guided injection is mandatory for all injected muscle groups. Ultrasound will be the preferred guidance technique. Alternatively, electromyography [EMG] or electrical stimulation [e-stim] may be used.

Local anesthesia and/or analgosedation may be used as necessary. Physiotherapy (e.g., strengthening, stretching, and motor training), orthotic management, and any other rehabilitation treatment are allowed, but should be kept preferably stable in MP. Casting of the treated UL(s) is not permitted during the MP of this study.

The maximum dose per injection site should be 25 U NT 201 for subjects of <25 kg BW. The maximum dose per injection site for subjects of ≥25 kg BW should be 50 U NT 201.

Doses and Treatment Combinations in MP:

In this study five treatment combinations will be possible based on the need for fixed dose treatment per UL and limitations of total body dose:

A: UL(s) treatment only (GMFCS I-V):

In MP in treatment combination A doses displayed in Table 1 will be applied in the three dose groups for uni- or bilateral treatment of UL spasticity only:

Table 1 Treatment Combination A: Dose Groups for uni- and bilateral UL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL(s)*	LL	Total	UL(s)*	LL	Total	UL(s)*	LL	Total
uni-lateral		U/kg BW <25kg	**8**		**8**	**6**		**6**	**2**		**2**
		≥25kg BW	**200**		**200**	**150**		**150**	**50**		**50**
bi-lateral		U/kg BW <25kg	**16**		**16**	**12**		**12**	**4**		**4**
		≥25kg BW	**400**		**400**	**300**		**300**	**100**		**100**

* Fixed total dose per side: 8/6/2 U/kg BW, respectively.

In the high dose group the total dose per UL is 8 U/kg BW NT 201 (maximum of 200 U per UL). Accordingly, the dose for treatment of both ULs is 16 U/kg BW NT 201 (maximum of 400 U).

In the mid dose group the total dose per UL is 6 U/kg BW NT 201 (maximum of 150 U per UL). Accordingly, the dose for treatment of both ULs is 12 U/kg BW NT 201 (maximum of 300 U).

In the low dose group the total dose per UL is 2 U/kg BW NT 201 (maximum of 50 U per UL). Accordingly, the dose for treatment of both ULs is 4 U/kg BW NT 201 (maximum of 100 U).

The clinical need for unilateral treatment of UL spasticity in this treatment combination, has to be **8 U**/kg BW NT 201 (maximum of 200 U) for[6]

[6] Maximum total body doses in this study protocol refer to subjects with BW ≥ 25kg. In subjects < 25kg doses will be adjusted to BW (see Appendix 16.4).

1. at least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW)

and

2. additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.

The clinical need for bilateral treatment of UL spasticity has to be for equal doses of **8** U/kg BW NT 201 (maximum of 200 U) **to each UL.** Dose per UL must be distributed on each side as described above for unilateral treatment.

No LL treatment will be performed in treatment combination A in MP and OLEX.

B: Unilateral UL and unilateral LL treatment GMFCS levels I-V:

In MP, in treatment combination B. doses displayed in Table 2 will be applied in the three dose group for unilateral UL and unilateral LL injection treatments:

Table 2 Treatment Combination B: Dose Groups for unilateral UL and unilateral LL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL(s)	LL	Total	UL(s)	LL	Total	UL(s)	LL	Total
uni-lateral	uni-lateral (ipsi-lateral)	U/kg BW <25kg	**8**	8	**16**	**6**	6	**12**	**2**	2	**4**
		≥25kg BW	**200**	200	**400**	**150**	150	**300**	**50**	50	**100**

In this combination unilateral treatment of UL spasticity is identical to regulations outlined for UL treatment in treatment combination A.

To be eligible for this scenario, subjects should have an additional clinical need for unilateral treatment of LL spasticity with **8** U/kg BW NT 201 (maximum of 200U).

Dose to the LL must be distributed to at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe as clinically needed.

C: Unilateral UL and bilateral LL treatment GMFCS I-III

D: Unilateral UL and bilateral LL treatment GMFCS IV and V

In MP, in treatment combinations C and D doses displayed in Table 3 will be applied in the three dose groups for unilateral UL and bilateral LL treatment:

Table 3 Treatment Combinations C and D: Dose Groups for unilateral UL and bilateral LL injections in MP (C: GMFCS I-III, D: GMFCS IV and V.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL(s)	LL*	Total	UL(s)	LL*	Total	UL(s)	LL *	Total
GMFCS I-III											
uni-lateral	bi-lateral	U/kg BW <25kg	**8**	12	**20**	**6**	9	**15**	**2**	3	**5**
		≥25kg BW	**200**	300	**500**	**150**	225	**375**	**50**	75	**125**
GMFCS IV, V											
uni-lateral	bi-lateral	U/kg BW <25kg	**8**	8	**16**	**6**	6	**12**	**2**	2	**4**
		≥25kg BW	**200**	200	**400**	**150**	150	**300**	**50**	50	**100**

* Total dose for both LLs. Dose distribution may vary between sides as clinically needed but dose ranges for muscles treated from Table 15 must be adhered.

In both combinations C and D unilateral treatment of UL spasticity is identical to regulations outlined for unilateral UL treatment in Treatment Combination A.

In Treatment Combination C subjects with GMFCS levels I-III should have a clinical need for additional bilateral treatment of LL spasticity with **12** U/kg BW (maximum of 300 U).

Dose to LLs must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

In Treatment Combination D subjects with GMFCS levels IV and V should have a clinical need for additional bilateral treatment of LL spasticity with **8** U/kg BW (maximum of 200 U).

Dose to LLs must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

E: Bilateral UL treatment and bilateral LL treatment (GMFCS I-III)

In MP, in treatment combination E doses displayed in Table 4 will be applied in the three dose groups for bilateral UL and bilateral LL treatment:

In this combination bilateral treatment of UL spasticity is identical to regulations outlined for unilateral UL treatment in treatment combination A.

In addition, eligible subjects should have a clinical need for bilateral treatment of LL spasticity with **4** U/kg BW (maximum of 100 U).

Table 4 Treatment Combination E.: Dose Groups for bilateral UL and bilateral LL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL(s)*	LL**	Total	UL(s)*	LL**	Total	UL(s)*	LL**	Total
GMFCS I-III											
bi-lateral	bi-lateral	U/kg BW <25kg	**16**	4	**20**	**12**	3	**15**	**4**	1	**5**
		≥25kg BW	**400**	100	**500**	**300**	75	**375**	**100**	25	**125**

* Fixed total dose per side: 8/6/2 U/kg BW, respectively.

** Total dose for both LLs. Dose distribution may vary between sides as clinically needed but dose ranges for muscles treated from Table 15 must be adhered.

Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.

Doses and Treatment Combinations in OLEX:

Subject eligible for continuation of injection treatment in OLEX will receive open-label injection treatment in doses as in the high dose group of MP regardless of their assignment to dose groups in MP (for details see sections of this synopsis on MP treatment above). In OLEX the treatment combination chosen in MP and the main clinical target patterns of UL(s) chosen at V2 must be kept throughout study participation.

Statistical analysis methods

Primary Efficacy Analysis:

Testing of the primary, co-primary and key-secondary efficacy variables will be performed in a 4-step approach using a hierarchical test procedure as described in detail below:

The primary efficacy variable is the change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4) of MP. A mixed model repeated measurement analysis (MMRM, two-sided, significance level α=0.05) with comparison of least square means will be used for the confirmatory analysis to detect differences between the high and low dose treatment groups. The dependent variable is the primary efficacy variable. The independent variables are defined as treatment group (high dose, low dose), site (or pooled sites), BoNT-A pre-treatment

status (pre-treated, treatment naïve) as fixed factors, visit*treatment as interaction term, and visit as repeated factor. The covariates are the AS score of the primary clinical target pattern at baseline (Day 1 of MP) and the GMFCS level at screening.

Co-primary efficacy variable: An analysis of covariance (ANCOVA) approach (2-sided, significance level alpha=0.05) with comparison of least square means will be used for the confirmatory analysis of the co-primary efficacy variable. The dependent variable is defined as the 'Investigator's GICS at Day 29 (Week 4) of MP'. The independent variables are defined as treatment group (high dose, low dose), site (or pooled sites), BoNT-A pre-treatment status (pre-treated, treatment naïve) as fixed factors and the covariates are the maximum AS score of the two possible primary clinical target clinical patterns flexed elbow or flexed wrist at baseline (Day 1 of MP) and the GMFCS level at Screening Visit.

Sites might be pooled for the statistical analysis, e.g., based on geographic criteria. If applicable, pooling of sites will be defined in the SAP.

Both, the primary efficacy variable and the co-primary efficacy variable have to show statistically significant treatment differences in order to prove superiority of high dose vs. low dose treatment.

Confirmatory testing will be performed on the full analysis set [FAS] of MP with accounting for missing values by using MMRM approach for the primary efficacy variable. In case of missing data in the co-primary efficacy variable these will be imputed by "0" (no change) (see Section 12.4.7.1).

If the confirmatory tests of the (co-)primary efficacy variables both yield significant results, in a second step using a hierarchical testing approach in the high dose treatment group, the key-secondary efficacy variable 'change from baseline in AS score of the **other treated main clinical target pattern** (i.e. of elbow flexors or wrist flexors, if treated) at Day 29 (Week 4) of MP' and the co-primary efficacy variable 'GICS at Day 29 (Week 4) of MP' for the subpopulation defined by this key-secondary endpoint will be compared to low dose treatment group in both efficacy variables. Other than using the key-seondary efficacy variable and the co-primary efficacy variable for this subpopulation, the analysis models will be identical to the analysis described above for the 1st step. Both, the key-secondary efficacy variable and the co-primary efficacy variable for the subpopulation have to show statistically significant treatment differences in order to prove superiority of high dose vs. low dose treatment in this subpopulation.

Only if the confirmatory analysis of step 2 yields a statistically significant result, in a third step a confirmatory analysis of the key-secondary efficacy variable 'change from baseline in AS score of treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist), at Day 29 (Week 4) of MP will be done. This variable has been chosen, since it is anticipated that the vast majority of subjects will have a combined clinical presentation of clinical patterns clenched fist and flexed wrist. Subjects

with either treatment alone (i.e. clenched fist or flexed wrist) with other clinical target patterns will be evaluated separately in a descriptive manner (see also Section 12.3.1.3).

Only if the confirmatory analysis of step 3 yields a statistically significant result, in a fourth step, using a hierarchical testing approach, the mid dose treatment will be compared to low dose treatment in both (co-)primary efficacy variables. Other than using the mid instead of the high dose group treatment data, the analysis models will be identical to the analysis described above for the 1st step. Both, the primary efficacy variable and the co-primary efficacy variable have to show statistically significant treatment differences in order to prove superiority of mid dose vs. low dose treatment.

For the confirmatory analyses a two-sided significance level of α=0.05 will be applied. A MRMM analysis as described for the primary efficacy variable will be applied for the change from baseline in AS score. An ANCOVA model as described for the co-primary efficacy variable will be applied for the Investigator's GICS. The analysis will be performed on the FAS of the MP.

Due to the hierarchical testing strategy of (co-)primary and key-secondary efficacy variables and the two dose group comparisons (high versus low and mid versus low), this four step hierarchical testing procedure ensures the overall type I level of 5% for the confirmatory tests. If one of four hierarchical tests does not yield a statistically significant result, the consecutive test(s) will still be performed but will be considered to be only descriptive.

All other test procedures will be explorative. Sensitivity analyses will be performed on the per protocol set [PPS] of MP (subset of the FAS of MP without major protocol deviations) as well as on the FAS of MP using last observation carried forward [LOCF] (for AS score) and, additionally, without missing value replacement (observed case analysis).

Secondary [redacted] efficacy variables will be analyzed descriptively. Statistical tests will be interpreted in an explorative manner.

Safety Analysis: Analysis of the safety variables will be performed on the Safety Evaluation Set [SES] of MP and OLEX using descriptive summary statistics, frequency tables, and, if applicable, shift tables/graphs. The SES of MP is the subset of all subjects who were treated in the MP with study medication at least once. The SES is the subset of all subjects treated in OLEX with study medication at least once.

2 STUDY ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	Function	Address
Merz Pharmaceuticals GmbH	Sponsor	Eckenheimer Landstrasse 100 60318 Frankfurt/Main Germany Telephone: +49-69-1503-0 Telefax: +49-69-1503-200
[redacted]	Clinical project manager	Telephone: [redacted] Telefax: Email:
[redacted]	Medical expert	Telephone: [redacted] Email:
[redacted]	Biostatistician	Telephone: [redacted] Telefax: Email:
[redacted]	Drug safety officer	Telephone: [redacted] Telefax: Email:

2.2 External responsibilities

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

The sponsor will maintain a list of all principal investigators and of all IECs/IRBs. Curriculum vitae of each investigator, names of all investigators as well as names and addresses of each IEC/IRB can be found in the trial master file.

Name	Function	Address
[redacted]	Coordinating investigator	[redacted] USA Telephone: [redacted] Telefax: Email: [redacted]
[redacted]	Contract Research Organization [CRO]	[redacted] Germany Telephone: [redacted] Telefax:
[redacted]	24 hrs emergency unblinding service	[redacted] Germany Telephone: [redacted] Telefax:
Data Monitoring Committee	Monitoring of AESIs/ SAEs/AEs (for details see separate DMC charter and Section 12.4.7.3)	Names and addresses are provided in a separate list Meeting locations will be determined prior to meetings
[redacted]	Central laboratory	[redacted] Germany Telephone: [redacted] Telefax: Email:
[redacted]	Central storage and distribution of IP	[redacted] United Kingdom Telephone: [redacted] Telefax: Email [redacted]

Name	Function	Address
[redacted]	SAE and AESIs reporting (CRO)	[redacted] **In case of fax failure**, use email as backup for all regions**:** [redacted] Postal address: [redacted] Germany **(postal address not for safety reporting)**
[redacted]	Laboratory for fluorescence immunoassay [FIA] detecting antibodies against BoNT-A	[redacted] - Germany Telephone: [redacted] Telefax:
[redacted]	Laboratory for Hemidiaphragm assay [HDA] detecting of neutralizing antibodies against BoNT-A	[redacted], Germany Telephone: [redacted] Telefax:
[redacted]	Electronic Case Report Form [eCRF]	[redacted] United Kingdom Telephone [redacted] Telefax: [redacted]
[redacted]	Interactive Voice/Web Response Systems [IV/WRS]	[redacted] Belgium Telephone: [redacted] Telefax: [redacted]

2.3 Committees

Safety data will be evaluated by an independent DMC at regular time intervals to ascertain protection of subject's safety (Appendix 16.2). Safety data will be evaluated without knowledge of efficacy data. If deemed necessary by the DMC, emergency unblinding in individual cases can be performed by the DMC (see Section 12.4.7.3). The DMC will advise the sponsor regarding subject withdrawals and/or study measures in case of relevant safety findings. The DMC will consist of members who are assigned to the DMC of the NT 201 pediatric clinical study program. The members are not associated with the sponsor or with the operative conduct of any study sponsored by Merz. Details on responsibilities and procedures to be followed by the DMC will be laid down in the DMC charter. A summarized description of the scope of work and operating procedures for the DMC is provided in Section 12.4.7.3.

3 ETHICS

3.1 Independent Ethics Committee/Institutional Review Board

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

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

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

3.2 Ethical conduct of the study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with 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.

3.3 Subject information and informed consent

3.3.1 Subject information

The term "subject" used throughout this document includes children (age 2-11 years) and adolescents (age 12-17 years inclusive). Prior to study enrollment, the subject (if applicable) and/or the legally acceptable representative[7] (e.g., parent(s), guardian) will be given full verbal and written information on the nature, objective, significance, expected

[7] 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.

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

3.3.2 Informed consent/assent

As a rule, a pediatric subject is legally unable to provide IC. Therefore, the children/adolescents 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 the subject 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 1 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.

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 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 (parents') willingness to continue participation in the study. In case of AEs, or poor tolerability to the IP, the subject or the parent(s) should inform the investigator, who then will make a judgment whether continuing 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. 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), who will be instructed to keep it in their possession at all times. The subject card will contain the following printed information:

- The name, address, and telephone number of the investigator or study site's 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.
- A 24-hour hotline number for emergencies and for an emergency unblinding service of subjects during their participation in the double-blind MP.

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 and the parent(s) may consult his/her physician for treatment options, and receive antispastic medication including BoNT treatment, alcohol, phenol injections as well as physiotherapy, orthotic management, and any other rehabilitation treatment 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 country in which the study is performed.

The subject (if applicable) and/or parent(s) will be informed by the investigator and through the IC form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the parent(s), if requested by the parent(s) 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 the 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 underlying disease or condition of the subject, 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.

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

Medical background

Cerebral palsy is described as a group of permanent disorders of the development of movement and posture, causing activity limitation, which is attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, by epilepsy and by secondary musculoskeletal problems [Rosenbaum 2007, Aisen 2011].

CP is the most common cause of the upper motor neuron syndrome [UMNS] in children [Fehlings 2010, Aisen 2011]. Patients with UMNS show a mixture of negative phenomena like muscle weakness, loss of dexterity and fatigability. Positive features of UMNS are increased muscle tone, muscle spasms, clonus, exaggerated deep tendon reflexes and most important spasticity [Mayer 2001]. The overall incidence of CP is estimated at around 2 per 1,000 neonates in developed countries [Aisen 2011]. The majority of CP patients (76-87%) suffer from spasticity [Lannin 2006].

Spasticity is a chronic, not fatal condition. In children/adolescents with UL spasticity, the treatment of UL flexor deformity, e.g., flexed elbow and flexed wrist, is crucial [Heinen 2010]. Most children/adolescents with CP suffer from combined UL/LL spasticity. So in addition to functional impairment by UL spasticity, these children present very frequently with equinus gait initially. In older children and adolescents, weakness of proximal LL muscles may result in various types of flexed knee gait [Mayer 2001, Love 2010]. Goals of spasticity treatments include reducing pain and muscle spasms, facilitating brace use, improving posture, minimizing contractures and deformity, facilitating mobility and dexterity, and improving patient ease of care as well as hygiene/self-care [Ward 2003, Hagglund 2005, Chaleat-Valayer 2011].

In a non-focal condition such as CP, a number of muscle groups must be targeted using a multi-level treatment approach in which overactive muscle groups have to be injected to achieve an improvement of limb motion and posture [Heinen 2010]. BoNT-A temporarily reduces spasticity in muscles and facilitates the use of other treatments, e.g., physical therapy and orthotic management. Early BoNT-A therapy may help maximizing the development potential, may delay or reduce the need for corrective orthopedic surgery, and may minimize the impact of commonly occurring secondary musculoskeletal impairment [Heinen 2006].

BoNT-A injections are given to multiple small and large muscles in doses tailored to the individual child's/adolescent's needs. If necessary, it may be administered in sequential injection treatments as long-term spasticity treatment. The efficacy of treatment over one or more injection treatments with BoNT-A for spasticity in children has been sufficiently

demonstrated in several trials [Sutherland 1999, Wissel 1999, Koman 2000, Ubhi 2000, Love 2001, Baker 2002, Polak 2002, Mall 2006, Bjornson 2007]. Currently, there are 2 BoNT-A preparations Dysport® [USAN: abobotulinumtoxinA, Ipsen] and BOTOX® [USAN: onabotulinumtoxinA, Allergan] licensed in e.g., some European countries, Australia, Canada, and/or Mexico for treatment of pediatric patients. Both products are approved for the treatment of dynamic equinus foot deformity due to spasticity in ambulant pediatric CP patients, two years of age or older. The WE MOVE organization provided clinicians with BOTOX® dose recommendations for children [Brashear and Mayer 2008]. Recent treatment guidelines document the therapeutic role of BoNT-A for reduction of muscle tone and improvement of function in current treatment regimens [Simpson 2008, Delgado 2010, Esquenazi 2010, Heinen 2010]. BoNT-A is an established option for safe and effective spasticity treatment in UL and LL in children/adolescents as to international consensus groups [Fehlings 2010, Love 2010].

Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) have a similar efficacy and safety profile in patients with blepharospasm or cervical dystonia when used in a dosing conversion ratio of 1:1 [Merz Pharmaceuticals (GmbH) 2012].

Investigational product

BoNT-A is produced by fermentation of the anaerobic bacterium strain *Clostridium botulinum* as part of a high molecular weight complex, which is formed by several hemagglutinins and other non-toxic non-hemagglutinin proteins. BoNT-A acts selectively on peripheral cholinergic nerve endings, inhibiting the release of the neurotransmitter acetylcholine, and thus reduces increased muscle tone by partial paralysis.

Xeomin® (NT 201, USAN: incobotulinumtoxinA) is the only marketed BoNT-A preparation that is free from complexing proteins. In animal models, NT 201 did not induce neutralizing antibodies [Jost 2007]. None of the adult subjects developed neutralizing antibodies when treated with up to 400 U NT 201 in a clinical study investigating treatment of adult post-stroke spasticity of the UL up to 89 weeks [Kanovsky 2011]. The highly purified nature of NT 201 may be thought to represent a clinical advantage compared with other BoNT-A complex preparations. A further advantage is that NT 201 can be stored and transported at room temperature (up to 25°C/77°F) which simplifies handling.

