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Merz Pharmaceuticals GmbH

Statistical Analysis Plan

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

Phase 3

MRZ60201_3072_1

EudraCT Number: 2012-005496-14/ IND Number: 110,686

Version 1.0, Final

Date: 18-OCT-2018

Author: [redacted]

SIGNATURE PAGE

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before breaking the blind.

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Author (print name)	Date (dd-mmm-yyyy)	Signature
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Peer Reviewer (print name)	Date (dd-mmm-yyyy)	Signature
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Study Medical Expert (print name)	Date (dd-mmm-yyyy)	Signature

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Study Medical Expert (print name)	Date (dd-mmm-yyyy)	Sign

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1 LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
AS	Ashworth scale
ATC	Anatomical therapeutic chemical classification
BDRM	Blind data review meeting
BMI	Body mass index
BOCF	Baseline observation carried forward
BoNT	Botulinum Toxin
[redacted]	[redacted]
CP	Cerebral palsy
CSP	Clinical study protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic case report form
Desc. stat.	Descriptive statistics
DMC	Data monitoring committee
EMG	electromyography
e-stim	electrical stimulation
FAS	Full analysis set
Freq.	Frequency table
GICS	Global Impression of Change Scales
GMFCS-E&R	Gross Motor Function Classification System (expanded and revised version)
IV/WRS	Interactive voice (web) response system
LOCF	Last observation carried forward principle
LL	Lower limb
MAS	Modified Ashworth scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MP	Main Period
n	Number of non-missing observations
Nexp	Number exposed
OLEX	Open-label extension
PBO	Placebo

PDF	Portable Document Format
PPS	Per protocol set
QPS	Questionnaire on Pain caused by Spasticity
SAP	Statistical analysis plan
SAS®	Statistical Analysis System software
SD	Standard deviation
SE	Standard error
SES	Safety evaluation set
SMQ	Standard MedDRA query
SOC	System organ class
TC	Telephone Contact
TEAE	Treatment emergent adverse event
TEAESI	Treatment emergent adverse events of special interest
TESAE	Treatment emergent serious adverse event
TFLs	Tables, figures and listings
UL	Upper limb
WHO	World health organization

2 GENERAL AND TECHNICAL ASPECTS

The objective of this statistical analysis plan is to specify the statistical analyses in more detail than stated in the clinical study protocol (CSP) and to be precise enough to serve as a guideline for statistical programming and creation of tables, figures and listings.

This statistical analysis plan is based on the clinical study protocol version 3.0, dated 07-APR-2016 and the following amendment no. 1, dated 24-APR-2015.

All programs will be written using Statistical Analysis System Software (SAS®) version 9.2 or higher. A font size of 10 points will be used for the tables and figures in section 14, corresponding to a line size of 111 digits and a page size of 42 lines for an output in A4 format. The font size of 10 points will also be used for all listings, if possible. If this is not possible, for listings, a minimum font size of 8 points with the line size of 140 points and page size of 52 lines will be used to produce the output in A4 format. Single SAS programs will be written for all tables and figures, and all listings, respectively. All outputs will be transferred into Portable Document Format (PDF)-files using the Merz internal SAS macro LST2PDF. These PDF-files will be generated separately for the tables and figures of section 14 and the listings of section 16.2 of the appendix of the clinical study report. Each PDF-file will include the corresponding table of contents, preceding the content of the file.

The standard tables, figures and listings (TFLs) will be applied.

3 CLINICAL STUDY DESIGN AND OBJECTIVES

3.1 Clinical Study Design

This is a prospective, multicenter, multi-national, randomized, double-blind, parallel-group, dose-response study in phase 3 of three doses NT 201. Subjects with upper limb spasticity alone or with combined upper limb (UL) and lower limb (LL) spasticity due to cerebral palsy (CP) will be treated. The study comprises a Main Period (MP) with a single double-blind treatment cycle with three dose arms (high, mid, low), followed by three open-label extension (OLEX) treatment cycles with a single treatment arm using the high dose regimen of MP. Each of the four treatment cycles has an observation period of 12 to 16 weeks, i.e. 14 weeks ± 14 days.

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 (U) 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 unilaterally or bilaterally and subjects may receive additional Botulinum Toxin (BoNT) injections in one out of five predefined treatment combinations (A-E) up to the maximum total dose applicable for their Gross Motor Function Classification System expanded and revised version (GMFCS-E&R) 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):

- Treatment Combination A: Unilateral or bilateral UL treatment only
- Treatment Combination B: Unilateral UL and unilateral LL treatment
- Treatment Combination C: Unilateral UL and bilateral LL treatment in GMFCS-E&R level I-III
- Treatment Combination D: Unilateral UL and bilateral LL treatment in GMFCS-E&R level IV-V
- Treatment Combination E: Bilateral UL and bilateral LL treatment in GMFCS-E&R level I-III

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.

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 (TC) (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.

3.2 Clinical Study Objectives

The objectives of the study are to investigate efficacy and safety of NT 201 in children (age 2-11 years) and adolescents (age 12-17 years inclusive) with UL spasticity alone or with combined UL and LL spasticity due to CP.

4 DETERMINATION OF SAMPLE SIZE

The sample size estimation for the primary efficacy variable ‘change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4)’ was based on data of a study with BoNT-A in the treatment of post-stroke UL spasticity in adults [Childers 2004 (1)]. In this trial a modification of the original 5-point AS to a 9-point scale by adding 4 half point increments was used. Since this modified Ashworth Scale (MAS) is very similar to the original Ashworth Scale (AS) used in the present study, it appeared to be justified to base the sample size calculation on the MAS results of the study by Childers et al.. In this study, a mean change from baseline in MAS scores at the elbow of -1.01 in the 180 U BoNT-A dose group and of -0.7 in the 90 U dose group were observed. It was assumed that the changes from baseline in AS for flexed elbow will be comparable to the one for flexed

wrist. The 180 U dose lies between the 200 U and the 150 U (for subjects ≥25kg) doses planned for the high and mid dose group in this study. Since published trial data for the exact doses planned in this trial did not exist, and doses of BoNT-A applied in spasticity show complex non-linear correlations to AS scores [Yablon 2011 (2)], it appeared to be justified to use the same assumptions for both dose groups.

Comparable Placebo (PBO)-controlled studies showed a low drop-out rate of 3% at the time of assessment of the primary efficacy variable. Therefore, a similarly small number of missing data for the primary efficacy endpoint was expected for this study. Consideration of assumptions above with a 3% rate of missing values and using last observation carried forward (LOCF) as originally planned in the CSP led to the group means μ_{NT201_high}= -0.98, μ_{NT201_mid}= -0.98 and μ_{NT201_low}= -0.68.

The assumption for a pooled common standard deviation (SD) was σ=0.6.

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, Statistical Analysis System software®).

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, Statistical Analysis System software®) in the primary efficacy variable.

For the co-primary efficacy variable 'Investigator's Global Impression of Change Scale (GICS) 4 weeks after injection', data from [Childers 2004 (1)] were used as well. In this study, a 9-point global assessment scale ranging from +4 (very marked improvement) to -4 (very marked worsening) was used to assess the response to treatment. In the group treated with 180 U Botulinum Toxin Type A, the mean response to treatment rated by the subject at week 3 was 1.4 points with a standard deviation of 1.0 points. Given that only PBO values for the global assessment scale were reported and since no global response compared to PBO had been detected in the 90 U dose group, data from the PBO group were used here. In the PBO group, the corresponding point estimator for the mean value was 0.8 points with a standard deviation of 0.8 points. It was assumed that the 9-point scale has a comparable effect size to the 7-point scale used in this study.

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 were planned to be randomized to the NT 201 high dose treatment group, at least 86 subjects were planned to be randomized to the NT 201 mid dose treatment group and at least 86 subjects were planned to be randomized to the NT 201 low dose treatment group.

5 ANALYSIS SET

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

Safety Evaluation Set (SES) of the Main Period

The SES of the Main Period is the subset of all subjects who receive study medication in the MP at least once.