Up to date NT 201 is approved in Argentina, Brazil, Canada, South Korea, Mexico, Russia, Uruguay, USA, and 19 European Economic Area [EEA] countries (including Germany). The 1st marketing authorization was granted by the BfArM in Germany on 31 May-2005, which is considered the International Birth Date of the product. The different national approvals cover a variety of indications such as blepharospasm, spasmodic torticollis, post-stroke spasticity of the upper limb, focal spasticity, strabismus, tremor, hyperkinetic facial lines, and glabellar frown lines. NT 201 is marketed under the brand names Xeomin®, Bocouture® (EEA only), Xeomin Cosmetic™ (Canada only for aesthetic use), and Xeomeen®(Mexico only).

4.2 Study rationale

This pivotal phase 3 study is part of an international pediatric study program for Xeomin® agreed with the US FDA. It will serve to collect first efficacy and safety data in the treatment of CP caused spasticity with NT 201 in a pediatric population. The study will compare NT 201 treatment in three dose arms (high and mid against low) with fixed doses for UL injection treatments. The focus of this study is to generate efficacy and safety data for the use of NT 201 in pediatric UL spasticity.

In complete contrast to adult UL post-stroke spasticity, in children/adolescents with CP isolated presentation of UL spasticity is rare. Only these children/adolescents would have no need for additional spasticity treatment in the LL(s). The main reason for this fundamental difference in clinical presentation between the most frequent forms of adult and pediatric spasticity is that in CP the brain damage is generally more widespread [Aisen 2011]. Even in children with territorial deficits due to cerebral hemorrhage related to preterm birth additional white matter abnormalities can be observed [Babcock 2009]. Most children/adolescents therefore present at least with unilateral CP with combined UL and LL involvement. Due to the scarcity of CP patients with isolated UL spasticity it is necessary to design pediatric UL efficacy trials for inclusion of subjects with combined UL/LL spasticity also.

The study will compare NT 201 treatments in the high dose group (8 U/kg BW NT 201 per treated UL, max. of 200 U) and in the mid dose group (6 U/kg BW NT 201 per treated UL, max. of 150 U) to active treatment in the low dose group (2 U/kg BW NT 201 per treated UL, max. of 50 U).

The number of published trials of evidence class II and higher in the indication UL spasticity in CP is limited [Simpson 2008]. Most studies have limitations in regard to control groups, outcome measures or even more important statistical power due to limited sample sizes. However, published studies used doses of onabotulinumtoxinA (Botox®) comparable to the Xeomin® doses in the present trial: Fehlings and coworkers applied 2-6U/kg BW Botox® to at least 3 UL muscles using a single blind design. Similarly, Wallen and coworkers used a treatment regimen with 0.5 to 2 U/kg BW onabotulinumtoxinA per treated muscle with a maximum dose of 12 U/kg BW (165.1+/-88.6 U) [Wallen 2007] and Russo et al. applied in a single-blinded controlled trial a mean of 8U/kg BW onabotulinumtoxinA (range 5.0-11.6U/kg BW) [Russo 2007]. Overall, published doses for UL treatment of CP spasticity are within the range of doses administered in the present study.

Although the main focus of efficacy assessment is treatment of UL(s) with fixed doses per dose group, injection doses to LL(s) in the respective treatment combinations allowed in this study will also reflect assignment to one of the three dose groups in the double-blind MP only. After completion of MP, all eligible subjects will continue in OLEX with three subsequent treatment cycles with injection doses of the high dose group of MP.

For safety reasons, the maximum total body dose in this trial will be 20 U/kg BW NT 201 (max. of 500 U) for subjects with GMFCS levels I-III and 16 U/kg BW (maximum of 400 U) for subjects of GMFCS level IV and V (for details see Section 8.1.1).

The study complements the overall clinical development program of NT 201 in indications such as treatment of post-stroke spasticity in the adult population.

Two BoNT-A preparations (Dysport® and BOTOX®) are licensed in some European countries, Australia, Canada, and/or Mexico for treatment of pediatric patients of the spastic upper limb deformity and dynamic equinus foot deformity. BoNT-A treatment of children/adolescents is often performed for several spasticity patterns. Several clinical study data for efficacy and safety of BoNT-A were reported for UL and LL [Fehlings 2000, Baker 2002, Speth 2005, Lowe 2006, Mall 2006, Russo 2007, Wallen 2007].

Currently, no randomized data of NT 201 in the pediatric population exists. This randomized parallel-group, dose-response study will observe the participating subjects in accordance with a high scientific standard, ICH-GCP, local laws and regulations, and international consensus recommendations on pediatric BoNT-A treatment.

Pediatric CP subjects with uni- and bilateral UL spasticity alone or combined with LL spasticity must have a clinical need for NT 201 treatment to be enrolled in this study. Distribution of CP spasticity and clinical need for treatment may not be 100% overlapping, e.g. a subject with bilateral UL spasticity may only have a need for NT 201 treatment in one UL.

Subjects pre-treated with BoNT-A or BoNT-A treatment-naïve children/adolescents will be eligible for this study. Treatment-naïve subjects are defined as those who have not received BoNT treatment for limb spasticity within the last 12 months. This regulatory definition aims to ensure the lack of assessment bias possibly caused by the subject's and/or parent's remembrance of former treatment effects. Subjects will be randomized to one of three treatment groups in MP in a ratio of 2 : 1 : 1 (High : Mid : Low dose of NT 201). This ratio attempts to minimize the number of subjects treated with doses less than the target dose of 8 U/kg BW per UL.

4.3 Risk-benefit assessment

There is no monitored experience in children/adolescents available for the BoNT-A preparation under investigation. NT 201 was subject to extensive toxicological and safety pharmacological testing in non-clinical as well as clinical studies, which showed that NT 201 is well tolerated and has an acceptable safety profile (see current IB [Merz Pharmaceuticals (GmbH) - IB]). In a juvenile toxicity study in rats, decreased mating rates and atrophy of the testicular germinal epithelium with subsequent hypospermia without functional consequences were observed at 30 Lethal Dose 50 (LD_{50}) Units [$LD_{50}U$]/kg. However, no indications of frank systemic toxicity other than growth retardation were seen at 10 $LD_{50}U$/kg and below. The clinical relevance of the findings from this animal study with these extremely high doses and reinjection already at

maximal paralysis is unknown. In a clinical setting, subjects are only re-injected upon recovery of the muscle function, usually 3 to 6 months after injection of BoNT-A. In this study investigators who are informed on preclinical safety data of NT 201 will judge the clinical need for an injection in doses of up to a maximum of 20 U/kg BW NT 201 at least 12 weeks after the last injection treatment. Two clinical studies with NT 201 in adult subjects with UL muscle spasticity after stroke and other etiologies with a maximum dose of 400 U NT 201, respectively, showed good efficacy and no safety issues [Barnes 2010, Kanovsky 2011].

In general, BoNT-A is well tolerated in children/adolescents [Naumann and Jankovic 2004, Lukban 2009, Heinen 2010]. Common undesirable effects after BoNT-A injection include local, generalized, or procedural AEs. Local AEs are usually mild and self-limiting. The most commonly reported local AEs after BoNT treatment in children/adolescents are potential and expectable consequences of overshooting muscle relaxation such as excessive localized weakness [Love 2010]. Systemic AEs related to BoNT-A include nausea, fatigue, bladder incontinence, flu-like symptoms, and rash [Naumann 2006, Howell 2007]. Procedural AEs include complications due to local anesthesia or analgosedation before injection.

A retrospective analysis supports the safety of high BoNT-A doses citing the occurrence of AEs in 261 subjects treated with doses of up to 25 U/kg BW [Willis 2007]. Occurrences of AEs ranged from 3.9%-8.6% with no trend to higher percentages of AEs in the highest dose group (20-25 U/kg BW). No case of iatrogenic botulism could be observed. The authors concluded that the safety profile of BoNT injections is comparable over all dose groups analyzed.

Subjects will be closely monitored for AEs occurring in this study. A DMC will be established to monitor for safety signals and to note unexpected hazard (see Section 12.4.7.3). Common AEs (>1/100, <1/10) listed in the current summary of product characteristics for Xeomin® regarding adult post-stroke spasticity of the UL are injection site pain, injection site hematoma, and muscular weakness [Merz Pharmaceuticals (GmbH) 2012].

At Baseline Visit V2 of MP and at all subsequent Control (Ctrl.) Visits and telephone contacts of MP and OLEX, subjects will be thoroughly monitored for AEs and AESIs. The site staff will even actively question the subject (if applicable) and the parent(s) or caregivers (if applicable) for signs of potential toxin spread such as swallowing difficulties, speech or breathing disorders, botulism, or muscular weakness.

As this is a clinical study in the 1st pediatric NT 201 development program, the adequate dose ranges were defined from international consensus statements with advice by a board of experts experienced in BoNT-A treatment of children/adolescents. Recommendations of international consensus groups for onabotulinumtoxinA (BOTOX®) are bridged to NT 201 on basis of demonstrated comparability of NT 201 for adult efficacy and safety in comparison to BOTOX® when investigated in a 1 : 1 ratio [Benecke 2005, Roggenkamper 2006, Jost 2007]. The maximum total body dose of 500 U NT 201 for

GMFCS levels I-III and 400 U NT 201 for GMFCS levels IV and V in this study is within the comparable upper limit of 400 to 600 U onabotulinumtoxinA (BOTOX®) for treatment in children/adolescents with CP by international recommendations [Heinen 2010, Love 2010]. Moreover, the maximum total dose of this study complies with the comparable maximum body dose recommendation by WE MOVE [Brashear and Mayer 2008].

Pediatric subjects are expected to benefit from local treatment with NT 201 in addition to their current management for spasticity. Subjects will continue any existing physiotherapy, orthotic management and antispastic medication (except for medication excluded in this study) to treat spasticity during the study. Mid and low dose treatment in 25% each of all subjects for one treatment cycle in MP are also considered to show treatment effects on limb spasticity (for details see Section 4.2).

Burden and risk level

The burden for the individual subject caused by this study is kept to a minimum. Injections of IP may be done under local anesthesia and/or analgosedation as appropriate to minimize discomfort and pain. Analgosedation will be performed by qualified anesthesia personnel in accordance to recommendations from the American Society of Anesthesiologists [American Society of Anesthesiologists - Anesthesia Care Team Committee 2009] (for further details see Section 8.1.1.2). Pre-treated subjects who needed general anesthesia for BoNT injections will not be eligible for this study, since general anesthesia will not be used in this study.

During this study, subjects may receive most of their pre-study medication, physiotherapy and other measures to treat spasticity (except casting of the UL during the MP, since it may bias the primary efficacy analyses). The investigator will check at each on-site visit that the individual subject receives appropriate concomitant medication/therapy.

Subjects in the mid and low dose arm may experience less effect compared to the high dose for only one treatment cycle in MP. However, doses especially in the mid dose group (6 U/kg BW NT 201 per UL) but also in the low dose group (2 U/kg BW NT 201 per UL) lie within the dose ranges of published clinical trials showing effects of BoNT-A treatments on spasticity [Fehlings 2000, Wallen 2004, Speth 2005, Wallen 2007].

The same dose group assigned to a subject for UL injections will be also applied for LL treatment (if applicable). This appears to be justified, since treatment errors with different dilutions strength for UL and LL treatments (e.g. by mixing up syringes with different dilution strength) may be considered a higher risk for a subject as compared to potentially smaller effects on LL spasticity compared to the high dose group for only one treatment cycle in MP.

The overall risk level indicated by the number of occurrences impacting the safety of an individual subject is moderate due to the good safety profile of NT 201 and the good

clinical experience in this indication with other BoNT preparations. The well experienced investigator will carefully reflect the clinical need for BoNT injection based on his/her experience-based clinical judgment and will use the pre-specified dosing scheme of this study protocol. If the dosing schemes specified in this clinical study protocol do not fit the subject's clinical needs for NT 201 injections, eligibility for study participation is not given. At each telephone or site contact (starting at V2), the investigator or authorized delegate will actively inquire the subject (if applicable) and/or parent(s) about the occurrence of AESIs. By regular review of all AEs including AESIs, the DMC will ensure additive control over the safety of the pediatric study population as well as over the individual.

In conclusion, the sponsor believes that this clinical study MRZ60201_3072_1 is carefully designed to minimize risks and to maximize potential benefits for the subjects.

5 STUDY OBJECTIVES

To investigate efficacy and safety of Xeomin® (incobotulinumtoxinA, NT 201) in subjects[8] with UL spasticity alone or with combined UL and LL spasticity due to CP with a 1st double-blind cycle, the MP, and three subsequent treatment cycles, the OLEX. Injection treatments in MP and OLEX will be followed by 12-16 weeks observation each.

During MP, in a three arm, parallel-group double-blind design subjects will receive one of three fixed doses of Xeomin® per treated UL.

- In the high dose group 8 U/kg BW NT 201 (maximum dose per UL: 200 Units for subjects ≥25kg BW).
- In the mid dose group 6 U/kg BW (maximum of 150 U) per UL.
- In the low dose group 2 U/kg BW (maximum of 50 U) per UL.

As clinically needed, UL treatment can be administered uni- or bilaterally with doses as outlined above for each treated UL.

Subjects may receive additional BoNT injections in one out five predefined treatment combinations up to the maximum total dose applicable for their GMFCS level (I-III: 20 U/kg BW NT 201, maximum of 500 U; IV and V: 16 U/kg BW NT 201, maximum of 400 U).

After completion of MP, all eligible subjects will continue treatment in OLEX with NT 201 doses as in the high dose group of MP.

[8] Subjects eligible for this study are children (age 2-11 years) and adolescents (age 12-17 years inclusive).

6 INVESTIGATIONAL PLAN

6.1 Overall study design

This prospective, multicenter, multi-national, randomized, double-blind, parallel-group, dose-response study in phase 3 of three doses Xeomin® will treat subjects with UL spasticity alone or with combined UL and LL spasticity due to CP. The study comprises a single double-blind treatment cycle (MP) with three dose arms followed by three open-label treatment cycles (OLEX) with a single treatment arm using the high dose regimen of MP.

The study consists of a screening period of 2 weeks and a total of four observation periods of 12 to 16 weeks, i.e. 14 weeks ± 14 days, after one double-blind injection treatment in MP and after three open-label injection treatments in OLEX. The duration of study participation for the individual subject is 50 to 66 weeks.

Treatment of UL(s) in MP will be administered in three parallel dose groups of NT 201 with fixed doses to UL(s):

- In the high dose group 8 U/Kg BW NT 201 (maximum dose per UL: 200 Units for subjects ≥25kg BW).
- In the mid dose group 6 U/kg BW (maximum of 150 U) per UL.
- In the low dose group 2 U/kg BW (maximum of 50 U) per UL.

As clinically needed, UL treatment can be administered uni- or bilaterally and subjects may receive additional BoNT injections in one out of five predefined treatment combinations (A-E) (for details on dose distribution to UL(s) and LL(s) see Section 8.1.1.2) up to the maximum total dose applicable for their GMFCS level (I-III: 20 U/kg BW NT 201, maximum of 500 U; IV and V: 16 U/kg BW NT 201, maximum of 400 U). In MP only, LL(s) treatment will be performed within the same dose groups as UL treatment, i.e. subjects in the mid and low dose group will receive 75% or 25%, respectively, of the dose in the high dose group to all limbs treated.

A total of 344 subjects (2 : 1 : 1 ratio) will be enrolled with:

- At least 172 subjects randomized to the high dose group.
- At least 86 subjects to the mid dose group.
- At least 86 subjects to the low dose group.

For details on the sample size calculation see Section 12.1.

This international study is planned to be performed in eligible investigational sites worldwide.

An independent DMC will be established to monitor the safety of subjects (see Section 12.4.7.3).

After all subjects have completed the End of Study Visit, the analysis of efficacy and safety data will be performed and reported in an integrated clinical study report.

The Flow Chart in Section 6.1.2 provides an overview of the study design. The overview of the study activities/visit schedule in Section 9.2 displays the procedures per visit. If possible, all visits should be performed at similar day time. The study includes the following visits:

Screening:

Screening Visit (V1):	Day -14 (Week –2) ± 5 days

Main Period (MP):

Baseline Injection Visit (V2):	Day 1, randomization
Telephone Contact (TC1):	Day 8 (Week 1) ± 3 days of MP
Ctrl. Visit (V3):	Day 29 (Week 4) ± 3 days of MP
Ctrl. Visit (V4):	Day 57 (Week 8) ± 3 days of MP
Optional Telephone Contact Wk12:	Day 85 (Week 12) ± 3 days of MP
Final Visit of MP (V5)	Day 99 (Week 14) ± 14 days of MP

Open-Label Extension Period (OLEX)

Injection Visit (V6, V10, V14):	Day 1 of the 2nd to 4th treatment cycle.
Telephone Contact (TC2, TC3, TC4):	Day 8 (Week 1) ± 3 days of 2nd to 4th treatment cycle.
Ctrl. Visit (V7, V11, V15):	Day 29 (Week 4) ± 3 days of 2nd to 4th treatment cycle
Ctrl. Visit (V8, V12, V16):	Day 57 (Week 8) ± 3 days of 2nd to 4th treatment cycle
End of Cycle Visit (V9, V13)	Day 99 (Week 14) ± 14 days of 2nd and 3rd treatment cycle
End of Study Visit (V17):	Day 99 (Week 14) ± 14 days of 4th treatment cycle.

Revisit for reinjection

If any eligibility criterion is not met either at the Final Visit of MP (V5) or at an End of Cycle Visit in OLEX (V9 or V13), the injection may be rescheduled within up to 16 weeks after the last injection treatment. An injection visit may be rescheduled ('revisit'), if the investigator assumes that the respective eligibility criterion is likely to be fulfilled within the remaining period of time to complete 16 weeks after the last injection treatment. For details on eligibility criteria see Section 7.3.1.

If the investigator assumes the criterion will not be met within up to 16 weeks after the last injection treatment, or if the subject does not fulfill all eligibility criteria at the rescheduled injection visit, the subject will be withdrawn from the study (see Section 7.4.1). A subject can perform only one revisit, i.e., the revisit cannot be repeated even if the limit of 16 weeks after the last injection has not been reached.

If rescheduling of an injection visit becomes necessary, this additional visit will be interposed into the regular visit series without affecting the numbering or time window of regular visits, i.e., the day of injection is designated as Day 1 of each cycle. If an End of Cycle Visit and an Injection Visit should not be performed on the same day (e.g., if a revisit is required), all procedures that would be transferred from the End of Cycle Visit to the Injection Visit must be performed again at the revisit. At a rescheduled injection visit (after eligibility criteria have been confirmed and before injection), AEs/AESIs, vital signs, concomitant medication, and efficacy assessments will be documented.

AESI monitoring and Safety Visit

To monitor potential spread of toxin, the subject (if applicable) and/or parent(s) or caregivers (if applicable) will be actively questioned for the occurrence of AESIs at each visit or Telephone Contact [TC] starting with Baseline Visit of MP (V2). If a TC identifies an (S)AE/AESI that needs confirmation or treatment (e.g., respiratory disorder, dyspnoea, aspiration, dysphagia, speech disorder, dysphonia, other signs of bulbar palsy or botulism), the investigator must schedule a Safety Visit [SV] in addition to scheduled visits as soon as possible after the Telephone Contact. SV are unscheduled extra visits for assessment of (S)AE/AESIs only.