Full Analysis Set (FAS) of the Main Period

The FAS of the MP 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 either an AS score in the clinical pattern flexed elbow or flexed wrist at baseline (Day 1), or the Investigator's GICS for upper limb at Day 29 (Week 4).

Per Protocol Set (PPS) of the Main Period

The PPS is the subset in the FAS of the MP without major protocol deviations. Major protocol deviations will be defined during the Blind Data Review Meeting (BDRM).

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

SES of the OLEX Period

The SES is the subset of all subjects who receive study medication at least once during the OLEX period.

FAS of the OLEX Period

The FAS is the subset of subjects in the SES of the OLEX for whom at least one post-baseline value of any efficacy variable in the OLEX is available.

Subjects which have not been treated according to the randomization list in the MP will be excluded from PPS of the MP. If subjects have not been treated according to the randomization list in the MP, tables performed on the SES will be analyzed as treated for the MP treatment group and tables performed on the FAS will be analyzed as randomized for the MP treatment group. If subjects have been treated with MP medication in the OLEX they will be analyzed regularly according to their planned high dose treatment of the OLEX regardless if they actually received low, high or mid dose. In the subject data listings the MP treatment group will be listed as randomized except for the section 16.2.7 and 16.2.8, here the actual MP treatment group will be listed.

6 VARIABLES FOR ANALYSIS

6.1 Efficacy Variables

6.1.1 Primary Efficacy Variable

The 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.

For subjects with bilateral UL treatment, the body side for analysis will be decided by the investigator at screening. If both main clinical target patterns elbow flexors and wrist flexors are qualified for primary efficacy analysis, an interactive voice (web) response system (IV/WRS) will select the primary clinical target pattern. The primary clinical target pattern will be set to missing for subjects whose primary clinical target pattern was not treated in the MP by mistake. As a consequence these subjects will not have the primary efficacy variable "change from baseline in AS in the primary clinical target pattern".

The AS is a well-known and validated scale to categorize the severity of spasticity by judging resistance to passive movement. Spasticity will be assessed separately for elbow flexors, wrist flexors, forearm pronators, finger flexors and thumb flexors if chosen for BoNT injection on the following 5-point scale:

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 and/or wrist flexors in at least one UL. 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.

6.1.2 Co-primary, Key-Secondary and Secondary Efficacy Variables

The co-primary efficacy variable, the key-secondary efficacy variables and the secondary efficacy variables will be determined for MP only.

- Co-primary efficacy variable is the Investigator's Global Impression of Change Scales (GICS) for upper limb at Day 29 (Week 4) of MP. The definition of this variable was changed compared to the CSP (for details see section 8).

The 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.

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 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.'

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

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 for the main clinical target pattern not analyzed as primary efficacy variable, in case two target patterns would qualify as main clinical target pattern.

- 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.

Secondary efficacy variables are:

- Change from baseline in AS score for each treated clinical pattern (e.g., flexed elbow, flexed wrist, clenched fist, pronated forearm and thumb in palm) of the UL at all other post baseline visits of MP (V3, V4, and V5). The definition of this variable was made more precise compared to the CSP (for details see section 8).

- 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 (V3, V4, and V5). In the definition of this variable the visit numbers were added.

The QPS is a patient-reported outcome for children and adolescents (2-17 years) with CP on spasticity-related pain. 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)/caregiver(s). In addition, parent(s)/caregiver(s) report on pain location and observed pain behaviors. 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". First it is always asked if spasticity-related pain for each activity situation occurred (Yes/No) and then how severe the experienced spasticity was (6-point rating scale) or how frequent pain behavior was observed (5-point rating scale).

From the self-administered version and from the interviewer-administered version of the QPS the QPS child/adolescent score will be calculated as sum of the activity related pain items No. 5, 7, 9, and 12 divided by 4. In case one or more of the 4 items are missing the corresponding QPS score will not be calculated. The item No. 3 of the self-administered version and the interviewer-administered version will be not included into this score, but will be assessed separately as child/adolescent general pain intensity item.