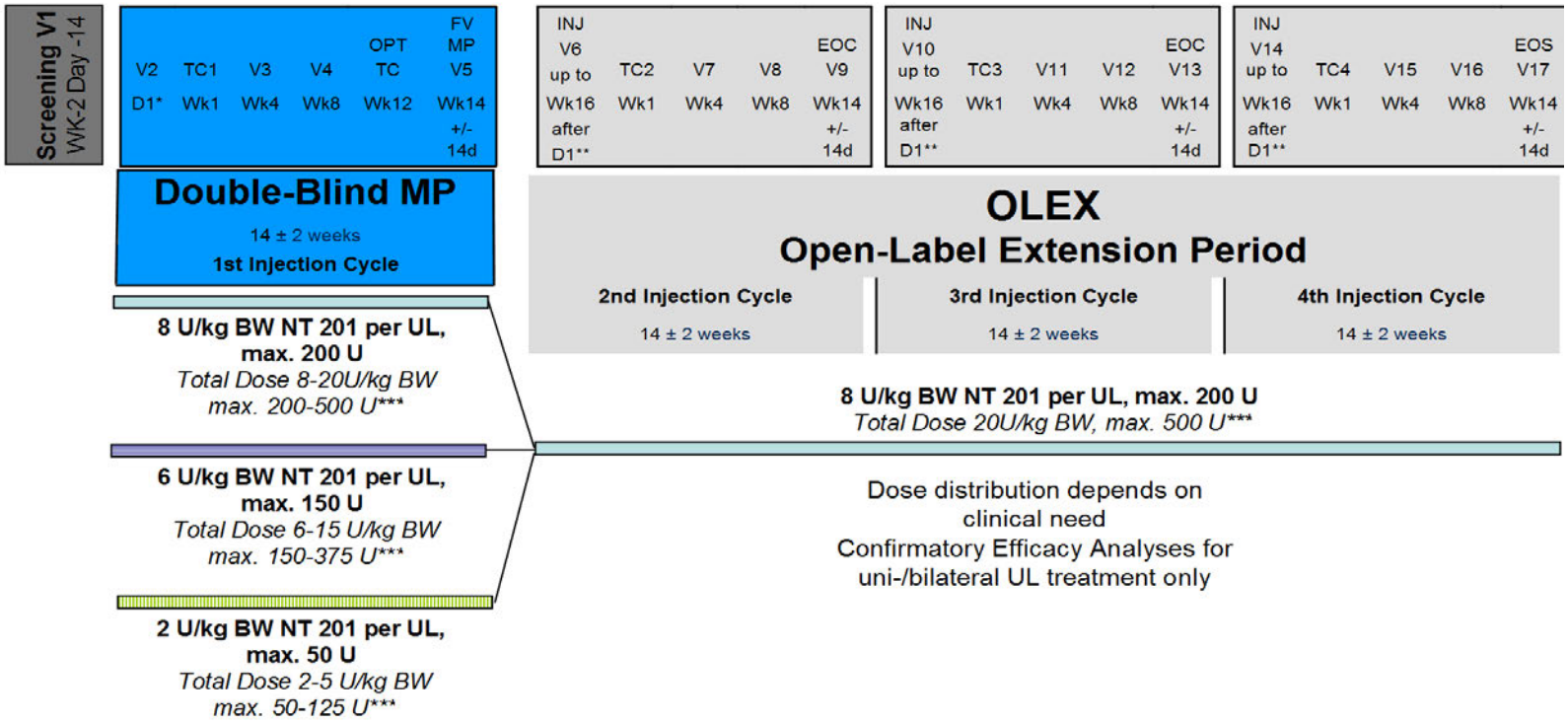
If a subject withdraws from participation during the study at any point of time, every attempt should be made to conduct the assessments foreseen for the End of Study Visit (V17).

6.1.1 End of study

The end of study will be defined as the End of Study Visit of the last subject.

6.1.2 Study flow chart

Figure 1 Study Flow Chart



Total study duration: 50 to 66 weeks, including 2 weeks screening and 4 treatment cycles 12 to 16 weeks each
* Day 1 of respective Injection cycle
** Day 1 of last Injection cycle. Days of INJ visits V6, V10 and V14 are D1 of the respective Injection Cycle
*** Maximum total dose dependent on combination of UL only or UL(s) and LL(s) combined treatment in five predefined treatment combinations (A.-E.)
BW: body weight, EOC: End of Cycle Visit, EOS: End of Study Visit, FV MP: Final Visit of MP, INJ: Injection, MP: Main Period,
OLEX: Open-Label Extension Period, OPT TC: Optional TC, TC: Telephone Contact, U: unit, V: Ctrl. Visit, Wk: Week, d: Day

6.2 Discussion of Study Design, Including Choice of Control Groups

The multicenter, double-blind, randomized, three dose arms parallel-group dose-response, design of this study is chosen to obtain scientifically robust data on efficacy and safety of NT 201 in treatment of UL spasticity in subjects with need for UL spasticity treatment alone or need for combined UL and LL spasticity treatment due to CP. By using a double-blind parallel-group design, study assessments will not be biased by investigator, subject and parent(s) or caregiver(s).[9] A superiority study with an adequate low dose group control holds validity for efficacy and safety with evidence based class 1.

An IV/WRS will be used to achieve an overall equal distribution of primary clinical target patterns (i.e. flexed elbow and flexed wrist) for primary efficacy analysis. Clinical patterns flexed elbow and flexed wrist only qualify as target patterns for primary efficacy analysis with an AS score ≥2 in elbow flexors or wrist flexors at Baseline Visit (Day 1) of MP, respectively. A combination of the two main clinical target patterns in this study, i.e., of flexed elbow and flexed wrist in subjects with pediatric CP is expected to be very frequent. For this reason, since at same AS scores a clinical decision on which of the two main clinical target patterns to select for primary efficacy analysis could not be operationalized, the clinical target pattern for primary efficacy analysis will be selected randomly by the IV/WRS (for details see Section 8.2.1). Accordingly, the respective treated pattern not selected for primary efficacy analysis in this subgroup of subjects will be analyzed as key secondary efficacy variable. If only one main clinical target pattern should present with an AS score ≥2, this pattern will be selected for primary efficacy analysis. Overall, a ratio of 1 : 1 between main clinical target patterns flexed elbow and flexed wrist will be ensured by stratified randomization using the IV/WRS.

To be eligible for this study with concealed allocation to treatment groups in MP, subjects must have a clinical need for the fixed dose of NT 201 specified for the high dose group (8 U/kg BW NT 201, maximum of 200 U per UL). Only pediatric subjects of age 2 to 17 years will be enrolled. A clinical benefit of local treatment with BoNT-A injections for children below age 2 years has not been established [Molenaers 2010].

Treatment allocation to one of three dose groups of NT 201 will be performed in a 2 : 1 : 1 randomization scheme to treat as few subjects with doses below the target dose of 8 U/kg BW per UL as necessary for statistical analysis.

Treatment with doses below 8 U/kg BW in 50% of enrolled subjects for only one treatment cycle in MP seems to be justified since all subjects may continue any existing stable antispastic medication, and all other medications that are not expected to interfere with BoNT-A and physiotherapy.

[9] In subjects, living e.g. in a special-care unit permanently or most of the time with caregivers being his/her main social contacts, a caregiver may replace parent(s) for the assessment of the respective scales and measures.

Since the 6 U/kg BW dose is only 25% less than the target dose of 8 U/kg per UL, relevant treatment effects in comparison to the low dose group are also expected in this dose group. In addition, clinical studies using onabotulinumtoxinA (BOTOX®) have shown a treatment effect even in the dose range injected in the low dose group of the present study. By comparing low dose with high and mid dose group in the MP of this study, valuable information not only on peak treatment effects but also on duration of treatment effects in relation to dose group will be obtained.

Local anesthesia and/or analgosedation for injection treatment are permitted to reduce discomfort for subjects and to facilitate injections for investigators. Subjects are expected to benefit from treatment with NT 201 in addition to the current antispastic therapy.

After Final Visit of MP, if all eligibility criteria are fulfilled subjects automatically pass to OLEX with three injections cycles with NT 201 administered in the dose regimen of the high dose group of MP.

7 STUDY POPULATION

The study population will consist of at least 344 subjects (age 2 to 17) with UL spasticity alone or with combined UL and LL spasticity due to CP. Subjects must have clinical need for injection treatment in the UL at least unilaterally. A subject may be enrolled, if she/he suffers from uni- or bilateral CP with clinical need for uni- or bilateral UL injections with BoNT for the treatment of spasticity regardless of GMFCS level. The subject should present an AS score ≥2 at least unilaterally in one or both of the main clinical target patterns of this study, flexed elbow and flexed wrist.

Overall, subjects must have a clinical need for a dose of 8 U/kg NT 201 per UL (maximum of 200 U) according to the experience-based clinical judgment of the investigator.

By using an IV/WRS an overall equal distribution of both main clinical target patterns (i.e. flexed elbow and flexed wrist) for primary efficacy analysis will be achieved. Of 172 subjects allocated in MP to the high dose group, 86 will be analyzed for AS score changes in the clinical pattern flexed elbow and 86 will be analyzed for flexed wrist as primary efficacy variable. Accordingly, 43 of the 86 subjects that will be allocated to the mid and to the low dose group will be analyzed primarily for flexed elbow and 43 will be analyzed primarily for flexed wrist.

Treatment-naïve subjects or pre-treated (non-naïve) subjects may enter the study. Treatment-naïve subjects will be defined as individuals who have not received BoNT treatment within the last 12 months for treatment limb spasticity. Pre-treated (non-naïve) subjects must not have received BoNT treatment in any indication within the last 14 weeks prior to the Screening Visit (V1). Selection of study population

Subjects of 2 to 17 years of age will be enrolled since benefit of local treatment with BoNT-A of children younger than 2 years of age has not been scientifically established. Affected subjects of 2 to 17 years are treated with BoNT-A in medical practice and are able to contribute to the chosen efficacy assessments with limitations specified in Section 9.1.1.

Subjects must have a clinical need according to the clinical judgment of the investigator for fixed total doses specified in five different treatment combinations (A-E; see also Section 7.2 and 8.1.1.2). The most frequent clinical patterns of spasticity in clinical practice will be prioritized for treatment in this study.

The main clinical target patterns of UL spasticity are flexed elbow and flexed wrist. Additional clinical patterns that are optional for injection treatment are clenched fist, thumb in palm and pronated forearm. Doses in optional clinical patterns have to be chosen not to exceed the maximum dose limit per limb, 8 U/kg BW NT 201 (max. of 200 U).

In combined UL and LL spasticity, subjects can present with clinical need for uni- or bilateral LL spasticity treatment in one or more of the following clinical patterns: pes equinus, flexed knee, adducted thigh, and/or extended great toe. Maximum doses for additional LL treatment are defined by number of limbs treated and GMFCS level. These specified dose limits must not be exceeded (see Section 8.1.1.2).

The investigator should consider whether the subject and the parent(s) are able to attend all scheduled study visits, e.g., long distance between home town and study site may reduce visit compliance. Furthermore, only subjects should be recruited who are not expected to have a need for non-authorized medication during the study (see Section 8.3.2). Referrals from clinicians and institutions treating possibly eligible subjects may support recruitment from the study site's pediatric subject pool. The recruitment strategy may differ according to local settings in the respective country. Recruitment advertisements according to local law and approved by the responsible IEC/IRB will be published as needed.

Gender distribution at enrollment will not be controlled in this study. Therefore, the gender distribution in this study is supposed to reflect the distribution in the underlying population, i.e., all children/adolescents with CP.

7.1 Inclusion criteria

Only subjects meeting all of the following inclusion criteria will be considered for study enrollment:

Inclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
1. Written informed consent obtained from the parent(s)[10] and assent by the subject (if applicable).	Administrative	X	
2. Understanding of study procedures and willingness to abide to all procedures during the course of the study by the subject (if applicable) and parent(s).	Administrative	X	

[10] 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.

Inclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
3. Female or male subject 2 to 17 years of age (inclusive).	Admini-strative	X	
4. Uni- or bilateral CP with clinical need for injections with NT 201 for the treatment of UL spasticity at least unilaterally.	Efficacy	X	X
5. Ashworth Scale [AS] score in the main clinical target patterns in this study - Flexed elbow: AS score ≥2 in elbow flexors (at least unilaterally) **and/or** - Flexed Wrist: AS score ≥2 in wrist flexors (at least unilaterally).	Efficacy	X	X
6. Clinical need according to the judgment of the investigator in one out of five treatment combinations (A-E, as shown below). AS score must be ≥2 for each target pattern chosen for injection at the Baseline Injection Visit V2.	Efficacy	X	X
A: UL(s) treatment **only** (GMFCS I-V): *Unilateral treatment of UL spasticity with* **8** U/kg BW NT 201 (maximum of 200 U) for[11]: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.			

[11] Up to 25kg BW dosing of NT 201 will be subject to BW-adjustment (see Appendix 16.4). Above 25kg fixed doses will be applied.

Inclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
or *Bilateral treatment of UL spasticity with* Equal doses of **8** U/kg BW NT 201 (maximum of 200 U) **to each UL.** Dose per UL must be distributed between: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.			
B: Unilateral UL and unilateral LL treatment (GMFCS I-V): *Unilateral treatment of UL spasticity with* **8** U/kg BW NT 201 (maximum of 200 U)[11] for: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached. **plus** *Ipsilateral unilateral treatment of LL spasticity with* **8** U/kg BW NT 201 (maximum of 200 U). Dose to LL must be distributed to at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe as clinically needed.			

Inclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
C: Unilateral UL and bilateral LL treatment (GMFCS I-III) *Unilateral treatment of UL spasticity with* **8** U/kg BW NT 201 (maximum of 200 U)[11] for: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached. **plus** *Bilateral treatment of LL spasticity with* **12** U/kg BW (maximum of 300 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.			
D: Unilateral UL and bilateral LL treatment (GMFCS IV and V) *Unilateral treatment of UL spasticity with* **8** U/kg BW NT 201 (maximum of 200 U) [11] for: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.			

Inclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
plus *Bilateral treatment of LL spasticity with* **8** U/kg BW (maximum of 200 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.			
E: Bilateral UL treatment and bilateral LL treatment (GMFCS I-III)			
Bilateral treatment of UL spasticity with Equal doses of **8** U/kg BW NT 201 (maximum of 200 U)[11] **to each UL.** Dose per UL must be distributed between: 1. At least one of the main clinical target patterns flexed elbow (**4** U/kg BW) and/or flexed wrist (**2** U/kg BW). **and** 2. Additional clinical patterns in the same limb (i.e., clenched fist, thumb in palm, and/or pronated forearm) with the remaining units until maximum dose of **8** U/kg BW (maximum of 200 U) for treatment of a single UL is reached.			
plus *Bilateral treatment of LL spasticity with* **4** U/kg BW (maximum of 100 U). Dose must be distributed into at least one of clinical target patterns pes equinus, flexed knee, adducted thigh, and extended great toe, on each side. Dose distribution may vary between sides as clinically needed.			

[redacted]

7.2 Exclusion criteria

Subjects having any of the following criteria, either at Screening (V1) and/or at Baseline (V2), will not be included in the study. For concomitant medication permitted only under certain precautions see Section 8.3.1.

Exclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
[redacted]			

[redacted]

Exclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
10. Treatment with BoNT (other than IP in this study) for any body region within 14 weeks prior to Screening Visit (V1), within the screening period and/or intended to be administered during the study period.	Efficacy	X	X
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Exclusion Criteria	Rationale	Screening (V1)	Baseline (V2)
[redacted]			

[redacted]

7.2.1 Eligibility criteria for OLEX injections

Eligibility criteria will be assessed at the Final Visit of MP (V5) at 14 ± 2 weeks after V2. In case the investigator is not certain when to schedule the Final Visit of MP at the Control Visit V4, 8 weeks after injection treatment in MP, the subject (if applicable) and/or parent(s) can be questioned at an optional TC (week 12 ± 3 days) about the need for reinjection with IP. If this optional TC should indicate need for reinjection, the Final Visit of MP will be scheduled. If reinjection should not appear to be necessary at the time of optional TC Wk12, the Final Visit of MP could be scheduled until up to 16 weeks after V2 at the latest. If eligibility for reinjection should not be given up to 16 weeks after the previous injection, the subject will be withdrawn from the study (see Section 7.4.1). In OLEX, eligibility will be assessed at End of Cycle Visits V9 and V13.

[15] Menarche is defined as the 1st menstrual bleeding in female signaling the possibility of fertility (even if ovulation usually occurs only within some months after the menarche

To qualify for reinjection in OLEX, per eligibility criterion No.1 all subjects in this study must have

a) a clinical need for injection of the main clinical target patterns of UL(s) chosen at the Baseline Injection Visit V2 (i.e. either flexed elbow or flexed wrist alone or flexed elbow and flexed wrist) with fixed dose per pattern defined in Table 14 **plus**

b) a clinical need for the total dose of **8 U**/kg BW NT 201 per UL (maximum dose of 200 U) per treated UL.

For the main clinical target patterns adaptations are only allowed within the dose ranges per muscle and number per injection sites given in Table 14 as long as the total fixed dose per main clinical target pattern is kept.

For the remaining dose not used for treatment of main clinical target patterns of the UL(s) adaptations in OLEX may also include change of clinical target patterns and change of doses per muscles and number of injection sites as long as the ranges of Table 14 are kept.

In subjects with additional treatment of LL(s) in treatment combinations B. – E. the clinical need must be for

a) unilateral or bilateral treatment of LL(s) as chosen at the Baseline Injection Visit V2.

b) The total dose of the treatment combination chosen at V2 (see also eligibility criterion No.2 below).

Only for injection treatment of the LL(s), it will be allowed to change the LL patterns chosen at V2 in further treatment cycles. Regulations for doses per muscle, number of injection sites of Table 15 and for total dose to the LL(s) must be respected.

It will not be allowed to change the treatment combination chosen at V2 or to change the body side of treatment in unilaterally treated subjects.

Only subjects meeting the following eligibility criteria will receive an NT 201 injection treatment in the 2nd to 4th cycle.

Eligibility Criteria	Rationale	Visits V5/6, V9/10 V13/14
1. Clinical need for injection of the main clinical patterns of the UL(s) treated in the previous treatment cycle with **8 U**/kg BW NT 201 per UL (maximum dose of 200 U).	Safety concern; efficacy	X

Eligibility Criteria	Rationale	Visits V5/6, V9/10 V13/14
2. For subjects with combined UL and LL treatment in the previous treatment cycle (Treatment combinations B-E): Clinical need for LL(s) treatment with dose of NT 201 used in the previous treatment cycle. In B: Unilateral LL with **8 U**/kg BW (maximum of 200 U) in subjects with unilateral UL treatment (GMFCS I-V). In C: Bilateral LL with **12 U**/kg BW (maximum of 300 U) in subjects with unilateral UL treatment (GMFCS I-III). In D: Bilateral LL with **8 U**/kg BW (maximum of 200 U) in subjects with unilateral UL treatment (GMFCS IV and V). In E: Bilateral LL with **4 U**/kg BW (maximum of 100 U) in subjects with bilateral UL treatment (GMFCS I-III).	Safety concern; efficacy	X
3. AS score ≥2 in the treated clinical patterns. For subjects with an AS score of 1, the investigator will decide on the clinical need for reinjection.	Efficacy	X
4. Agreement of investigator and subject (if applicable) and parent(s) on the need for reinjection.*	Admini-strative	X
5. No infection and/or inflammation in the area of the planned injection points.	Safety concern	X
6. Negative pregnancy test for female with history of menarche.**	Safety concern	X

* It is at the discretion of the investigator to decide whether reliable statements on the need for a reinjection can be obtained from the subject or have to be retrieved from a parent(s) only.

** Menarche is defined as the 1st menstrual bleeding in female signaling the possibility of fertility (even if ovulation usually occurs only within some months after the menarche).

7.3 Removal of subjects from treatment or assessment

7.3.1 Discontinuation of subjects

In accordance with the Declaration of Helsinki and the IC form, the subject or parent(s) may discontinue the study at any time without any penalty or loss of benefits to which the subjects is otherwise entitled (see Section 7.4.3). Both the discontinuation of study and the reason(s) why the study was prematurely discontinued must be recorded in the subject's file and the eCRF. Date and discontinuation circumstances should be stated. Further details on discontinuation could be documented in the respective section of the "End of Study" form of the eCRF.

Subjects must be discontinued from the study by the investigator at any time for any of the following reasons:

- Withdrawal of IC.
- Treatment with any other IP in another clinical study.
- Treatment with any BoNT other than study medication.
- Pregnancy (no further administration of IP(s), blood draw, or any other interventional procedure will be performed; see Section 10.4).
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.
- AESIs of severe intensity that represent respiratory function disorders or swallowing disorders will trigger the premature termination of a subject without re-exposition 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.
- Injection treatment cannot be performed for any reason, not even with local anesthesia and/or analgosedation.
- Eligibility criteria are not met after the previous injection of IP in the respective treatment cycle (MP or OLEX) (see Section 7.3.1).

The DMC may recommend further criteria for discontinuation. Deviations from this study protocol, or conditions comprising exclusion criteria established in Section 7.3 that arise after the subject has been included in the study may (but will not necessarily) lead to the discontinuation of subject's study participation. All such conditions must be properly documented.

Any subject who discontinues from the study due to AEs will be treated according to standard clinical strategies. All pertinent information concerning the AE will be documented in the subject's file as well as in the eCRF AE report form (and in addition in an SAE or AESI report form, if applicable).

Following discontinuation, a final examination (End of Study Visit) should be performed for safety reasons. However in a pregnant female no invasive assessments, e.g., blood sampling should be performed. The pregnancy has to be followed up until the date of delivery (see also Section 10.4). The investigator is required to make every effort to contact the subject (if applicable) or parent(s) lost to follow-up, and all such efforts should be documented in the subject's file (e.g., times and dates of telephone contact, copies of letters).

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

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

- 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 subjects.
- AESIs of severe intensity that represent respiratory function disorders or swallowing disorders, that are deemed to be related to IP administration, and are lasting >1 week will trigger premature termination of the study. The threshold for premature study termination is set to at least five subjects experiencing those AESIs for the 1st 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.

- New scientific data on the IP(s) do not justify a continuation of the study.

- Recommendation of the DMC.

- 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 requirements.

- The sponsor decides to terminate the study or study site at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the IEC/IRB has decided to 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 (if applicable) and the parent(s) and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, study sites, the IEC/IRB, and regulatory authorities of the termination or suspension of the study, as well as provide reasons for the action.

7.3.3 Provision of care for subjects after study discontinuation

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

Subjects who discontinue prematurely may receive treatment at the discretion of the investigator (e.g., referral to orthopedic surgery, switch to another BoNT, oral/intrathecal antispastic medication, and local alcohol or phenol injections). The investigator and/or the subject's physician are free to apply any approved antispastic treatment, physiotherapy, orthotic management, and any other rehabilitation treatment to treat spasticity.

8 TREATMENTS

8.1 Investigational product(s)

8.1.1 Description of investigational product(s)

In the double-blind MP, subjects will be randomly allocated to receive active treatment in one of three parallel dose groups (high, mid, and low).

In the open-label OLEX, all subjects will receive active treatment in the same dose group.

Active treatment:	NT 201, 100 units, powder for solution for injection
International non-proprietary name of active ingredient:	An international non-proprietary name for the drug substance has not been assigned. The assigned USAN for the active ingredient is incobotulinumtoxinA.
Excipients:	Sucrose, human serum albumin.

The IP will be supplied in a clear glass vial. Each vial of NT 201 contains an amount of sterile lyophilized solid material with biological activity of 100 mouse LD_{50}U(calculated median lethal intraperitoneal dose), which corresponds to approximately 600 pg of neurotoxin. 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.

In MP only, PBO will be used for preparation of the injection solution for the mid and low dose group. PBO vials with lyophilisate have identical appearance and solution properties to NT 201 vials. The PBO vials contain human serum albumin and sucrose but do not contain NT 101.

PBO for IP preparation for mid and low dose group:	PBO vial containing excipients of NT 201, powder for solution for injection
Excipients:	Sucrose, human serum albumin.

The IP might be supplied in more than one shipment at different time points of the study.

8.1.1.1 Instructions for preparation

[redacted]

[redacted]

[redacted]

8.1.1.2 Instructions for administration

Process for determination of injection scheme

In this study five pre-defined treatment combinations (A-E, see below) of UL alone or combined UL and LL injections will be allowed. The investigator first has to judge based on his clinical experience in the indication spasticity due to CP, if treatment in one of the five combinations is appropriate for the clinical condition of a subject. This judgment will be based on the dose administered in the high dose group of this trial since (a) actual randomization to dose groups in MP will be blinded and (b) all subjects will receive

doses of MP's high dose group in OLEX. Since the actual dose of IP in MP will be blinded, injection volume per muscle and per pattern will be controlled and documented in the eCRF. Conversion of NT 201 doses to volumes will be facilitated by a conversion table (see Appendix 16.5).

Dose calculations for injection treatment in an individual subject should also consider the GMFCS levels I-III or IV-V, the total dose per kg BW, the maximum dose allowed in this study, the selection of clinical patterns for treatment, the dose per muscle, and the dose per injection site.

To be eligible for injection with IP each clinical target pattern in UL(s) and LL(s) must show an AS score of ≥2 at the Baseline Injection Visit V2.

In OLEX, eligibility for reinjection among other criteria is given at an AS ≥2 in the respective clinical pattern. At AS=1 the decision for injection is up to the investigator. At AS=0 no injection is allowed. For eligibility criteria for reinjection in OLEX see also Section 7.3.1.

The investigator will distribute the fixed dose per UL between selected muscles within pre-defined dose ranges and number of injection sites per muscle (see Table 14 and Table 15). The main clinical target patterns for UL treatment chosen at V2 must be kept throughout study participation and must be injected with a fixed total dose (see Table 14). For subjects with bilateral UL treatment the main clinical target patterns of both sides must be kept. Adaptations for the main clinical target patterns are only allowed within the dose ranges per muscle and number per injection sites given in Table 14 as long as the total fixed dose per main clinical target pattern is kept.

Depending on which body side(s) and limb(s) are affected by UL spasticity, uni- or bilateral UL will be administered in five treatment combinations (A-E) at Baseline Injection Visit V2 (see for details see Table 6 to Table 13). It will not be allowed to change the treatment combination chosen at V2 or to change the body side of treatment in unilaterally treated subjects.

In subjects with additional treatment of LL(s) in treatment combinations B. – E. it will be allowed to change the LL patterns chosen at V2 in further treatment cycles. Regulations for doses per muscle, number of injection sites of Table 15 and for total dose to the LL(s) must be respected.

It is recommended to consider pre-existing medical co-morbidities, muscle size and activity, and experience from previous BoNT treatments of the subject (if applicable). No more than 20 U/kg BW NT 201 (max. total body dose of 500 U for subjects ≥ 25 kg BW) will be injected in this study. For safety reasons, the upper dose limit for subjects with GMFCS levels IV-V is restricted to 16 U/kg BW NT 201 (max. total body dose of 400 U for subjects ≥ 25 kg BW).

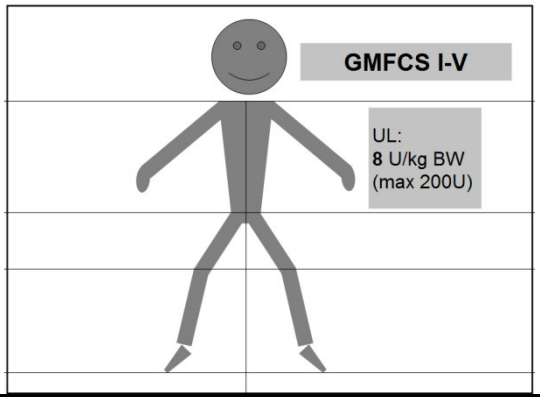
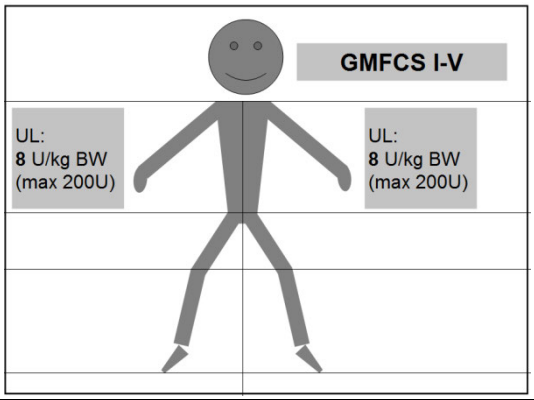
Doses for subjects of <25 kg BW are displayed in tables Appendix 16.4. Above 25 kg BW fixed doses will be injected. The distribution of the total dose to clinical patterns per limb in this study is as follows:

Treatment Combination A: Uni- or bilateral UL treatment only

Subjects with clinical need for *unilateral* UL injection of NT 201 must have a need for a total injection dose of 8 U/kg BW (maximum of 200 U) to the one UL chosen for treatment only (see Table 6). At least one main clinical target pattern (flexed elbow or flexed wrist) must be treated.

The dose not needed for treatment of main clinical target patterns must be distributed to additional optional clinical patterns (for details see Table 14). The maximum total dose per limb (based on dose decisions using the high dose group) must not be exceeded. The selection of main clinical target patterns must not be changed throughout the entire duration of study participation.

Table 6 Treatment Combination A: Clinical Need for uni- or bilateral UL treatment only (GMFCS levels I-V)

	Unilateral UL treatment	Bilateral UL treatment
UL	Clinical need for total dose per UL **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm.	Clinical need for total dose per UL **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm. Selection of clinical patterns and dose distribution may vary within predefined ranges between sides as clinically needed.
LL	No LL treatment	No LL treatment
		

The total dose of NT 201 administered for unilateral UL injections in treatment combination A in MP ranges from 2 U/kg BW (maximum of 50 U) to 8 U/kg BW (maximum of 200 U) (see also Table 7). In bilateral UL treatment subjects must have a clinical need for an equal dose of 8 U/kg BW NT 201 per limb (maximum of 200 U per UL).

For unilateral and for bilateral UL treatment the same regulations for selection of clinical patterns for treatment apply (for details see Table 14). Between ULs, selection of clinical patterns for treatment and doses per muscles may vary within pre-specified ranges as clinically appropriate. The selection of main clinical target patterns must not be changed throughout the entire duration of study participation. For primary efficacy analyses one UL must be chosen at the Baseline Injection Visit and must be kept throughout the entire study participation.

Table 7 Treatment Combination A: Dose Groups for uni- and bilateral UL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL(s)*	LL	Total	UL(s)*	LL	Total	UL(s)*	LL	Total
uni-lateral		U/kg BW <25kg	**8**		**8**	**6**		**6**	**2**		**2**
		≥25kg BW	**200**		**200**	**150**		**150**	**50**		**50**
bi-lateral		U/kg BW <25kg	**16**		**16**	**12**		**12**	**4**		**4**
		≥25kg BW	**400**		**400**	**300**		**300**	**100**		**100**

* Fixed total dose per side: 8/6/2 U/kg BW, respectively.

The total dose of NT 201 administered for bilateral UL injections in treatment combination A in MP ranges from 4 U/kg BW (maximum of 100 U) to 16 U/kg BW (maximum of 400 U) (see also Table 7).

Treatment Combination B: Unilateral UL and ipsilateral unilateral LL treatment

In subjects with a clinical need for combined unilateral UL and ipsilateral unilateral LL injections, treatment combination B can be chosen. Details on the distribution of the clinical need are given in Table 8.

UL treatment will be administered as described above for unilateral UL treatment only, after investigators have assessed a clinical need for a dose of 8 U/kg BW NT 201 (maximum of 200 U) for the UL intended to treat at V2 and at Injection Visits in OLEX. The dose distribution to UL and LL in the three dose groups of MP is displayed in Table 9. In OLEX subjects will continue to receive open-label treatment in the dose of the high dose group of MP (see Table 9).

For LL treatment of spasticity investigators can choose from clinical patterns pes equinus, flexed knee, adducted thigh and extended great toe as clinically needed. In addition to the presence of a clinical need, target patterns must have an AS score ≥2 to qualify for treatment at the Baseline Injection Visit (V2) of MP. For reinjection in OLEX, an AS ≥ 2 is also necessary on the day of the Injection Visit. At AS=1 the decision for injection is up to the investigator. At AS=0 no injection is allowed.

The total dose of NT 201 administered for unilateral UL and unilateral LL injections in treatment combination B in the three dose groups in MP ranges from 4 U/kg BW (maximum of 100 U) to 16 U/kg BW (maximum of 400 U) (see also Table 9).

According to the subjects' clinical need for injection, dose per muscle and number of injection sites have to be chosen to be within predefined ranges as displayed in Table 14 and Table 15.

Table 8 Treatment Combination B: Clinical need for unilateral combined UL and unilateral LL treatment (GMFCS levels I-V)

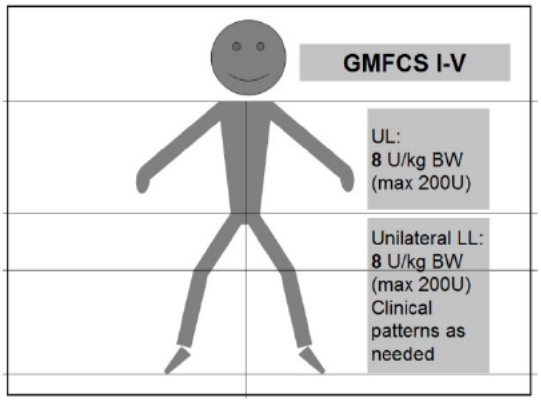
Unilateral UL	Total dose per UL **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm.
Unilateral LL	Total dose per LL **8** U/kg BW, max. 200 U NT 201 Treatment of at least one clinical target pattern chosen form pes equinus, flexed knee, adducted thigh, extended great toe.
	

Table 9 Treatment Combination B: Dose Groups for unilateral UL and unilateral LL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL	LL	Total	UL	LL	Total	UL	LL	Total
uni-lateral	uni-lateral	U/kg BW <25kg	**8**	8	**16**	**6**	6	**12**	**2**	2	**4**
		≥25kg BW	**200**	200	**400**	**150**	150	**300**	**50**	50	**100**

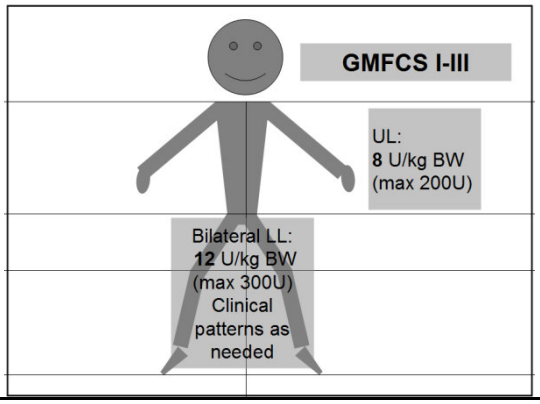
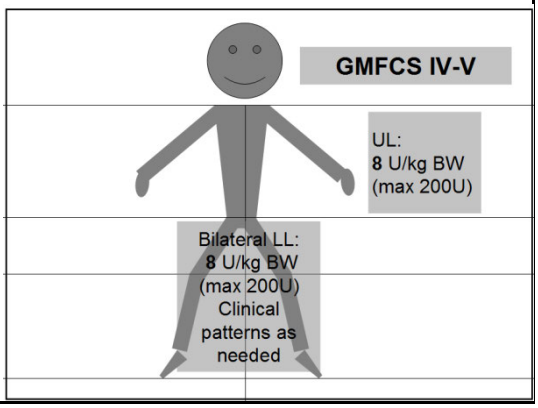
These tables are also applicable in MP, since dose decisions will be performed assuming that the subject will get treatment in the high dose group. BW-adjusted doses for subjects < 25kg BW are summarized in Appendix 16.4.

No dose adjustment to GMFCS levels is necessary since the total body dose of 16 U/kg BW NT 201 equals the dose limit for subjects with GMFCS levels IV and V.

Treatment Combination C + D: Unilateral UL and bilateral LL treatment in GMFCS level I-III and GMFCS level IV, V

In subjects with a clinical need for combined unilateral UL and bilateral LL injections, treatment combinations C or D can be chosen depending on the subjects GMFCS level. Details on the distribution of the clinical need are given in Table 10.

Table 10 Treatment Combinations C and D: Clinical need for unilateral UL and bilateral LL treatment

	C: GMFCS I-III	D: GMFCS IV and V
Uni-lateral UL	Clinical need per UL for **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm.	Clinical need per UL for **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm.
Bilateral LL	Clinical need for total dose for both LLs **12** U/kg BW, max. 300 U NT 201 Treatment of at least one clinical target pattern chosen form pes equinus, flexed knee, adducted thigh, extended great toe. Selection of clinical patterns and dose distribution may vary within predefined ranges between sides as clinically needed.	Clinical need for total dose for both LLs **8** U/kg BW, max. 200 U NT 201 Treatment of at least one clinical target pattern chosen form pes equinus, flexed knee adducted thigh, extended great toe. Selection of clinical patterns and dose distribution may vary within predefined ranges between sides as clinically needed.
		

In the scenario of combined unilateral UL and bilateral LL treatment, UL treatment will be performed as described in treatment combination A (see above). In MP, subjects will receive treatment to UL and LL in three different dose groups of NT 201 (for details see Table 11). An overview of the selection of clinical patterns for UL and LL treatment are given in Table 14 and Table 15.

Table 11 Treatment Combinations C and D: Dose Groups for unilateral UL and bilateral LL injections in MP (C: GMFCS I-III, D: GMFCS IV and V).

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		UL	LLs *	Total	UL	LLs*	Total	UL	LLs*	Total
C: GMFCS I-III											
uni-lateral	bi-lateral	U/kg BW <25kg	**8**	12	**20**	**6**	9	**15**	**2**	3	**5**
		≥25kg BW	**200**	300	**500**	**150**	225	**375**	**50**	75	**125**
D: GMFCS IV, V											
uni-lateral	bi-lateral	U/kg BW <25kg	**8**	8	**16**	**6**	6	**12**	**2**	2	**4**
		≥25kg BW	**200**	200	**400**	**150**	150	**300**	**50**	50	**100**

* Total dose for both LLs. Dose distributions may vary between sides as clinically needed but dose ranges for muscles treated from Table 15 must be adhered.

Doses for bilateral LL treatment will have different dose limits in treatment combination C and D depending on the GMFCS level of an individual subject. This regulation is applied to keep the overall total body dose per GMFCS level with fixed doses to the UL.

For treatment combination C, GMFCS levels I-III, the dose limit for both LLs is 12 U/kg BW NT 201 (maximum dose of 300 U).

For treatment combination D, GMFCS levels IV, V, the dose limit for both LLs is 8 U/kg BW NT 201 (maximum dose of 200 U).

The total dose of NT 201 administered for unilateral UL and bilateral LL injections in treatment combination C and D in the three dose groups in MP ranges from 4 U/kg BW (maximum of 100 U) to 20 U/kg BW (maximum of 400 U) (see also Table 11).

As for other clinical target patterns in addition to a clinical need for injection, subjects must have an AS score ≥ 2 at baseline. At the time point for reinjection, AS must be ≥2 again. If the AS score is 1, it is the investigator's decision whether reinjection is needed. At AS = 0 no reinjection is allowed.

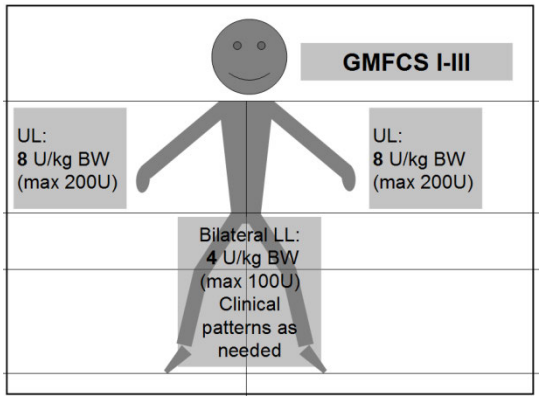
Doses to LL may be distributed unequally, if clinically needed. Dose per single LL should not exceed 8 U/kg BW NT 201 that is the upper dose limit for LL treatment per

side in the NT 201 pediatric spasticity program. For details on LL treatment see also Table 15.

Treatment Combination E: Bilateral UL and bilateral LL treatment in GMFCS level I-III

In the scenario of combined bilateral UL and bilateral LL treatment, treatment of ULs will be performed as described in treatment combination A (see above). For details on clinical need in treatment combination E see Table 12. In MP subjects will receive treatment to UL and LL in three different dose groups of NT 201 (see Table 13). An overview of the selection of clinical patterns for UL and LL treatment are given in Table 14 and Table 15.

Table 12 Treatment Combination E: Clinical need for bilateral UL and bilateral LL treatment GMFCS levels I-III

	GMFCS I-III
Bilateral UL	Clinical need for equal dose per upper limb of **8** U/kg BW, max. 200 U NT 201 Treatment of at least one main clinical target pattern (flexed elbow and/or flexed wrist). + Additional clinical patterns chosen from clenched fist, thumb in palm, and/or pronated forearm.
Bilateral LL	Clinical need for additional total dose for both LLs **of 4** U/kg BW, max. 100 U NT 201 Treatment of at least one clinical target pattern chosen form pes equinus, flexed knee, adducted thigh, extended great toe. Selection of clinical patterns and dose distribution may vary within predefined ranges between sides as clinically needed.
	

Doses for bilateral LL treatment will have different dose limits in treatment combination C and D depending on the GMFCS level of an individual subject. This regulation is applied to keep the overall total body dose per GMFCS level with fixed doses to the UL.

For treatment combination E, GMFCS levels I-III, the dose limit for both LLs is 4 U/kg BW NT 201 (maximum dose of 100 U).

Table 13 Treatment Combination E: Dose Groups for bilateral UL and bilateral LL injections in MP.

Treated Limbs			High Dose			Mid Dose			Low Dose		
UL	LL		ULs*	LLs **	Total	ULs*	LLs **	Total	ULs*	LLs**	Total
GMFCS I-III											
bi-lateral	bi-lateral	U/kg BW <25kg	**16**	4	**20**	**12**	3	**15**	**4**	1	**5**
		≥25kg BW	**400**	100	**500**	**300**	75	**375**	**100**	25	**125**

* Fixed total dose per side: 8/6/2 U/kg BW, respectively.

** Total dose for both LLs. Dose distributions may vary between sides as clinically needed but dose ranges for muscles treated from Table 15 must be adhered.

Since the dose for bilateral UL treatment is already 16 U/kg BW, this scenario excludes additional treatment of LLs in subjects with GMFCS levels IV and V. In subjects with GMFCS level I-III only 4 U/kg BW NT 201 may be distributed to both LL. Even with this limited total dose to LLs regulations for minimum doses per muscles and number of injection sites have to be respected (see also Table 15).

Dosing of muscles and number of injection sites

The dose ranges for the NT 201 group are based on recommendations of the Movement Disorder Society [Brashear and Mayer 2008] and were adapted according to recommendations of an international clinical expert advisory board [Merz Pharmaceuticals GmbH 2011].

Dose ranges for clinical patterns of spasticity, respective muscles and injection site numbers per pattern for UL and LL treatment are displayed in Table 14 and Table 15. For subjects of <25 kg BW doses for muscles and injection site numbers are subject to adjustment by BW. The smallest step for dose adjustment allowed will be 2.5U. At an IP concentration of 50 U/mL, these steps equal a reduction by 0.05ml.

UL treatment in clinical target patterns

In children/adolescents with CP the most frequent clinical patterns of UL spasticity are flexion patterns, i.e. flexed elbow, flexed wrist and clenched fist. Two out of these three patterns are main clinical target patterns in the present study: flexed elbow and flexed

wrist. Injection treatment in at least one of these main clinical target patterns in this study is mandatory. The dose in both patterns is fixed.