From the parent/caregiver version the QPS parent/caregiver score will be calculated as sum of the items No. 9b, 10b. 11b, and 13b divided by 4. In case one or more of the 4 items are missing the corresponding QPS score will not be calculated. The item No. 8 of the parent/caregiver version will be not included into this score, but will be assessed separately as parent/caregiver general pain frequency item.

The QPS scores will be calculated separately for upper limb spasticity-related pain and for lower limb spasticity-related pain. 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 of the CSP.

- Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) of MP for upper limb. The definition of this variable was changed compared to the CSP (for details see section 8).

The question of the GICS for the Child/Adolescent is: 'What is your overall impression of change of your upper limb tightness due to treatment, compared to the condition before the last injection? Please check the one option that best fits your overall impression of change.'

The question of the GICS for the Parent/Caregiver is: 'What is your overall impression of change of child's/adolescent's upper limb spasticity (tightness) due to treatment, compared to the condition before the last injection? Please check the one option that best fits your overall impression of change.'

The same 7-point Likert scale as for the investigator will be used that ranges from -3 = very much worse to +3 = very much improved:

[redacted]

6.2 Pharmacodynamic Variables

Not applicable.

6.3 Pharmacokinetic Variables

Not applicable.

6.4 Pharmacogenetic Variables

Not applicable.

6.5 Safety Variables

6.5.1 Primary Safety Variable

Not applicable.

6.5.2 Secondary Safety Variables

Secondary safety variables of the MP comprise:

- Occurrence treatment emergent adverse events (TEAEs)
- Occurrence of treatment emergent adverse events of special interest (TEAESIs)
- Occurrence of serious TEAEs
- Occurrence of TEAEs related to treatment as assessed by the investigator
- Occurrence of TEAEs by worst intensity
- Occurrence of TEAEs by worst causal relationship
- Occurrence of TEAEs by worst outcome
- Occurrence of TEAEs leading to discontinuation

Secondary safety variables of the OLEX Period comprise:

- Occurrence of treatment emergent adverse events (TEAEs) overall and per treatment cycle.
- Occurrence of treatment emergent adverse events of special interest (TEAESIs) overall and per treatment cycle.
- Occurrence of serious TEAEs 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 worst outcome overall and per treatment cycle. The definition of this variable was changed compared to the CSP (for details see section 8).
- Occurrence of TEAEs leading to discontinuation overall and per treatment cycle.

6.5.3 Other Safety Variables

Other safety variables of the MP comprise:

- Investigator's Global Assessment of Tolerability at the Final Visit of MP V5 (In the definition of this variable the visit number was added.)
- Vital signs (blood pressure, heart rate) at all visits of MP
- Body Mass Index (BMI), weight and height at Screening V1, Baseline Injection Visit V2, at the Final Visit of MP V5
- Clinical chemistry, differential count and hematology at Screening V1
- Occurrence of antibodies against BoNT-A in subjects ≥21 kg BW at Screening V1
- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the Columbia-Suicide Severity Rating Scale (C-SSRS) This scale is used to assess suicidality prospectively in this clinical study at baseline and all post-baseline visits of the MP.

Other safety variables of the OLEX comprise:

- Investigator's Global Assessment of Tolerability at Day 99 (Week 14) of all OLEX cycles, i.e. at End of Cycle Visit (V9, V13) and at End of Study Visit (V17). In the definition of this variable the visit numbers were added.

- Vital signs (blood pressure, heart rate) at all visits of OLEX period (V6, V7, …, V17). In the definition of this variable the visit numbers were added.

- BMI, weight and height at all Injection Visits of OLEX (V6, V10 and V14) and at the End of Study Visit (V17). If V5 and V6 will be performed at the same day, BMI, weight and height can be transferred from V5 to V6.

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

- Occurrence of antibodies against BoNT-A in subjects ≥21 kg BW at the End of Study Visit (V17). In the definition of this variable the visit numbers were added.

- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the Columbia-Suicide Severity Rating Scale (C-SSRS) This scale is used to assess suicidality prospectively at all OLEX visits.

6.6 Other Variables

Other variables of interest are:

- Subject dispositions (including number of subjects enrolled, number of discontinuations and reason for discontinuations)

- Demographic data

- Other baseline characteristics such as:

    - Medical history and concomitant diseases

    - Previous and concomitant therapies, including medication and non-drug treatment

    - CP history (including main cause for cerebral palsy, affected limbs (UL unilateral left, UL unilateral right, ULs bilateral, LL unilateral left, LL unilateral right, LLs bilateral), duration since first diagnosis of spasticity, and duration since the first diagnosis of cerebral palsy)

    - Primary clinical pattern

    - GMFCS-E&R level:
      1 = Level I: Walks without Limitations

2 = Level II: Walks with Limitations
3 = Level III: Walks Using a Hand-Held Mobility Device
4 = Level IV: Self-Mobility with Limitations; May Use Powered Mobile
5 = Level V: Transported in a Manual Wheelchair

- Planned treatment of spasticity: treatment combinations A, B, C, D, and E, limbs planned to be treated (lower limb right, lower limb left, upper limb right, and upper limb left), and primary body side for analyses, if bilateral: This variable was added in the SAP (for details see section 8).

- BoNT-A pre-treatment status

- Use of local anesthesia/analgosedation for injection treatments:
    - Inhalative sedatives (e.g. nitrous oxide, sevoflurane)
    - Oral sedatives (e.g. benzodiazepines, antihistamines)
    - Rectal sedatives (e.g. benzodiazepines)
    - Parenteral sedatives (e.g. benzodiazepines, propofol)
    - Topical/Local anaesthetics (e.g. lidocaine/prilocaine cream)
    - Oral analgesics (e.g. paracetamol, opioids)
    - Rectal analgesics
    - Parenteral opioid analgesics
    - Parenteral non opioid analgesics
    - Topical cooling (e.g. cooling spray)
    - Other

- Monitoring during sedation (yes/no): This variable was added in the SAP (for details see section 8).

- Injection guidance technique (ultrasound, electromyography (EMG)/ electrical stimulation (e-stim), e-stim, EMG): This variable was added in the SAP (for details see section 8).

- Treatment compliance: This variable was added in the SAP (for details see section 8).

- Extent of exposure (injected volume, injected units, number of injected sites per body side, per clinical pattern, and per muscle and in total, and frequency of treated limbs

and number (%) of subjects with unilateral and with bilateral treatment by upper and lower limbs): This variable was added in the SAP (for details see section 8).

- Length of injection cycles and the total observation period in weeks over the entire study. This variable was added in the SAP (for details see section 8).

7 STATISTICAL ANALYSIS METHODS

7.1 Efficacy Variables

All efficacy analyses will be based primarily on the FAS and additionally in the MP, for sensitivity purposes, on the PPS. For analysis of the MP the FAS of the MP will be used and for analysis of the OLEX Period the FAS of the OLEX Period will be used. Statistical tests will be two-sided hypothesis tests for between-treatment differences of the MP and two-sided hypothesis tests for before treatment versus after treatment comparisons of the OLEX Period data in general. In the MP treatment differences will be tested for comparison of the high versus low dose treatment group and the mid versus low dose treatment group, respectively. The efficacy analysis of the MP and of the OLEX will be performed by Main Period treatment group (high, mid, low) and in total. For this purpose the Main Period treatment group as randomized instead of as treated will be used. In the unlikely case that a subject has received mid or low dose instead of the planned high dose during the OLEX Period, he/she will be analyzed in total group of the OLEX tables together with all other subjects with the correct high dose treatment. Continuous variables (values and changes from baseline/cycle baseline) will be summarized by number of non-missing observations (n), mean, standard deviation, 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. The base for percentages will be all subjects treated in the respective cycle (Nexp = number exposed), in the respective limb and clinical target pattern, if analysis is done per limb and or per clinical target pattern. A missing line will be given for subjects treated in the respective cycle but not observed at the respective visit, in order to have 100% given for the sum of the single observations. Subjects, who were treated in the respective cycle, will not be included in the efficacy analysis of this cycle. Two-sided 95% confidence limits and descriptive p-values will be given, where appropriate. Descriptive summary statistics will be performed at all visits and if applicable for the changes from baseline of the MP (Day 1) to all post-baseline visits of the MP and of the OLEX, and from Day 1 of each treatment cycle to all post baseline Control Visits of the respective treatment cycle. For subjects with bilateral treatment, body sides will be analyzed separately per primary and per non-primary body side, where applicable. In case that for any subject end of cycle visit of cycle x and injection visit of cycle x+1 are on the same day the respective data will be used for the analysis of both visits for parameters which are to be assessed at injection visits as well.