For treatment of flexed elbow, injection of biceps brachii is mandatory. The investigator can select one of the two other muscles contributing to spasticity of elbow flexion, i.e. brachialis and brachioradialis, for injection.

The selection of 2 out of 3 muscles for treatment of flexed elbow must be fixed at the baseline injection visit and kept throughout the entire study.

Subjects with clinical need for treatment of flexed elbow will receive 4 U/kg BW NT 201 (maximum of 100 U). In the clinical pattern flexed wrist the fixed dose is 2 U/kg BW NT 201 (maximum of 50 U). If this pattern is chosen, both muscles must be injected. Another subgroup of children/adolescents is expected to present with spasticity of finger flexors (clenched fist). Here, a fixed dose of 2 U/kg BW NT 201 (maximum of 50 U) will be administered. If this pattern is chosen, both finger flexors must be injected, i.e. flexor digitorum superficialis and profundus.

In the other optional clinical target patterns thumb in palm and pronated forearm, investigators can choose muscles as needed as long as the upper dose limits per UL and injection session are respected. At least one muscle per pattern must be injected.

Detailed tables for injection doses per treatment scheme and BW-adjusted dosing displaying respective injection volumes, minimum and maximum dose per pattern and muscles by BW are displayed in Appendix 16.4. The transfer of IP doses into injection volumes may be supported by Table 27, Appendix 16.5.

LL treatment in clinical target patterns

For subjects with a clinical need for LL injection treatment, investigators can choose from the following clinical patterns: pes equinus, flexed knee, adducted thigh, and extended great toe. For flexed knee or adducted thigh investigators are free to choose muscles but have to respect dose ranges per muscle and number of injection sites (see Table 15).

Dosing for subjects with GMFCS level IV and V

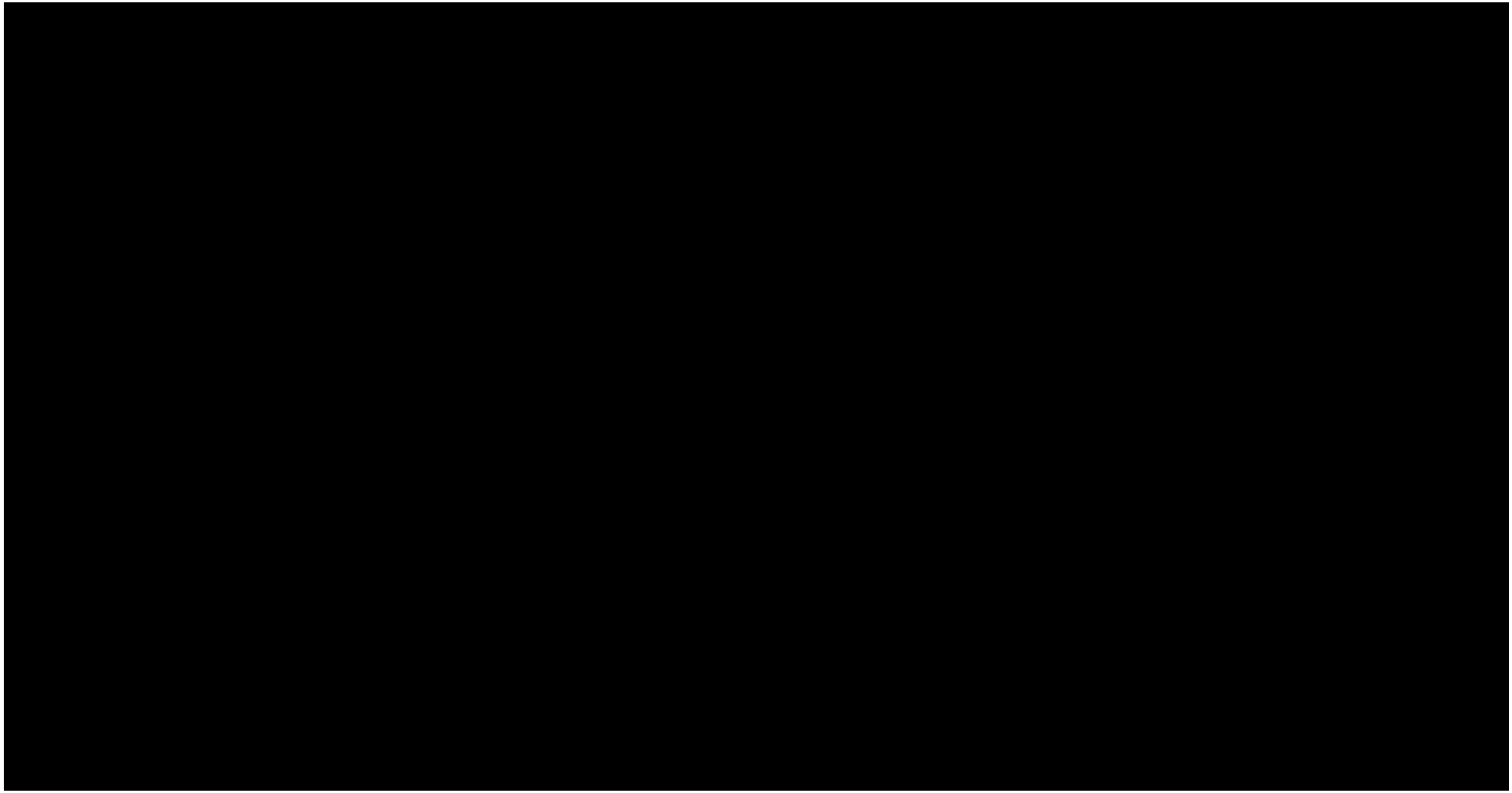
To account for the reduced total body dose of 16 U/kg BW NT 201 (maximum of 400 U for subjects ≥ 25kg BW) instead of 20 U/kg BW NT 201 (maximum of 500 U NT 201) for GMFCS levels I-III specific dose reductions have been introduced in this study. To allow for comparability of efficacy and safety outcomes, the doses to UL(s) are fixed for all GMFCS levels. The uniform dose per treated UL is 8 U/kg BW NT 201 (maximum dose of 200 U). The maximum dose per LL in this study is also 8 U/kg BW NT 201 (maximum dose of 200 U). Limitation of the total dose to LLs in subjects with GMFCS levels IV and V is only necessary in the scenario of unilateral UL plus bilateral LL treatment (treatment combination D. Subjects with GMFCS level IV and V will only

receive 8 U/kg BW as total dose to LLs instead of 12 U/kg BW in subjects with GMFCS level I-III.

Because of the limitation of the total body dose, bilateral LL(s) treatment in combination with bilateral UL treatment will only be allowed for subjects with GMFCS levels I-III at a dose to both LLs of 4 U/kg BW NT 201 (maximum of 100 U).

Dose reduction will not be achieved by reducing the dose to individual muscles but by prioritizing the most important muscles for injection in an individual subject. Therefore, the doses for LL injection treatment displayed in tables for BW-adjusted dosing (see Appendix 16.4) are uniform for all treatment scenarios in this study (see also same section above).

Table 14 Dose ranges for UL clinical patterns and muscles in the High, Mid and Low Dose Group of MP



Injection treatment and post-injection measures

NT 201 will be injected as intramuscular injection at the Baseline Injection Visit of MP and all Injection Visits of OLEX.

If needed, subjects will receive local anesthesia and/or analgosedation to reduce injection related pain and discomfort and to facilitate the injection procedure for the investigator. Analgosedation will be performed by qualified anesthesia personnel only. Procedures will include information of the subject and parent(s) before the start of analgosedation, medication with anesthetics, maintenance and monitoring (e.g., cardiovascular and respiratory). If analgosedation is intended to be used in a subject for the first time, fitness for analgosedation must be ensured first by a general pediatric examination. Fasting times required for some forms of analgosedation (e.g., nitrous oxide) have to be met.

Localization of the target muscle by palpation and anatomical landmarks alone was shown to be inaccurate, except for the gastrosoleus complex [Chin 2005]. To confirm the correct placement of the injection needle in this clinical study, all injections must be guided by at least one of three forms of technical guidance: ultrasound, electrical stimulation [e-stim], and/or electromyography [EMG]. Ultrasound will be the preferred guidance technique. All investigators performing injections of IP must be experienced in technically guided BoNT treatment of children and adolescents with CP.

The maximum dose per injection site should be 25 U NT 201 with a maximum volume of 0.5 mL per injection site for subjects of <25 kg BW. The maximum dose per injection site for subjects of ≥25 kg BW should be 50 U NT 201 with a maximum volume of 1.0 mL per injection site.

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

Following injection of IP, the subject will be under observation for at least 30 min. The subject (if applicable) and parent(s) or caregiver(s) (if applicable) will be asked if any AE has occurred within the 30 min since injection.

8.1.2 Packaging and labeling

Boxes of IP containing NT 201 and PBO vials, if applicable, will be sent to the study sites. If necessary during the course of the study, study sites will be replenished with all study materials. The investigator will administer the IP to the subject during the injection visits only. IP will not be handed over to subjects or parents.

The study medication in MP and OLEX will be labelled according to regulatory requirements in the participating countries. The labels will include as minimum information name and address of the sponsor, study reference number, EudraCT/IND number, medication number, dosage form, route of administration, quantity of dosage

units, batch number, directions for use, storage conditions, period of use and 'For clinical study use only'. Parts of the study medication might be subject of a reduced labelling according to the applicable regulations.

If exchange of IP due to the expiry date should become necessary or if the retest date is extended, the IP will be replaced or relabeled in due time.

Main Period:

For the double-blind MP of this study, the IP for all three dose-groups will have the same printed label information on the outer packaging (box) and the glass vials. See Section 8.4 for details on the blinding procedures planned for MP.

For the double-blind MP, medication kits with one outer box labeled with a medication (randomization) number will be provided. The outer box contains syringes, needles and sterile 0.9% saline for reconstitution purposes, pooling syringes, transfer needles and syringe connectors as well as an inner box including four vials of study medication. Syringes and needles for injection will be provided separately. An inner box of the high dose group contains four vials NT 201. For the mid dose group an inner box contains three vials NT 201 and one PBO vial. An inner box of the low dose group contains one vial NT 201 and three vials PBO. Each of the four vials will be reconstituted with 2 mL sterile 0.9% saline. If a vial should be broken, or a medication inner box should become unusable for any reason, vials from the medication inner box must not be used and the whole box must be replaced from the site stock of study medication using the IV/WRS. As outlined in Section 8.1.1.1 based on the information on chosen treatment combination and BW, the IV/WRS will assign either one or two medication kits with four vials of IP each in MP and OLEX.

OLEX:

In OLEX, two different medication kits will be supplied. A second medication kit will only be necessary for treatment combinations C and E and subjects with BW over 20kg. In both scenarios the total dose exceeds the dose of 400 U provided with a medication kit with 4 vials NT 201. This second medication kit will only contain 1 vial NT 201 with 100U.

For each treatment cycle in OLEX either one (treatment combinations A-E, for C and E subjects with BW <20kg only) or two different medication kits (treatment combinations C and E with subject BW of >20kg) will be assigned via IV/WRS (see also Section 8.1.1.1). The outer box of the medication kit with 4 vials only contains syringes, needles and sterile 0.9% saline for reconstitution purposes as well as an inner box including four vials of study medication. The smaller medication kit contains one vial NT 201 only.

If a vial should be broken, or if a medication inner box should become unusable for any reason, vials from the medication box must not be used and the whole box (either 4 vial box or 1 vial box, as applicable) must be replaced from the site stock of study medication using the IV/WRS.

Only in OLEX, the actual number of vials to be reconstituted depends on the total body dose to be administered (see also Section 8.1.1.2). In contrast to MP, the vials need not to be pooled to achieve the correct final concentration of IP.

For example, for a total body dose of 200 U NT 201 two vials have to be reconstituted, for 400 U four vials from one medication kit, and for 500 U four vials from big and one vial from the small medication kits have to be dissolved. In any case, the total body dose should be calculated before reconstitution to know the exact number of vials for reconstitution and to be able to provide this data to the IV/WRS. For calculations of BW-adjusted dosing the BW will be measured at the respective Injection Visit. Up to 0.4 kg BW will be rounded down. At 0.5 kg and above BW will be rounded up.

8.1.3 Storage of investigational product(s)

The IP will be shipped at ambient temperature. Shipment will be performed under temperature control. Unopened vials should be stored within a temperature range from +2 to +25°C (36-77°F). It is recommended not to freeze the study medication. During storage the minimum/maximum temperature will be recorded in a temperature log. During storage the temperature log should be maintained every business day. For storage of reconstituted IP, see Section 8.1.1. IP must be stored in a locked place during all study periods.

8.1.4 Accountability for investigational product(s)

It is the responsibility of the investigator or pharmacist according to local law to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the 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, date of delivery, quantities, batch number, expiration date, and the medication number assigned to the IP. The form should be filed with the inventory/drug accountability records.

Upon receipt of IP, the investigator or a pharmacist according to local law will visually inspect the shipment and verify the number and condition of IP. Receipt of IP will be confirmed via an IV/WRS by the investigator or authorized site staff. An acknowledgment of receipt form will be send by IV/WRS which should be filed with the inventory/drug accountability records. Use of IV/WRS will be laid down in a user manual.

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 drug accountability and treatment compliance, see Section 8.2.5.

8.1.5 Destruction of investigational product(s)

Upon the completion or termination of the study, all unused and/or partially used IP vials must be returned to the sponsor. Reconstituted but not used IP has to be inactivated at the clinical sites (see Section 8.1.1.1) before used IP vials could be returned to the sponsor. The sponsor or an authorized party will destroy the IP after completion of the clinical study report taking into account local legislation.

8.2 Treatments administered

The study will randomize subjects into three dose groups of NT 201 in MP. In OLEX all subjects will be treated open-label in one dose group with doses equal to the high dose group in MP. The treatment scheme and dose per UL(s) and doses for LL(s) will depend on an individual subject's need for treatment of spasticity. For details of administration, please refer to Section 8.1.1.2.

8.2.1 Methods of assigning subjects to treatment groups

The study is planned as an international multi-center study. At the Baseline Injection Visit (Day 1) of the double-blind MP, subjects will be assigned to one of three dose groups of NT 201 (high, mid, and low) according to a 2 : 1: 1 randomization scheme.

Randomization will be balanced in blocks of appropriate size. The distribution of the IP to the investigational sites and the randomization will be controlled by IV/WRS to ensure a number of enrolled subjects approximately according to the randomization ratio of 2 : 1 : 1 in the three treatment groups. Subjects discontinued from the study will not be replaced.

In this study, two main clinical target patterns have been defined, i.e. *flexed elbow* with an assessment of the AS score for elbow flexors and *flexed wrist* with an assessment of the AS score for wrist flexors. Randomization will be stratified by primary clinical pattern (elbow flexors/flexed wrist) in a 1:1 ratio within each dose group.

In practice, a subject may have up to two main clinical target patterns qualifying for primary efficacy analysis based (a) on the clinical need for IP injection and (b) on the presence of an AS score ≥2 in elbow or wrist flexors. Since no clinical algorithm is existent to decide which of both main clinical target patterns to take for primary efficacy analysis in such a situation, an IV/WRS will be used to achieve an overall equal distribution of primary clinical target patterns flexed elbow and flexed wrist in this study. The selection will be performed by the IV/WRS before randomization to treatment groups (i.e. to one of three dose groups of NT 201 in MP). In case only one main clinical target pattern qualifies for primary efficacy analysis, this pattern will be selected by the IV/WRS. If both main clinical target patterns would qualify for primary efficacy analysis,

the selection has to be in a way that after randomization the distribution of primary clinical target patterns is balanced as much as possible in both treatment groups, or at random, if this is not possible.

For bilateral treatment of UL spasticity both sides must (a) have a clinical need for IP injection treatment in the clinical patterns allowed in this study according to the clinical judgment of the investigator and (b) an AS score ≥2 on each side. For subjects with bilateral UL treatment, the body side for primary efficacy analysis will be decided by the investigator at screening based on clinical judgment.

The responsible randomization officer of the sponsor will allocate treatments to subjects using the computerized randomization program RANCODE (Version 3.6, IDV Datenanalyse und Versuchsplanung, Gauting, Germany). At the injection visit (Day 1) of MP at the investigational site, the IV/WRS will assign to each subject a medication (randomization) number for the medication to be used in MP. At each injection visit in OLEX a separate medication number will be assigned for the medication to be used at the respective visit. The medication (randomization) number(s) of MP will be recorded along with the date of randomization in the eCRF. The medication numbers of OLEX will be recorded with the reinjection dates in the eCRF.

The MP randomization schedule will be sealed and locked in the corporate quality systems of the sponsor and will not be accessible prior to unblinding of MP.

As all subjects in OLEX will receive NT 201, no further randomization is required at the start of this study period.

8.2.2 Selection of doses in the study

In the MP of this study, subjects will be treated in three dose groups NT 201. Doses for each treated UL will be fixed (for details see Section 8.1.1.2). In MP, at least 86 subjects will be randomized to each the mid and the low dose group. Depending on the clinical need for LL injections in addition to UL treatment, a total dose of up to 500 U NT 201 can be administered according to pre-defined treatment combinations (B-E) (see Section 8.1.1.2).

BoNT has proven to be safe and efficacious in the pediatric population with CP in clinical studies. Recommendations by the US organization WE MOVE™ [Brashear and Mayer 2008] and international consensus guidelines state 400 to 600 U BOTOX® as upper total dose limit [Fehlings 2010, Heinen 2010, Love 2010]. The updated European consensus 2009 paper on the use of BoNT for children with CP [Heinen 2010] recommends based on clinical studies a total body dose for BoNT treatment using onabotulinumtoxinA (BOTOX®) of up to 20-25 U/kg BW. This recommendation is based on two BOTOX® trials with multi-level/multi-muscle treatment using doses of 20-30 U/kg BW [Heinen 2006, Molenaers 2009].

In the present combined three arm dose-response and open-label extension study, the maximum dose for unilateral UL treatment is defined to be 8 U/kg BW NT 201 with a maximum dose for subjects ≥ 25kg BW of 200 U per limb. Regardless of combinations of limb treatment needed by an individual subject total body dose limits must be met. For subjects of GMFCS levels I-III this total body dose limit for NT 201 is 20 U/kg BW (maximum 500 U for subjects ≥ 25kg) and for GMFCS levels IV and V 16 U/kg BW (maximum 400 U for subjects ≥ 25kg). These regulations for the safety of subjects are based on the above mentioned data from children/adolescents treated with onabotulinumtoxinA and on the recommendation of the advisory board of six international experts in pediatric CP treatment [Merz Pharmaceuticals GmbH 2011].

As NT 201 has been shown to be used in a ratio of 1 : 1 (NT 201 : BOTOX®) in non-clinical and clinical studies [Benecke 2005, Roggenkamper 2006, Jost 2007], the dosing recommendations for the NT 201 group are justified to be transferred to NT 201. In the MP of this study, the high and the mid dose group of NT 201 treatment will be compared to the low dose group for pediatric use for regulatory purposes [US Food and Drug Administration 2011]. Furthermore, the study will collect experience with standardized dose ranges for NT 201 in uni- and bilateral UL spasticity treatment in pediatric subjects.

The dosing ranges for muscles displayed in Table 14 and Table 15 were adapted according to current expert opinion [Brashear and Mayer 2008] in personal communication with an international advisory board. Each investigator will decide, if maximum dose per UL (8 U/kg BW, 200 U for subjects ≥ 25 kg) and total body doses of 16 to 20 U NT 201/kg BW (maximum 400 U to 500 U for subjects ≥ 25kg BW) and the clinical patterns specified fit an individual subject's need for treatment of spasticity (see also Section 8.1.1.2).

In summary, the selected doses in the NT 201 group and the chosen distribution ranges per muscle are justified to investigate efficacy and safety of NT 201 in the treatment of UL spasticity alone and of combined UL and LL spasticity due to CP in children/adolescents (age 2 to 17 years).

8.2.3 Selection and timing of doses for each subject

The investigator will decide with his/her experience-based judgment in botulinum toxin treatment of CP in conjunction with considering the AS in the target joints, whether treatment of the subject within specified dose limits and treatment patterns in this study is appropriate.

The investigator will assess the current clinical pattern of spasticity of UL(s) and LL(s), if applicable, and will decide which muscles require treatment with BoNT. The investigator will define one UL at the Screening Visit that will serve for (primary) efficacy analyses throughout MP and OLEX. In accordance with inclusion criteria, the AS score of all treated clinical patterns of spasticity including the main clinical target patterns (either flexed elbow or flexed wrist) must be ≥2 at the Baseline Injection Visit V2.

If the contralateral UL is also treated, secondary efficacy analyses in the main clinical target pattern(s) of this limb also will be performed. Allowed adjustments will help tailoring the NT 201 treatment to the individual condition of a subject by deciding on the treated clinical patterns, the dose per selected muscles and the number of injection sites. Details of the treatment are described in Section 8.1.1.2.

After the screening period, IP will be injected once at the Baseline Injection Visit (V2) of the double-blind MP and up to three times in OLEX, if eligibility criteria for reinjection are met up to 16 weeks after the previous injection (for details on eligibility criteria see Section 7.3.1).

8.2.4 Duration of treatment per subject

The screening period before (baseline) injection treatment in MP lasts up to 2 weeks ± 5 days. In MP, subjects will receive one injection treatment followed by an injection-free observation period of 14 weeks ± 14 days (12 to 16 weeks, see Study Flow Chart in Section 6.1.2). After the Final Visit of MP, the subject will continue treatment in OLEX with up to three open-label treatment cycles. Therefore, the total study duration for a single subject is 50 to 66 weeks from Screening Visit to the end of the observation period (End of Study Visit V17). In OLEX cycles also, subjects should show need for reinjection 14 weeks ± 14 days after the previous injection.

8.2.5 Treatment compliance

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

At the beginning of the study, the site will receive drug accountability forms to document how and when IP is administered, returned unused or returned as used empty vials from the site. IP in used, partially filled vials should be inactivated and discarded before returning (methods of inactivation are described in Section 8.1.1.1). Drug accountability forms will be made available to the authorized individuals (e.g., monitor, auditor) and include the following information: study number, dates, quantities, and the medication number assigned to the IP and pediatric study subjects.

8.2.6 Treatment of overdose

An overdose is defined as any deviation from the dose specified in the protocol (doses that are higher than recommended). Any overdose must be recorded in the IP section of the eCRF. Any case of overdose leading to AE(s), SAE(s) or AESI(s) must be reported to the CRO in an expedited manner using the appropriate (SAE) reporting form (see Section 10.1).

A vial with 100 U NT 201 contains less than 1/100 of the estimated adult human lethal dose for BoNT-A following intravenous or intramuscular application (see current IB for additional details [Merz Pharmaceuticals (GmbH) - IB]). As treatment with IP is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this study is estimated to be very low.

There is no significant information regarding overdose from clinical studies in adults with 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 hrs after exposure [Arnon 2001]. Furthermore, signs and symptoms of overdose can result in ptosis, generalized muscle weakness and paralysis of respiratory muscle leading to aspiration pneumonia. Clinical cases of iatrogenic botulism after BoNT injection were reported for four adult patients whose clinical signs were consistent with those of naturally occurring botulism [Chertow 2006].

Symptoms of overdose are not immediately apparent following injection. By the time symptoms of intoxication are observed, treatment with anti-toxin will no longer be effective because the neurotoxin has already irreversibly blocked the transmitter release. Compounds releasing ACh (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

The concomitant medication page in the eCRF should include a detailed list of all medications the subject had received for a period of at least 4 weeks previous to the Screening Visit. Previous phenol and alcohol injections within the last 6 months and BoNT treatments to any body region regardless of the time of administration prior to the Screening Visit should be documented. The record of previous and concomitant medication should include the drug name (trade or generic), route of administration (e.g.,

intravenous, oral), total daily dose/unit (expressed in mg, mL, or IU), indication, the start and stop date (if applicable, date with day, month, and year) for each medication, and if the medication is ongoing at the beginning of the study (concomitant medication).

Similar kind of information should be collected and assessed for any non-drug treatment applied during the study that may have an impact on study results, e.g., physiotherapy, orthotic management, or other rehabilitation measures to treat spasticity. Changes in non-drug treatment (including changes of regimen) during the study are to be documented in the subject's file and in the eCRF. No recording of information on non-drug treatment for the period before the screening is necessary. It also should be noted whether the non-drug treatment is ongoing at the end of the study.

8.3.1 Authorized Concomitant Medication/Treatment

The following concomitant medication/treatment is permitted during the study:

- Drugs acting as central muscle relaxants (e.g., oral baclofen tizanidine) and/or benzodiazepine medication (e.g., diazepam) and/or any other medication with effects on spasticity (e.g., gabapentin, dronabinol) if administered at a stable dose within 2 weeks prior to Screening Visit (V1), within the screening period and for the duration of MP. Administration of benzodiazepines in addition to stable treatment is only allowed as part of an analgosedation procedure on days of injection visits in MP and OLEX after completion of all other study assessments (see also below).

- Antidepressant medication if administered at a stable dose within the 2 weeks prior to Screening Visit (V1), within the screening period and until the end of MP.

- Physical therapy (e.g., strengthening, stretching, and motor training), orthotic management other than casting, and any other rehabilitation treatment are allowed but should preferably be kept stable during study participation. Removable casts will be only allowed in the OLEX of this study.

- At the day of injection visits in MP and OLEX local anesthesia and analgosedation are allowed after completion of all efficacy and safety assessments.

The following concomitant medication is permitted under certain precautions:

- Orally administered drugs that interfere with neuromuscular transmission should be avoided or used with extreme caution because the effect of BoNT might be affected.

- Aminoglycoside antibiotics and spectinomycin because the effect of Botulinum toxin might be potentiated. Alternative treatment options of intercurrent acute infection include 2nd and 3rd generation cephalosporines (e.g., cefazoline, ceftriaxone, ceftazidime), carbapenemes (e.g., imipenem), or nitrofuranes (e.g., nitrofurantoin).[17]

[17] For anti-infective treatment, choice of antibiotics should be made according to guidelines for pediatric use and recommendations of SmPCs for the respective drug (formulation).

- Parenterally administered drugs that interfere with neuromuscular transmission (e.g., tubocurarine-type muscle relaxants used in anesthesia) should be used with extreme caution because the effect of BoNT might be potentiated.

- Aminoquinolines (chloroquine, hydroxyl-chloroquine) because they antagonize the onset of paralysis of BoNT.
- Vaccinations necessary during the course of this study should be performed at least 6 weeks after injections of IP because vaccination side effects (e.g., fatigue) could confound efficacy and safety assessments.

8.3.2 Non-authorized concomitant therapies

These items exclude subjects at Screening and Baseline Injection Visit (see Section 7.3) and are not allowed during the entire study duration:

- Botulinum toxin of any serotype (other than study medication) in any body region within 14 weeks prior to Screening Visit V1 and/or within the screening period.

- Phenol or alcohol injections into any body region within 6 months prior to Screening Visit V1 and/or within the screening period.

- Administered within 2 weeks prior to Screening Visit V1, within the screening period, and/or intended to be administered during the study period:

    - Drugs acting as peripheral muscle relaxants (e.g., dantrolene).

    - Intrathecal baclofen.

    - Oral anticoagulants.

    - Serial casting or functional electrical stimulation of the target joint(s) for injection. Casting will be forbidden during MP, but removable casts will be allowed in OLEX.

- Vaccination within 2 weeks prior to study participation (V1) and/or within the screening period.

- Surgery in the target UL(s) intended to treat spasticity within 12 months prior to Screening Visit (V1), within the screening period or planned for the time of participation in this study.

- Physiotherapy, occupational therapy, or any other rehabilitation measures to treat spasticity (including splinting) is not permitted **prior** to study assessments on the day of any visit as this might influence evaluation of the severity of spasticity.

8.4 Blinding

The study will be conducted in a double-blind fashion in MP only. In OLEX only open-label treatment will be administered. The vials of all three dose groups in MP will have the same appearance. The identity of individual IP will remain unknown to the investigator, medical staff, and subjects. All other individuals involved in the study (e.g., clinical project manager, medical expert, biostatistician, monitors and personal at CRO) will also remain blinded.

A DMC will assess the safety of subjects by safety data reviews throughout the study (see Section 12.4.7.3). The treatment code of an individual subject may be unblinded within the DMC if necessary for the safety evaluation. Detailed procedures for the evaluation of safety data and unblinding will be laid down in the DMC charter. All safety aspects with lifted blind discussed during DMC meetings will be provided for filing in the trial master file only after data base lock and subsequent unblinding of the study.

8.4.1 Emergency envelopes

The RANCODE computer randomization program (see Section 8.2.1) will be used to prepare one complete set of sealed emergency envelopes, which contains all randomization numbers. In case of an emergency, this set of envelopes will allow unblinding of the IP for an individual subject while maintaining the overall study blind. Emergency envelopes will be used by “Infraserv GmbH & Co. Hoechst KG” for emergency unblinding during out-of-office hours.

At the end of study all emergency envelopes must be returned to the randomization officer at the sponsor. Any opened emergency envelope must be returned bearing the date and reason for opening, as well as the initials and signature of the person responsible for breaking the blind.

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

Merz Global Drugs Safety will receive IV/WRS access and a password for unblinding.

The chairperson of the DMC will also receive IV/WRS access and a password enabling him/her to break the blinding code of subjects via this system. The DMC chairperson is responsible for the safekeeping of the password but may delegate this task to the office manager of the DMC.

During its monitoring, the DMC may require to know 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 give advice. In case of such safety concerns which require unblinding of a subject by the DMC, the DMC should confer with Merz prior to performing unblinding of the subject via IV/WRS. Detailed procedures for unblinding in case of a safety concern are laid down in the DMC charter. All non-blinded safety aspects discussed during DMC meetings will be provided for filing in the trial master file only after data base lock and subsequent unblinding of MP.

Further the CRO will also receive IV/WRS access and a password for regulatory unblinding and suspected unexpected serious adverse reaction [SUSAR] reporting to competent authorities and IEC(s)/IRB(s). Personnel involved in unblinding procedures at the CRO will maintain the blinding of all other members of the operational team at Merz and at the CRO.

8.4.2 Unblinding procedures

The blind of MP will not be broken except for the circumstance mentioned for emergency unblinding described above until the blind data review meeting [BDRM] has convened, the statistical analysis plan [SAP] of the MP has been finalized, and the database has been closed. After the blind of MP has been broken, the statistical analysis of results of MP will proceed, which will be documented according to GCP.

9 STUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 Assessments

The following efficacy and safety assessments will be performed during this double-blind, randomized, parallel-group three arm dose-response study. The assessments on the AS used as efficacy variables will be performed by trained investigators only (see Sections 9.1.1.1 and 9.1.1.2). The assessment of AS must be performed after the assessment of GICSs at week 4 of all treatment cycles of MP and OLEX. On days of injection visits, all assessments have to be performed prior to injection treatments. For standardization of laboratory test results, a central laboratory will analyze blood samples in this multi-center study.

An overall description of the study plan is provided in Section 6.1 and in the Flow Chart in Section 6.1.2. The time schedule of assessments is detailed in Section 9.2. A tabular overview of study assessments is given in Table 16 and Table 17.

9.1.1 Clinical evaluations

At the beginning of the study, information such as the subject's medical history, all past and concomitant medications within the last 4 weeks, phenol and alcohol injections within the last 6 months and BoNT medication regardless the time of administration prior to the Screening Visit will be recorded from the subject's file or from information given by the subject (if applicable) and the parent(s) (Section 8.3). Other data will be collected as required, including information obtained from physical and neurological examinations. The GMFCS level will be assessed as described in Appendix 16.8. A review of this information will allow the investigator to assess whether the subject should be enrolled at the Screening Visit. Other screening data will be collected at the Baseline Injection Visit before decision for eligibility and randomization.

Instructions regarding assessments on the scales will be provided in a manual for investigators and will be trained at the investigators' meeting(s) before study start. The same investigator must perform the ratings on the AS at Baseline Injection Visit and Control Visit at Week 4 in MP. Also at all other site visits this investigator should preferably perform the AS ratings to reduce variability of assessments. Preferably the same investigator should interview the subject (if applicable) and the parent at all visits. Preferably, the same parent(s) or caregiver (if applicable)[18] should rate on scales at all visits. Preferentially, all study visits are performed at a similar day time throughout the study to reduce variability of assessments.

[18] In subjects, living e.g. in a special-care unit permanently or most of the time with caregivers being his/her main social contacts, a caregiver may replace parent(s) for the assessment of the respective scales and measures,

Rating on the Investigator's GICS at Control Visit V3 must be performed by the same investigator, who had performed clinical assessment and evaluation of the subject at the Baseline Injection Visit V2. [redacted] The degree of spasticity may change over time, which can be caused either by the natural course of the disease or by treatment. In this clinical study, deterioration of the scores obtained from the scale ratings will generally not be considered as an AE as the score is an efficacy variable and will be biometrically analyzed as such. However, if the investigator considers the deterioration to be unrelated to the underlying disease and rather as an AE, this must be documented on the AE form in the eCRF.

9.1.1.1 Ashworth Scale (AS)

The AS is a well-known and validated scale to categorize the severity of spasticity by judging resistance to passive movement [Ashworth 1964]. In the original and the modified version it is widely used to assess treatment effects of BoNT in clinical studies on adult spasticity [Simpson 1996, Pandyan 1999, Brashear 2002, Barnes 2010] and in many pediatric CP studies (for an overview see [Lukban 2009]).

A placebo-controlled phase 3 study with NT 201 in adults showed robust efficacy results using the original version of the AS [Kanovsky 2009]. This study will use the original form of the AS for efficacy evaluation.

Spasticity will be assessed on the following 5-point scale at visits as outlined in Table 16 and Table 17:

- 0 = No increase in tone.
- 1 = Slight increase in tone giving a "catch" when the limb was moved in flexion or extension.
- 2 = More marked increase in tone, but limb easily flexed.
- 3 = Considerable increase in tone - passive movements difficult.
- 4 = Limb rigid in flexion or extension.

In order to be enrolled, subjects must have an AS score of ≥2 points for elbow flexors or wrist flexors in at least 1 UL (see inclusion criterion in Section 7.2). For initiation of treatment in this study all chosen clinical patterns (UL and LL) must have an AS score ≥2 at the Baseline Injection Visit V2 of MP.

The passive movement of each treated joint will be carried out over a duration of about 1 s (1 s should be determined by counting "one thousand and one"). The assessment will be performed for no more than 3 consecutive times. All investigators involved in the

assessment on the AS must be trained for the rating in this study and training must be documented. A pre-study rater training session will be performed at the investigator meeting to reduce inter-rater variability throughout investigational sites. Any investigator who did not participate at the investigator meeting will receive training documents including a manual on AS assessment for self-study. Assessment of the AS must only be conducted by trained investigators.

The same investigator must perform AS assessment at Baseline Injection Visit V2 (before IP administration) and at Control Visit V3 at Week 4 of MP for an individual subject. The same investigator should preferably perform AS assessments at all other study visits in MP [redacted] for an individual subject.

It is mandatory for the investigator to assess the clinical patterns flexed elbow, flexed wrist, and clenched fist in the UL(s) selected for treatment. This means, that for unilateral UL treatment, these three patterns of the treated body side have to be assessed, whereas for bilateral treatment the three respective clinical patterns of both ULs have to be evaluated with the AS. Furthermore, the AS has to be utilized for each other treated UL or LL clinical pattern, such as thumb in palm, pronated forearm, pes equinus, flexed knee, and adducted thigh. An exemption is the clinical pattern extended great toe, for which no AS assessment has to be documented.

Limb positioning for each AS assessment will be described in an instructional outcome manual, must be documented with the AS assessment and also recorded in the eCRF. The limb positioning chosen for AS testing by the investigator in an individual subject at V2 has to be kept throughout study participation. Reasons for deviations from the initially chosen positioning e.g. newly developed contractures have to be documented in the eCRF.

9.1.1.2 Global Impression of Change Scales (GICS)

The Global Impression of Change Scales (GICS) are subjective global outcomes to assess independently the investigator's, child's/adolescent's, and parent's or caregiver's (if applicable) impression of change due to treatment. Caregiver(s) may substitute parent(s) for the assessment of GICS, if they are main social contacts of subjects, e.g. in a special-care home.

At Week 4 of each treatment cycle in MP [redacted] the investigator, child/adolescent (if applicable), and parent(s) or caregiver (if applicable) evaluate the global change of spasticity separately in UL and LL (if applicable). The GICS will be provided in local language.

Since the Investigator's GICS is based on the clinical impression of the change due to treatment of the subject's spasticity compared to the condition before the last injection, the same investigator, who has performed clinical assessments at the Baseline Injection Visit V2 of MP must rate on this scale at Control. Visit V3 at Week 4 of MP. [redacted]

[redacted] All assessments of GICS will be made before AS assessments in order not to be confounded by these assessments.

The question of the GICS for the investigator is:

'Based on your clinical experience, what is your overall impression of change of the subject's upper/lower limb spasticity due to treatment, compared to the condition before the last injection?

Please check the one option that best fits your overall impression of change.'

For the GICS versions for child/adolescent and parent(s)/caregiver please refer to Appendix 16.3. For children/adolescents and parent(s) or caregivers who are not willing or able to the self-assessment, the respective GICS versions will not be assessed. If children/adolescents can not self-complete the questionnaire due to e.g. motor abilities, the clinical staff can ask the GICS. Only one score for parent(s) or caregiver will be recorded in the eCRF even when more than one parent or caregiver is present at study visits. Therefore, parents/caregivers have to agree on the assessment or the assessment has to be delegated to one person.

The response option for all GICS versions is a common 7-point Likert scale that ranges from -3 = very much worse to +3 = very much improved:

+3	☐	Very much improved
+2	☐	Much improved
+1	☐	Minimally improved
0	☐	No change
-1	☐	Minimally worse
-2	☐	Much worse
-3	☐	Very much worse

9.1.1.3 Questionnaire on Pain caused by Spasticity (QPS)

The QPS is a patient-reported outcome for children and adolescents (2-17 years) with CP on spasticity-related pain. A self-report version for the children/adolescent, an interview-version for the children/adolescent, and a proxy-report version for the parent(s)/caregiver are available for both UL and LL spasticity-related pain assessment. For this study, in addition to the UL versions that will be used for all subjects/parents/caregivers the LL versions will also be used for subjects with treatment combinations including UL and LL

treatment. While pain intensity is reported by the children/adolescents, pain frequency (based on observed pain behaviors) will be documented by the parent(s)/caregivers. Thus, the information provided by the children/adolescents complements the one of the parents/caregivers. Pain intensity and frequency of the QPS are assessed for general pain and for four different activity situations. The situations are described in different questions for rest, normal day activities, physical exercise and for an individually defined 'very hard thing to do".

The parent/caregiver version of the QPS should be always completed and always (if possible) from the same parent/caregiver throughout the study. Caregiver(s) may substitute parent(s) for the assessment of QPS, if they are main social contacts of subjects, e.g. in a special-care home. Based on the cognitive, communicative, and motor abilities of a subject, the QPS will be self-administered by the subject or the interview version will be used by the site staff. If no assessment by the subject is possible due to age or cognitive impairments, only the parent(s)/caregiver will complete their instrument version.

The assessment of spasticity associated pain by the subject or parent(s)/caregiver will be done at all personal visits in MP [redacted] Only the QPS versions applicable for the chosen treatment combination (A-E) will be utilized (i.e. UL or UL and LL). The different final versions of the questionnaire are displayed in Appendix 16.6.

[redacted]

[redacted]

9.1.1.5 Investigator's Global Assessment of Tolerability

The Investigator's Global Assessment of Tolerability is an estimation made at the end of treatment cycles in MP and OLEX. This evaluation bases on a 4-point ordinal scale proved useful in several phase 3 clinical studies conducted with NT 201 (see IB for additional information [Merz Pharmaceuticals (GmbH) - IB]).

The global assessment will be made on the following 4-point ordinal scale (see Table 16 and Table 17):

- 1 = very good.
- 2 = good.
- 3 = moderate.
- 4 = poor.

The investigator will assess the scale at the Final Visit of MP V5, the End of Cycle Visits V9 and V13 and at the End of Study Visit (V17).

9.1.1.6 Adverse Events and Adverse Events of Special Interest

Subjects (if applicable) and parent(s) or caregivers (if applicable) will be requested to report all AEs to the investigator or site staff. It is the obligation of the investigator and/or any delegate to detect AEs by questioning the subject (if applicable) and parent(s) or caregiver(s) (if applicable) at each site visit or telephone contact.

For the detection of AESIs possibly indicating toxin spread, the investigator or delegate must actively question the subject (if applicable), the parent(s) or the caregiver (if applicable) at visits and TC. Caregiver(s) may qualify for being questioned for AEs/AESIs, if they are the main social contacts of subjects, e.g. in a special-care home. The questioning and documentation of answers will be standardized. To facilitate detection of AEs related to toxin spread active questioning for AESI will start before the 1st injection in this study at V2. Thereby, investigators will be able to detect pre-existing symptoms and conditions that could possibly confound AESI questioning. If an (S)AE is detected at AESI questioning at V2 this has to be recorded accordingly in the eCRF.

If a TC identifies a (S)AE/AESI that needs confirmation or treatment, (e.g., respiratory disorder, dyspnoea, aspiration, dysphagia, speech disorder, dysphonia, other signs of bulbar palsy or botulism) the investigator must schedule a Safety Visit [SV] in addition to the scheduled visits as soon as possible after the TC.

At injection visits, AE questioning will be done prior to and 30 min after injection treatment. (see Section 10.1).

All AEs observed throughout the course of the study must be documented in the eCRF. For definitions and details regarding documentation and reporting of AEs see Sections 10.1 to 10.3.

9.1.1.7 Physical and Neurological Examination

The investigator will perform physical and neurological examinations for subjects at Screening Visit, at the Final Visit of MP and at the End of Study Visit (V17) (see Table 16 and Table 17). The physical and neurological examination will cover standard physical and neurological examinations. Any abnormal findings will be documented in the subject's medical file. The investigator will confirm the conduct of these investigations in the eCRF.