For efficacy variables the last measurement before start of treatment is defined as baseline value.

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

1. Step: Primary and co-primary efficacy variables for high dose vs. low dose.

2. Step: First key-secondary efficacy variable and co-primary efficacy on subpopulation variables for high dose vs. low dose.

3. Step: Second key-secondary efficacy variable for high dose vs. low dose.

4. Step: Primary and co-primary efficacy variables for mid dose vs. low dose.

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.

The estimand of interest of this study is the treatment effect measured by the primary and co-primary efficacy variables in all subjects of FAS of the MP regardless of adherence to randomization list.

7.1.1 Primary Efficacy Variable

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 (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 following working hypotheses will be tested by use of a two sample t-test:

$$H_0: \mu_{NT201\_high} - \mu_{NT201\_low} = 0 \quad vs. \qquad H_1: \mu_{NT201\_high} - \mu_{NT201\_low} \neq 0$$

with μ denoting the mean change from baseline. Stronger negative differences between least square mean estimates as defined by the working hypotheses thereby indicate better results (stronger reduction of AS from baseline to V3) in the high dose group compared to the low dose group.

Estimates for least square means will be derived from the mixed model repeated measures where the dependent variable in the model is defined as the change from baseline in the AS. The independent variables are defined as treatment group (high dose, low dose), pooled sites, BoNT-A pre-treatment status (pre-treated, treatment naïve) as fixed factors, visit*treatment as interaction term, and visit as repeated factor. Covariates are the AS score of the primary clinical target pattern at baseline (Day 1 of MP) and the GMFCS-E&R level at screening. The following SAS code will be used:

```
proc mixed data = dataset;
    class treatment site btx subject visit;
    model AS_change = treatment site btx AS_baseline GMFCS
                      visit visit*treatment / solution ddfm=kr;
    repeated visit / subject= subject TYPE=un;
    lsmeans visit*treatment / diff cl pdiff;
run;
```

Sites will be pooled for the statistical analysis based on geographic criteria. For definition of pooling rules please refer to section 7.7.6.

Confirmatory testing will be performed on the FAS of MP with accounting for missing values using the mixed model repeated measures (MMRM) approach.

In order to investigate the impact of missing values and different approaches for imputation, further sensitivity analyses will be performed on the PPS as well as on the FAS of the MP using the LOCF principle and without missing replacement (observed case analysis). For this purpose the statistical model as described above but without visit*treatment as interaction and without visit as repeated factor will be applied for LOCF analysis and for observed case analysis. Since there is no assessment of AS between baseline and V3, the baseline observation will be carried forward to Week 4 equals the LOCF analysis. Therefore the LOCF method is equivalent to the baseline observation carried forward (BOCF) method in this special case. The following SAS code will be used:

```
proc mixed data = dataset;
      class treatment site btx;
      model AS_change_wk4 = treatment site btx AS_baseline GMFCS / solution
      ddfm=kr;
      lsmeans treatment / pdiff CL alpha=0.05;
run;
```

Further, a non-parametric Wilcoxon rank-sum test will be performed as sensitivity analysis of the primary efficacy variable to investigate the impact of potential deviations from the assumption of normal distribution (for FAS of the MP and PPS subset, using LOCF). The following working hypotheses will be tested:

H_0: Prob. distributions for high dose group and low dose group are identical

vs.

H_1: Prob. distribution for high dose group shifted to right or left of distribution for low dose group.