9.1.1.8 Vital Signs

Vital signs (i.e., systolic and diastolic blood pressure, heart rate) will be assessed at each visit (see Table 16 and Table 17). Vital signs will be recorded in sitting or lying position after the subject has rested for at least 5 minutes.

9.1.1.9 Body Weight and Height

Body weight (BW) and height will be assessed at Screening, at the Baseline Injection Visit V2, at the Final Visit of MP V5, at all Injection Visits of OLEX (V6[19], V10 and V14) and at the End of Study Visit (V17) (see also Table 16 and Table 17).

9.1.2 Laboratory evaluations

9.1.2.1 Clinical and research laboratory evaluations

Laboratory evaluations will be performed as possible for the age group of the subject. The bulletin of the World Health Organization [WHO] 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 8 weeks were

[19] If visits at the end of treatment cycle in MP or OLEX (i.e. V5, V9, and V13) and the Injection Visit of the following cycle (i.e. V6, V10, and V14) will be performed on the same day, BW and height can be transferred.

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.

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 as well as for testing antibodies against BoNT 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 BW

Maximum blood volume per withdrawal: 1% of TBV

Maximum blood volume withdrawn per 12 weeks: 3% of TBV

A central laboratory capable to properly handle the relatively small samples volumes (as compared to those usually obtained from adult subjects) will perform the analyses. The following blood (serum) volumes are necessary to result in sufficient samples for the respective tests:

- Clinical chemistry (including glucose, AP): 1.2 mL blood
- Hematology: 1.2 mL blood
- Fluorescence immunoassay [FIA]: 4.0 mL blood (1.5 mL serum)
- Hemidiaphragm assay [HDA]: 10.0 mL blood (4.0 mL serum)

9.1.2.1.1 Clinical chemistry and hematology

Blood samples for the determination of clinical chemistry (including blood glucose and AP) and hematology will be drawn in volumes appropriate for the BW of the subject at Screening Visit (V1), at the Injection visit (V6) and at the End of Study Visit (V17).

Blood samples will be analyzed at a central laboratory that is capable to handle small volumes from pediatric samples. The amount of blood, number, kind and size of tubes, sample processing at the site as well as storage conditions will be specified in a separate instruction manual provided by the central laboratory. Depending on the involved countries and their county specific regulations, local laboratories could be involved as needed.

Clinical chemistry analysis includes the following serum parameters: sodium, potassium, creatinine, urea/blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, AP, gamma glutamyl transferase, total bilirubin, glucose, and total cholesterol. Based on lab values for creatinine and on the subject's height on the day of the blood draw the glomerular filtration rate [GFR] will be estimated [eGFR]. This calculation will be done using the "Schwartz" formula [Schwartz 2009, Schwartz 2009].

Hematology will be assessed at the same visits as clinical chemistry. Hematologic analysis of EDTA blood comprises hemoglobin, hematocrit, erythrocytes (red blood count), leukocytes (white blood count), lymphocytes (absolute), monocytes (absolute), neutrophils (absolute), eosinophils (absolute), basophils (absolute), platelets.

Any laboratory result outside the normal range must be graded by the investigator or delegate as "abnormal, not clinically relevant" or "abnormal, clinically relevant". A laboratory abnormality should be regarded as an AE if the investigator judges the value to be significantly worse than prior to study start or if relevant abnormal values are newly detected during the study, i.e., from signature of IC onwards. Relevant abnormal laboratory values should be recorded on the AE Form of the eCRF.

9.1.2.1.2 Pregnancy Testing

In females with history of menarche (i.e., 1st menstrual bleeding), samples drawn for serum clinical chemistry will also be used to determine human chorionic gonadotropin at Screening and at the End of Study Visit (V17). On injection days (Injection Visits V6, V10 and V14), urinary pregnancy tests will be performed. If required by country-specific regulations, urinary pregnancy tests may also be performed at all other personal contacts in MP and OLEX (see also Table 16 and Table 17).

9.1.2.1.3 Antibodies against Botulinum Toxin

For analysis of antibodies against BoNT blood amounts appropriate in the context of all blood withdrawals during the study for the weight group of the subject will be taken (Section 9.1.2.1).

The serum amount necessary for FIA-AB is 1.5 mL and 4 mL for HDA. The estimated blood amount to yield the required serum amount is 4 mL for FIA-AB and 10 mL for HDA. For subjects ≥21 kg BW samples will be collected at the start of the study at Screening Visit and at the End of Study Visit (V17). For subjects <21 kg BW no blood samples for analysis of antibodies against BoNT will be taken to avoid an additional blood draw, if blood draw for the sample used for HDA testing would be only performed after a positive result of the FIA-AB test.

Sample work-up at the study site include 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 reacts with the toxin, but the FIA-AB is not capable to discriminate between neutralizing and non-neutralizing antibodies [Göschel 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.

9.1.2.2 Specimen preparation, handling, storage, and shipping

Blood samples for clinical chemistry, hematology, and human chorionic gonadotropin will be tested by a central laboratory and will be handled according to the instructions of the central laboratory.

Blood samples intended for determination of antibodies against BoNT-A will be analyzed by [redacted] and [redacted]. Details of storage and coding as well as shipping procedures for these samples will be provided in a separate manual of operations.

No biological samples will be retained after this clinical study after the final clinical study report for this clinical study has been established.

9.2 Visit schedule

The purpose of the Screening Visit (V1) is to perform the check of a subject's eligibility for study participation. If all inclusion criteria and none of the exclusion criteria to be checked at Screening Visit (V1)/Baseline Injection Visit (V2, Day 1) are met (see Sections 7.2 and 7.3, the subject will be randomized to one of three dose groups of NT 201 by the IV/WRS. In subjects where both main clinical target patterns would qualify for injection, the main clinical target pattern for primary efficacy analysis will be randomized by an IV/WRS (for details see Section 8.2.1). After randomization, subjects will receive their 1st injection treatment with NT 201.

In OLEX three further treatments with NT 201 with the dosing regimen of the high dose group of MP will follow. After injections on the days of injection visits, the subject will be observed for a minimum of 30 minutes for immediate safety issues. The effect and safety of the treatment will be further observed until Week 12 to 16 (Week 14 ± 2 weeks) in each cycle of MP and OLEX.

Including Screening and Baseline Injection Visit, the subject and the parent(s) will come to the site for 14 visits and will have four telephone contacts. The number of visits may increase, if the Injection Visits of OLEX will be scheduled to revisits to a maximum of 17. To get additional information for scheduling reinjection at the end of MP, one additional optional telephone contact can be performed. Subjects (if applicable) and/or the parent(s) will be contacted by telephone at 7 days after injection treatments (TC1, TC2, TC3 and TC4 at Day 8 of the respective MP or OLEX treatment cycle).

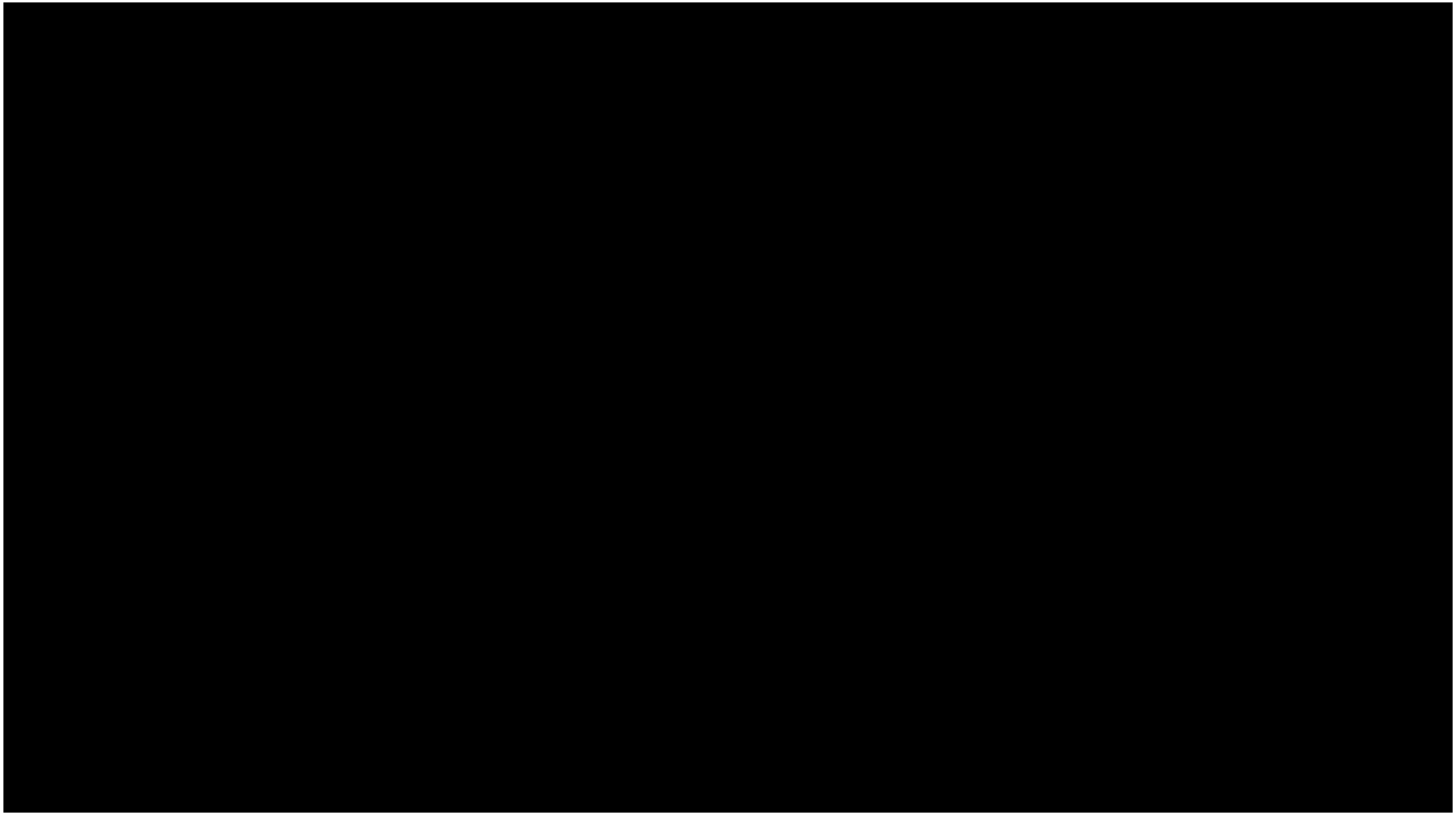
If any Telephone Contact identifies an (S)AE/AESI that needs confirmation or treatment (e.g., respiratory disorder, dyspnoea, aspiration, dysphagia, speech disorder, dysphonia, other signs of bulbar palsy or botulism), the investigator will schedule a SV as soon as possible after the Telephone Contact. At 28 and 56 days after injection treatment of each cycle subjects will have Control Visits at the site (V3, V7, V11 and V15 at Day 29 and V4, V8, V12, and V16 at Day 57, respectively).

In case eligibility criteria for reinjection are not fulfilled at a scheduled visit (Final Visit of MP or End of Cycle Visits V9 and V13) at the end of an treatment cycle, the Injection Visit of the following treatment cycle can be postponed and rescheduled within up to 16 weeks after the previous injection treatment (for details see Section 6.1)

Attempt should be made to arrange all visits at the same day time for an individual subject (i.e., morning or afternoon) to standardize treatment and assessment conditions. [20] The End of Study Visit will be at Week 14 ± 2 weeks (Day 99 ± 14 days) of 4th treatment cycle. Study activities and visit schedule are detailed in Table 16 and Table 17.

[20] If the Final Visit of MP and the 1st Injection Visit of OLEX will be performed on the same day the results of these assessments can be transferred from V5 to V6.

Table 16 Overview of Study Activities Main Period MP



[redacted]

[redacted]

Table 17 Overview of Study Activities in Open-Label Extension Period OLEX

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., investigator, subject- and/or parent-reported outcome variables during the course of the study) are not intended to 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. Pre-existing conditions that do not worsen during the course of the study are not reportable as AEs. Abnormal clinical relevant laboratory values obtained during the screening period will only meet AE criteria if newly detected. However, if laboratory values resulting from pre-existing conditions worsen to clinical relevance during the course of the study AE criteria are met.

The period of observation for an AE extends from the time when the IC form was signed until the End of Study Visit, i.e., 12 to 16 weeks after last administration of IP in OLEX. Any medical occurrence that happens between the time when the IC form is signed and the 1st intake of IP is an AE and has to be documented in the subject's file and in the eCRF AE report form. Any ongoing AEs will not be followed up after the End of Study Visit, which is scheduled up to 16 weeks after last injection of IP in OLEX.

Data pertaining to AEs will be collected during each study visit based on the subject's (if applicable) or parent(s)'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's file and on the eCRF AE report form. The following information must be recorded:

- AE diagnosis or main symptom.
- Date of onset.
- Date of worsening.
- Intensity (maximum observed; see Section 10.1.1).
- Causal relationship (not related, related, see Section 10.1.2).
- Serious (yes or no, see Section 10.2).

- Outcome (see Section 10.1.3).
- Action taken with IP(s) (see Section 10.1.3).
- AE leading to discontinuation of the study (yes or no).
- Stop date.

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

In case of an SAE, or AESI (alert term, as defined in Section 10.3), the investigator must also complete an SAE report form or AESI report form and report it to the CRO within 24 hours, as described in Section 10.2 and 10.3.

Treatment of overdose with IP 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 the daily activities.

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

10.1.2 Definition of causal relationship with investigational product(s)

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(s) taken with IP:

- Drug withdrawn.
- Dose reduced.
- Dose increased.
- Dose not changed.
- Unknown.
- Not applicable.
- Drug withdrawn temporarily

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.[30]
- Unknown.

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.[31]
- Requires inpatient hospitalization, or prolongation of existing hospitalization.

[30] If there is more than 1 AE, only the AE leading to death will be attributed with a 'fatal' outcome.

[31] The term 'life-threatening' in the definition of 'serious' refers to an event in which the child/adolescent 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.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Consists of any other medically important condition.[32]

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. Hospitalizations for analgosedation starting one day before or on the day of injection treatment (V2 and V7) for organizational reasons only (e.g. to allow for an early start of the Injection Visits in the morning in subjects living far from the site) are generally not regarded as SAEs. However, if any event during or after analgosedation would trigger an overnight stay, this will qualify as SAE. The same applies, if analgosedation was started in an outpatient setting at the site and then has be changed to an inpatient setting, e.g. due to an unexpetedly long monitoring phase post intervention.

All SAEs that occur during the study period, whether considered to be related to IP 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, initials).
- 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 individual(s) listed below.
[redacted]

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

If SAE fax fails, use email as back-up for all regions:

Email: [redacted]

If the report is sent via email then the completed and signed fax form must be attached to the email. A simple notification email of the event is not sufficient.The CRO will transmit all SAE reports within 1 business day to Merz drug safety.

The investigator, Merz Pharmaceuticals GmbH, and the CRO will comply with the applicable regulatory requirements related to the reporting of suspected unexpected serious adverse reactions [SUSAR]s to the regulatory authorities and the IEC(s)/IRB(s).

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

The investigator must supply further supporting information within 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 drug safety department at 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 a final outcome and date are available. These SAEs will be followed-up only in the Global Drug Safety database after final SAE reconciliation is completed.

All SAEs will be reviewed by the DMC. Details will be described in a DMC charter.

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

10.3 Adverse events of special interest (alert terms)

AEs occurring after treatment that are thought to possibly indicate toxin spread are defined as AESIs (see Table 18). The subject (if applicable) and parent(s) will be actively asked by the investigator or an authorized delegate at each visit starting at V2 as well as during the telephone contact (starting at TC1 in MP) if any of the AESI occurred since the last contact. The questioning and documentation of answers will be standardized. AESI questioning at V2 will facilitate recording of pre-existing conditions and/or possibly undetected (S)AEs that could confound AESI questioning post injection of IP.

The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, by telefax to the responsible CRO within 24 hrs of knowledge of the event. The CRO will transmit these AESIs to Merz Pharmaceuticals GmbH. Each

AESI must be reported by the site on the AESI reporting form. Moreover, AESIs should be reported on the general pages of the eCRF as well as in the subject's file. The AE form in the eCRF as well as the eCRF pages for Medical History/Concomitant Diseases and for Previous/Concomitant Medication and Non-Drug Treatment shall be faxed/sent along with the AESI reporting form.

Table 18 List of Adverse Events of Special Interest Possibly Indicating Toxin Spread

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

All AESIs will be reviewed by the DMC on a regular basis. Details will be described in a DMC charter. For this study, the AEs in Table 18 are defined as AEs of special interest.

10.3.1 Expected adverse events

Expected AEs are those listed in the reference safety information of the current IB [Merz Pharmaceuticals (GmbH)]. Indication-specific expected AEs are not yet available as upper limb spasticity in children and adolescents is a new explorative indication.

10.3.2 Unexpected adverse events

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

10.4 Pregnancy

Each pregnancy that starts during the study must be reported by the investigator to the drug safety department of the CRO within 24 hours of learning of its occurrence (see Section 10.2 for reporting address). Pregnancies and pregnancy follow-up should be reported on a pregnancy monitoring form. Pregnancies should be followed up until delivery. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the IP Each normal pregnancy has to be reported as a non-serious AE (drug exposure before or during pregnancy). Any abnormal pregnancy or pregnancy outcome has to be reported as SAEs. If pregnancy occurs before injection visits, the female will meet exclusion criteria. If pregnancy occurs after the 1st injection visit (V2), participation in the study will continue with all applicable visits until the end of the respective cycle (except invasive procedures such as blood drawing). A final examination (End of Study Visit, also except for invasive procedures such as blood drawing) should be performed at the end of the respective cycle. After the End of Study Visit the study participation will be terminated.

10.5 Other safety variables

In addition to the assessment of AEs, the following safety variables will be observed during this study. For additional details see Sections 9.1.1.5 to 9.1.1.9.

- Investigator's Global Assessment of Tolerability.
- Vital signs (blood pressure, heart rate).
- BW, height.

- Clinical chemistry (including AP, blood glucose) and hematology.
- Occurrence of subjects with antibodies against BoNT-A.

11 DATA QUALITY ASSURANCE

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

11.1 Standardization procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data including methods to ensure standardization among sites (e.g., training, newsletters, investigators' meeting, monitoring, and central laboratories). Investigators will be trained on the scales, on injection techniques and on IP handling during the investigators' meeting. Any investigator who did not participate at the investigators' meeting will receive training documents for self-study. Injections and assessment of scales must only be conducted by trained investigators.

This study will be monitored regularly by a qualified monitor from the CRO according to GCP 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 should be entered and/or filed in the respective subject's 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 the subject (if applicable) and the parent(s) have agreed to the primary physician being informed). The subject's file must also contain a descriptive statement on the IC procedure (see Section 3.3.2).

Electronic data capture using eCRF is planned to be used at all study sites.

All entries have to be entered 1st in the subject file, e.g., details on IP administrations, questioning of AESIs [redacted]. The participation in this study must be appropriately documented in the subject's file with study number, subject number, and date of subject information, date of IC, and date of each visit.

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. 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 any corrections of initial data.

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

11.3 Data management

Data required according to this protocol is to be recorded in the web-based eCRFs (electronic data capture system [redacted]) provided by Merz Pharmaceuticals/[redacted]. All persons who will enter data into the eCRF will be trained by e-learning tool. After the successful completion of the training all participants will receive a training certificate. The access to the e-learning and to the eCRF is password controlled.

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

Laboratory and antibody data will be received electronically and merged to the eCRF data (but not uploaded into the EDC system). Plausibility checks will be performed to ensure correctness and completeness of these data. The sponsor's data management function will be responsible for data processing, in accordance with the sponsor's data management procedures.

Database close will occur only after quality control procedures have been completed.

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

After all data of OLEX are entered and all queries are solved, the database of OLEX will be closed. In case of any changes to the data after database close, these changes will be documented according to respective SOP.

11.4 Monitoring

This study will be monitored regularly by a qualified monitor from the CRO according to GCP guidelines and the respective SOPs. Monitors will be trained during a monitoring training meeting. 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 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.

In addition, the monitor will check whether all AEs (including pregnancies), AESIs, 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's files prior to 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 screening/enrollment log.

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 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 contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). 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 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/unblinding of MP or database close of OLEX, 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 including MP and OLEX.

12.1 Determination of sample size

[redacted]

An estimated total number of 258 (with randomization ratio of 2:1) subjects will provide 96.5% power to show a statistically significant difference between the NT 201 high dose group (172 subjects) and the NT 201 low dose group (86 subjects) at an alpha level of 0.05 (two-sided t-test, [redacted]

An estimated total number of 172 subjects (with randomization ratio of 1:1) will provide 90.3% power to show a statistically significant difference between the NT 201 mid dose

group (86 subjects) and the NT 201 low dose group (86 subjects) at an alpha level of 0.05 (two-sided t-test, [redacted] in the primary efficacy variable.

For the co-primary efficacy variable 'Investigator's GICS 4 weeks after injection' again data of [Childers 2004] were used. [redacted]

When conservatively accounting for missing data of about 3% and considering the required N=258 (randomization ratio 2:1) subjects for the treatment comparison of the primary efficacy variable a mean treatment response difference of 0.582 points with a pooled common standard deviation of 1 will still provide 99.2% power to show statistically significant superiority in the co-primary variable in favor of NT 201 high dose group versus low dose group.

An estimated total number of N=172 subjects (with randomization ratio of 1:1) will provide 96.7% power to show a statistically significant difference between the NT 201 mid dose group (86 subjects) and the NT 201 low dose group (86 subjects) at an alpha level of 0.05 in the co-primary efficacy variable.

It is estimated that the sample size of N=344 subjects will provide 95.7% power (product of the single power calculations for both the primary and the co-primary efficacy variable for the high versus low dose treatment comparison) to show a statistically significant difference between NT 201 high dose and NT 201 low dose group. A power of 87.3% is provided for the treatment comparison of the mid versus the low dose in both primary and co-primary efficacy variables.

Using a randomization ratio of 2:1:1 at least 172 subjects will be randomized to the NT 201 high dose treatment group, at least 86 subjects will be randomized to the NT 201 mid dose treatment group and at least 86 subjects will be randomized to the NT 201 low dose treatment group.

12.2 Analysis sets

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

Safety Evaluation Set (SES)

The SES is the subset of all subjects treated in the MP with study medication at least once.

Full Analysis Set (FAS)

The FAS is the subset in the SES of the MP for whom the primary efficacy variable or co-primary efficacy variable is available (i.e., all subjects who have at least an AS score in the clinical pattern flexed elbow or flexed wrist at baseline (Day 1) or the Investigator's GICS at Day 29 (Week 4)).

Per Protocol Set (PPS)

The PPS is the subset in the FAS of the MP without major protocol deviations. Major protocol deviations will be defined during the BDRM for MP.

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

Safety Evaluation Set (SES)

The SES is the subset of all subjects treated in OLEX with study medication at least once.

Full Analysis Set (FAS)

The FAS is the subset in the SES of OLEX for whom at least one value of the AS score in the OLEX for the primary clinical pattern flexed elbow or flexed wrist is available.

12.3 Variables for analysis

12.3.1 Efficacy variables

12.3.1.1 Primary efficacy variable

Primary efficacy variable and the co-primary efficacy variable will be determined for MP only.

- Primary efficacy variable is the change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4) of MP.
  An IV/WRS will be used for selection and randomization to treatment groups in MP, if two main clinical target patterns would qualify for primary efficacy analysis based

on (for further details see Section 8.2.1)
(a) clinical need for IP injection in combination with
(b) an AS score of ≥2.

The other main clinical target pattern (if treated) will be analyzed as key secondary variable (see below). For subjects with bilateral UL treatment, the body side for analysis will be decided by the investigator at screening (for details see Section 8.2.1).

- Co-primary efficacy variable is the Investigator's GICS at Day 29 (Week 4) of MP.

12.3.1.2 Key-Secondary and secondary efficacy variables

Secondary efficacy variables will be determined for MP only.

Key-secondary efficacy variables are:

- Change from baseline in AS score of the **other treated main clinical target pattern** (i.e. of elbow flexors or wrist flexors, if treated) at Day 29 (Week 4) of MP. This analysis will be performed in case two target patterns would qualify as main clinical target pattern for the main clinical target pattern not analyzed as primary efficacy variable. For subjects with bilateral UL treatment body side to be analyzed is decided by investigator at screening (for details on definition see 8.2.1).

- Change from baseline in AS score of treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Day 29 (Week 4) of MP. For subjects with bilateral UL treatment body side to be analyzed is decided by investigator at screening (for details on definition see 8.2.1).

Secondary efficacy variables are (MP only):

- Change from baseline in AS score for each treated clinical pattern (e.g., flexed elbow, flexed wrist, clenched fist, etc.) of the UL at all other post baseline visits of MP. For subjects with bilateral UL treatment body side to be analyzed is decided by investigator at screening.

- Change from baseline in scores of pain intensity (from subjects) and pain frequency (from parent/caregiver) assessed with 'Questionnaire on Pain caused by Spasticity [QPS]' to all post baseline visits of MP.

- Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) of MP.

[redacted]

[redacted]

12.3.2 Pharmacodynamic variables

Not applicable.

12.3.3 Pharmacokinetic variables

Not applicable.

12.3.4 Pharmacogenetic variables

Not applicable.

12.3.5 Safety variables

12.3.5.1 Primary safety variables

Not applicable

12.3.5.2 Secondary safety variables

Secondary safety variables will be determined for MP and all OLEX cycles. Safety variables comprise:

- Occurrence of TEAEs overall and per treatment cycle.
- Occurrence of TEAESIs overall and per treatment cycle.
- Occurrence of TESAEs overall and per treatment cycle.
- Occurrence of TEAEs related to treatment as assessed by the investigator overall and per treatment cycle.
- Occurrence of TEAEs by worst intensity overall and per treatment cycle.
- Occurrence of TEAEs by worst causal relationship overall and per treatment cycle.
- Occurrence of TEAEs by final outcome overall and per treatment cycle.
- Occurrence of TEAEs leading to discontinuation overall and per treatment cycle.

12.3.5.3 Other safety variables

Other safety variables will be determined for MP and all OLEX cycles. Safety variables comprise:

- Investigator's Global Assessment of Tolerability at Day 99 (Week 14) of MP and all OLEX cycles.
- Vital signs (blood pressure, heart rate) at all visits of MP and all OLEX cycles.
- BMI, weight and height at Screening V1, Baseline Injection Visit V2, at the Final Visit of MP V5, at all Injection Visits of OLEX (V6[33], V10 and V14) and at the End of Study Visit (V17).

[33] If V5 and V6 will be performed at the same day, BW and height can be transferred from V5 to V6.

- Clinical chemistry and hematology at Screening V1, the Injection Visit V6 of OLEX and the End of Study Visit (V17).

- Occurrence of antibodies against BoNT-A in subjects ≥21 kg BW.

12.3.6 Other variables

Other variables of interest are the subject dispositions, demographic data, baseline characteristics such as medical history, concomitant diseases, previous and concomitant therapies, CP history (e.g., distribution, comorbidities), clinical patterns, GMFCS level, BoNT-A pre-treatment status, and use of anesthesia/analgosedation for injection treatments.

12.4 Statistical analysis methods

12.4.1 Efficacy variables

All efficacy analyses will be based primarily on the FAS and additionally, for sensitivity purposes, on the PPS. Statistical tests will be two-sided hypothesis tests for between-treatment differences in general. Treatment differences will be tested for comparison of the high versus low dose treatment group and the mid versus low dose treatment group, respectively.

Continuous variables (values and changes from baseline) will be summarized by number of non-missing observations (N), mean, SD, median, 1st and 3rd quartile, minimum, and maximum or/and as counts and percentages. For qualitative variables, absolute and percent frequencies (N, %) and, if applicable, shift tables will be displayed. Two-sided 95% confidence limits and descriptive p-values will be given, where appropriate.

Descriptive summary statistics will be performed at all visits of MP and OLEX and if applicable for the changes from baseline (Day 1 of each treatment cycle) to all post-baseline visits of each treatment cycle.

12.4.1.1 Primary and key-secondary efficacy variables

Testing of the primary, co-primary and key-secondary efficacy variables will be performed in a 4-step approach using a hierarchical test procedure as described in detail below.

The primary efficacy variable is the change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4) of MP. A mixed model repeated measurement analysis (MMRM, two-sided, significance level α=0.05) with comparison of least square means will be used for the confirmatory analysis to detect differences between the high and low dose treatment groups. The dependent variable is the primary efficacy variable. The independent variables are defined as

treatment group (high dose, low dose), site (or pooled sites), BoNT-A pre-treatment status (pre-treated, treatment naïve) as fixed factors, visit*treatment as interaction term, and visit as repeated factor. The covariates are the AS score of the primary clinical target pattern at baseline (Day 1 of MP) and the GMFCS level at screening.

Co-primary efficacy variable: An ANCOVA approach (2-sided, significance level alpha=0.05) with comparison of least square means will be used for the confirmatory analysis of the co-primary efficacy variable. The dependent variable is defined as the 'Investigator's GICS at Day 29 (Week 4) of MP'. The independent variables are defined as treatment group (high dose, low dose), site (or pooled sites), BoNT-A pre-treatment status (pre-treated, treatment naïve) as fixed factors and the covariates are the maximum AS score of the two possible primary clinical target clinical patterns flexed elbow or flexed wrist at baseline (Day 1 of MP) and the GMFCS level at Screening Visit.

Sites might be pooled for the statistical analysis, e.g., based on geographic criteria. If applicable, pooling of sites will be defined in the SAP.

Both, the primary efficacy variable and the co-primary efficacy variable have to show statistically significant treatment differences in order to prove superiority of high dose vs. low dose treatment.

Confirmatory testing will be performed on the FAS of MP with accounting for missing values by using MMRM approach for the primary efficacy variable. . In case of missing data in the co-primary efficacy variable these will be imputed by "0" (no change) (see Section 12.4.7.1).

If the confirmatory tests of the (co-)primary efficacy variables both yield significant results, in a second step using a hierarchical testing approach in the high dose treatment group, the key-secondary efficacy variable 'change from baseline in AS score of the **other treated main clinical target pattern** (i.e. of elbow flexors or wrist flexors, if treated) at Day 29 (Week 4) of MP' and the co-primary efficacy variable 'GICS at Day 29 (Week 4) of MP' for the subpopulation defined by this key-secondary endpoint will be compared to low dose treatment group in both efficacy variables. Other than using the key-seondary efficacy variable and the co-primary efficacy variable for this subpopulation, the analysis models will be identical to the analysis described above for the 1st step. Both, the key-secondary efficacy variable and the co-primary efficacy variable for the subpopulation have to show statistically significant treatment differences in order to prove superiority of high dose vs. low dose treatment in this subpopulation.

Only if the confirmatory analysis of step 2 yields a statistically significant result, in a third step, a confirmatory analysis of the key-secondary efficacy variable 'change from baseline in AS score of clinical target pattern clenched fist (in subjects treated in combination with flexed wrist), at Day 29 (Week 4) of MP will be done. This variable has been chosen, since it is anticipated that the vast majority of subjects will have a combined clinical presentation of clinical patterns clenched fist and flexed wrist. Subjects

with either treatment alone (i.e. clenched fist or flexed wrist) with other clinical target patterns will be evaluated separately in a descriptive manner (see also Section 12.3.1.3).

Only if the confirmatory analysis of step 3 yields a statistically significant result, in a fourth step, using a hierarchical testing approach, the mid dose treatment will be compared to low dose treatment in both (co-)primary efficacy variables. Other than using the mid instead of the high dose group treatment data, the analysis models will be identical to the analysis described above for the 1st step. Both, the primary efficacy variable and the co-primary efficacy variable have to show statistically significant treatment differences in order to prove superiority of mid dose vs. low dose treatment.

For the confirmatory analyses a two-sided significance level of α=0.05 will be applied. A MRMM analysis as described for the primary efficacy variable will be applied for the change from baseline in AS score. An ANCOVA model as described for the co-primary efficacy variable will be applied for the Investigator's GICS. The analysis will be performed on the FAS of the MP.

Due to the hierarchical testing strategy of (co-)primary and key-secondary efficacy variables and the two dose group comparisons (high versus low and mid versus low), this four step hierarchical testing procedure ensures the overall type I level of 5% for the confirmatory tests. If one of four hierarchical tests does not yield a statistically significant result, the consecutive test(s) will still be performed but will be considered to be only descriptive.

Further, a non-parametric Wilcoxon rank-sum test will be performed as sensitivity analysis of the primary efficacy variable and of the co-primary efficacy variable to investigate the impact of potential deviations from the assumption of normal distribution (for FAS and PPS subset, using LOCF in case of the primary efficacy variable and imputing missing data by "0", i.e. no change, for the co-primary efficacy variable).

All other test procedures will be explorative. Sensitivity analyses will be performed on the PPS of MP as well as on the FAS of MP using last observation carried forward [LOCF] (for AS score) and, additionally, without missing value replacement (observed case analysis).

12.4.1.2 Secondary efficacy variables (MP only)

The difference between treatment groups in the change from baseline in AS score for each treated clinical patterns (e.g., flexed elbow, flexed wrist, flexed fingers) of the UL at all other post baseline visits will be analyzed by a MMRM analysis as described for the primary efficacy variable.

Pain intensity (from subjects) and pain frequency (from parent/caregiver) assessed with QPS will be analyzed by using frequency tables and descriptive summary statistics at all visits and for changes from baseline to all post-baseline visits.

Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) will be analyzed descriptively by an analysis of covariance model as described for the co-primary efficacy analysis.

These tests will be descriptive and interpreted in an explorative manner. Treatment comparisons will be tested for comparison of the high versus low dose treatment group and the mid versus low dose treatment group, respectively. Furthermore descriptive summary statistics will be performed for all secondary efficacy variables at all visits and for the changes from baseline to all post-baseline visits. Summary statistics are defined as N, mean, standard deviation, median, 1st and 3rd quartile, minimum and maximum or/and as counts and percentages.

MMRM analysis as well as observed case analyses and LOCF of the secondary efficacy variable AS will be performed on the FAS and PPS of MP. For these variables LOCF is considered as conservative approach. Handling of missing data of MP for further secondary efficacy variables will be defined in the SAP.

[redacted]

12.4.2 Pharmacodynamic variables

Not applicable.

12.4.3 Pharmacokinetic variables

Not applicable.

12.4.4 Pharmacogenetic variables

Not applicable.

12.4.5 Safety variables

All safety analyses will be performed on the SES of MP and OLEX using descriptive summary statistics, frequency tables, and, if applicable, shift tables and shift graphs. Analyses will be based on both, total population and by MP treatment group.

Adverse events

Analyses of adverse events will be performed for total dose group in addition to total population and MP treatment group. AEs will be coded by system organ class and preferred term level according to the MedDRA version in effect at the time the respective databases of MP and of OLEX Period, respectively, are closed. Only TEAEs will be analyzed. Non-TEAEs are defined as baseline complaints and will be listed only.

For MP, only TEAEs of the MP will be analyzed, which are defined as AEs with onset or worsening on or after date and time of the first MP administration and before date and time of the first OLEX administration at V6. For subjects who do not receive an OLEX administration all AEs with onset or worsening on or after date and time of the first MP administration will be considered as TEAEs of MP.

-AEs starting in MP and not having resolved at the Final Visit V5 of MP will be followed and further documented during OLEX.

For OLEX period, only TEAEs of the OLEX will be analyzed, which are defined as AEs with onset or worsening on or after date and time of the first OLEX administration at V6.Frequencies will be calculated for TEAEs on the system organ class level and on the preferred term level. For all TEAEs the occurrence, worst intensity, final causal relationship to treatment assessed by investigator, and final outcome will be summarized by counts and percentages for all visits and overall. Listings and, if applicable, tables displaying frequencies of TEAEs leading to discontinuation, TESAEs, TEAESIs, and deaths will also be provided.

Additional subgroup analyses (e.g., classes for GMFCS level, age groups, use of anesthesia/analgosedation for injection treatment) will be specified in detail in the SAP.

Other safety variables

Laboratory evaluations, vital signs, BMI, weight, height, Investigator's Global Assessment of Tolerability, and incidences of subjects with antibodies against BoNT-A will be analyzed descriptively (values and changes from baseline) and screened for individual notable values and/or changes.

12.4.6 Other variables

Subject dispositions, demographic data, and other baseline characteristics such as medical history and concomitant diseases, previous and concomitant therapies, CP history (e.g., distribution, comorbidities), clinical patterns, GMFCS level, BoNT-A pre-treatment status at screening and use of anesthesia/analgosedation for injection treatments will be presented using standard descriptive statistics. No homogeneity tests will be performed.

Demographic data will be summarized for the SES (MP and OLEX), the FAS (MP and OLEX), and the PPS (MP only). Clinical patterns, AS scores at baseline and GMFCS level at Screening will be summarized descriptively for the FAS (MP and – for selected baseline clinical patterns only - OLEX) and the PPS (MP only).

Frequencies of concomitant medication will be given based on different Anatomical Therapeutic Chemical classification [ATC] system of the WHO code levels for the SES (MP and OLEX), the FAS (MP and OLEX), and the PPS (MP only). Indications for concomitant therapies will not be coded and will only be listed. Medical history and concomitant diseases as well as non-drug treatment will be described based on MedDRA system organ class and preferred term levels for the SES (MP and OLEX).

12.4.7 Special statistical/analytical issues

12.4.7.1 Discontinuations and missing data

Discontinued subjects will not be replaced (see Section 8.2.1).

The primary and secondary efficacy variables AS will be analyzed on the FAS and PPS of the MP using MMRM for accounting for missing data. As sensitivity analysis for the primary efficacy variable and for the secondary efficacy variables of the AS score an ANCOVA model without repeated measures will be applied. The LOCF will be followed on the FAS and PPS, i.e., the baseline observation will be carried forward to Day 29 (Week 4) of MP and the last non-missing value before a missing value will be carried forward to all further visits with missing values. In addition, further sensitivity analysis for the primary and secondary efficacy variables, the so-called observed case analysis without missing data replacement, will be performed on the FAS and PPS of the MP to explore the impact of the respective missing imputation principle.

In case of missing data in the co-primary variable these will be imputed by "0" (no change). Assuming a similar percentage of missing data in all three treatment arms this

imputation leads to a decreased difference of the treatment effects. For this reason the "no change" imputation is considered as conservative approach. Sensitivity analyses for the co-primary efficacy variable by using the so called 'observed case analysis' without missing data replacement will be performed on the FAS and PPS to explore the impact of missing values.

For other secondary [redacted] efficacy variables, missing data of the MP will be replaced using an appropriate imputation method specified in detail in the SAP.
Missing data will not be replaced for OLEX.

In case further missing value replacement strategies will be applied on any variables these will be described in detail in the SAP before unblinding of the MP data.

12.4.7.2 Interim analyses

No formal interim analyses are planned.

An overall study report will be written after completion of OLEX, giving the efficacy and safety results of the entire study.

12.4.7.3 Data monitoring committee

An independent DMC will be assigned to monitor subject's safety throughout the clinical course of the study (see Appendix 16.2). It will consist of an uneven number of physicians, e.g., three physicians, to achieve a decision of majority. DMC members must be experienced in the indication and population and will not be involved in any study conduct sponsored by Merz. An independent biostatistician may complement the DMC. The primary purpose of the DMC is to safeguard subject. The DMC provides a mean to rapidly note an unexpected hazard that may lead to study termination.

The DMC will meet at regular intervals during MP and OLEX to discuss and decide upon safety issues. The treatment code of individual subjects may be unblinded by the DMC if necessary for evaluation purposes (see Section 8.3.2).

If indicated, the DMC will make recommendations regarding withdrawals, and/or measures for the study in case of relevant safety findings. Details on responsibilities and procedures to be followed by the DMC will be laid down in the DMC Charter.

12.4.7.4 Multiple comparisons/multiplicity

Due to the hierarchical testing strategy described, no further alpha-adjustment for multiple testing is necessary as it ensures the overall type I level of 5% for the confirmatory tests. Please see Section 12.4.1.1 for details.

12.4.7.5 Examination of subgroups

Subgroup analyses will be performed for the AS regarding treatment group, site (or pooled sites), BoNT-A pre-treatment status, GMFCS level groups at baseline, and AS baseline value. In addition, subgroup analysis for the AS regarding subjects with unilateral and bilateral treatment will be performed. If applicable, the influence of these subgroups will also be analyzed for the other efficacy variables. Potential effects of the use of local anesthetics and/or analgosedation on AS and adverse event/adverse events of special interest will be analyzed descriptively.

Details of subgroup analyses and additional subgroup analyses (e.g., gender, dose group, age, group [2-5, 6-11, 12-17 years], weight, height) will be specified in detail in the SAP.

13 DATA HANDLING AND RECORDKEEPING

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

13.1 Corrections to data

All data required by this clinical study protocol are to be recorded on eCRF (electronic data capture system [redacted]) as soon as possible. Direct entries are not allowed; data must be transcribed from the source (e.g., subject file) to the eCRF.

If corrections are necessary, an authorized member of the investigator's staff will enter the correct data in the web-based eCRF. The audit trail in [redacted] documents all changes. Edit checks issue automatic queries during data entry when a field is not populated to specifications defined in the DVP. Manual queries (to be answered by site staff) can be raised during source data verification, medical or safety review, and data management review.

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

13.2 Recordkeeping

Essential documents should be retained until at least 2 years after the last approval of a marketing application (whether pending or contemplated) in an ICH region, or at least 2 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 investigational site include (among other documents):

- Subject's files.
- Subject's 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.
- CD/DVD with eCRF data and any associated subject-related source data (or, where applicable, authorized copies of source data).
- Signed IC forms.

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

13.3 Destruction of study documents

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

14 PUBLICATION POLICY

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 relevant commitments of pharmaceutical industry associations. Study registration may include a list of the investigational sites.

The study results will be submitted for 1st full publication in an appropriate medical journal, and publishing details will be given in the clinical study agreement. The principal investigator of each site will be mentioned in the acknowledgement of the publication.

Further submission for publication (e.g., poster, journal) concerning study results after an initial full journal publication 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.

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