The Wilcoxon rank-sum test will be performed by use of the following SAS code:

```
proc npar1way data=dataset wilcoxon;
    class treatment;
    var AS_change_wk4;
    exact;
```

```
run;
```

Furthermore, descriptive summary statistics, shift tables and frequency tables of changes will be given for the primary efficacy variable.

7.1.2 Co-Primary, Key-Secondary and Secondary Efficacy Variables

Co-primary efficacy variable:

1. 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 high dose vs. low dose treatment. No α-adjustment for multiplicity is necessary.

The co-primary efficacy variable is the Investigator's Global Impression of Change Scales (GICS) for upper limb at Day 29 (Week 4) of MP. As for the 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) for upper limb of MP'. The independent variables are defined as treatment group (high dose, low dose), 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 target clinical patterns flexed elbow or flexed wrist at baseline (Day 1 of MP) and the GMFCS-E&R level at Screening Visit. The following SAS code will be used:

```
proc mixed data = dataset;
    class treatment site btx;
    model I_GICS_wk4 = treatment site btx max_AS_baseline GMFCS / solution;
    lsmeans treatment / pdiff CL alpha=0.05;
run;
```

Positive values for differences between least square mean estimates as defined by the working hypotheses (see primary efficacy variable) thereby indicate better results (higher GICS values at Day 29, Week 4) in the high dose group as compared to the low dose group. Confirmatory testing will be performed on the FAS of MP with replacement of missing data, setting all missing values of the co-primary efficacy variable to "0" (no change).

Further sensitivity analyses will be performed on the PPS as well as on the FAS of the MP and the PPS without missing replacement (observed case analysis).

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

Furthermore, frequency tables and descriptive summary will be performed for the co-primary efficacy variable.

Key-secondary efficacy variables and co-primary efficacy variable restricted to subpopulation:

2. Step: If the confirmatory tests of the primary efficacy variables and the co-primary efficacy variable both show significant results, then the hierarchical testing approach will be continued in a second step. In this second step the following two variables will be tested for high dose group versus low dose group:

- First 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

- Co-primary efficacy variable: Investigator's Global Impression of Change Scales (GICS) for upper limb at Day 29 (Week 4) for the following subpopulation:

This analysis will be done for the subpopulation defined by this key-secondary endpoint, that means only subjects having two main clinical target patterns will be included into the anaylsis. All subjects with only one main target pattern will be excluded from the analysis. The analysis models will be identical to the analyses described above for the 1st step using the the key-secondary variable instead of the primary variable and the co-primary variable restricetd to the subpopulation instead of the co-primary variable of the unrestricted population.

Both, the first 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.

3. Step: Only if the confirmatory analysis of step 2 yields a statistically significant result, in a third step, a confirmatory analysis of the second 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 as other efficacy variables (see also section 6.1.3 and 7.1.3).

4. Step: 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 for the primary efficacy variables and the co-primary efficacy variable. The analysis models will be identical to the analyses described above for the 1st step replacing high dose group with mid dose group. 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 and analysis models as described for the (co)-primary efficacy variables will be applied. The

analysis of the primary efficacy variable and of both key-secondary efficacy variables will be performed on the FAS of the MP with an MMRM approach. For the co-primary efficacy variable and the co-primary variable restricetd to the subpopulation, missing data will be imputed by "0", i.e. no change.

All other test procedures will be explorative. Sensitivity analyses will be performed on the PPS of MP using the MMRM approach, as well as on the FAS and the PPS of MP using a mixed model approach without repeated measures first with the LOCF principle and second without replacement of missing values (i.e., observed case analysis). As the GICS is measured at Control Visit V3 only it is not possible to apply a model based analysis like mixed model repeated measurement.

Secondary efficacy variables:

All secondary variables will be analyzed on the FAS of the MP and the PPS. All 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.

Ashworth scale of the UL

The difference between treatment groups in the change from baseline in AS score for each treated clinical pattern (e.g., flexed elbow, flexed wrist, flexed fingers) of the UL at all other post-baseline visits will be analyzed by a mixed model repeated measurement analysis as described for the primary efficacy variable. Furthermore, descriptive summary statistics, shift tables and frequency tables of changes will be given. Besides the model based missing value imputation approach, a mixed model without repeated measures will be applied with missing values imputed by LOCF and observed case analyses.

Questionnaire on Pain caused by Spasticity

All analyses regarding the QPS will be performed separately for upper limbs and for lower limbs. The QPS child/adolescent score, the child/adolescent general pain intensity item, the QPS parent/caregiver score, and the parent/caregiver general pain frequency item will be analyzed by using descriptive summary statistics at all visits and for changes from baseline to all post-baseline visits. The child/adolescent general pain intensity item and the parent/caregiver general pain frequency item will additionally be analyzed by using frequency tables. All other single items of the QPS will be listed.

The QPS child/adolescent score and the QPS parent/caregiver score will be analyzed by an ANCOVA. The dependent variable is defined as the change from baseline in the QPS score. The independent variables are defined as treatment group (high dose and in 2nd step mid dose vs. low dose), pooled sites, BoNT-A pre-treatment status (pre-treated, treatment naïve) as fixed factors and the covariates are the QPS score at baseline (Day 1 of MP) and the GMFCS-E&R level at Screening Visit. LOCF as well as observed case analyses will be performed.

In these frequency tables of the child/adolescent general pain intensity item and descriptive summary statistics of the QPS child/adolescent score and the child/adolescent general pain intensity item and the ANCOVA of the QPS child/adolescent score, subgroup analyses will be done for the self-administered version and for the interviewer-administered version in addition to the pooled analysis. LOCF for the QPS child/adolescent score and the child/adolescent general pain intensity item will only be applied for the pooled version if both versions (self-administered and interviewer-administered) are missing. For the self-administered and interviewer-administered version no LOCF will be performed.

Not all children and adolescents are able to make the QPS assessment self-administered or interviewer-administered version at all visits, which will presumably lead to a high number of missing values for the QPS child/adolescent score and the child/adolescent general pain intensity item. For this reason observed case analyses of QPS child/adolescent score and child/adolescent general pain intensity item is of main interest and the LOCF analysis is only a sensitivity analysis, which must be interpreted with caution.

Global Impression of Change Scales

Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS for upper limb at Day 29 (Week 4) will be analyzed descriptively by an ANCOVA model as described for the co-primary efficacy analysis. Furthermore, frequency tables, Wilcoxon rank-sum tests and descriptive summary will be performed. Missing values will be replaced by "0" (no change) as for the co-primary efficacy variable and an observed case analyses will be performed. Not all children and adolescents are able to make the GICS assessment, which will presumably lead to a high number of missing values for the Child's/Adolescent's GICS. For this reason observed case analyses of Child's/Adolescent's GICS is of main interest and the worst case analysis is only a sensitivity analysis, which must be interpreted with caution.

[redacted]

[redacted]

[redacted]

7.2 Pharmacodynamic Variables

Not applicable.

7.3 Pharmacokinetic Variables

Not applicable.

7.4 Pharmacogenetic Variables

Not applicable.

7.5 Safety Variables

All safety analyses of the MP will be performed on the SES of the MP. All safety analyses of the OLEX Period will be performed on the SES of the OLEX period. Analyses will be based on both, total population and by Main Period treatment group (high, mid, low). For this purpose the Main Period treatment group as treated instead of as randomized will be used. In the unlikely case that a subject has received mid or low dose instead of the planned high dose during the OLEX Period, he/she will be analyzed in total group of the OLEX tables together with all other subjects with the correct high dose treatment.

For safety variables the last measurement before start of treatment is defined as baseline value.

7.5.1 Primary Safety Variable

Not applicable.

7.5.2 Secondary Safety Variables

Adverse events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0). For MP, only treatment emergent adverse events (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. TEAEs of the OLEX are defined as AEs with onset or worsening at or after date and time of the first OLEX administration at V6. TEAEs will be allocated to an injection cycle x in the OLEX Period, if adverse events has onset or worsening on or after injection x and before injection x+1 (if applicable). TEAEs of the OLEX will be analyzed in total and per treatment cycle. Additionally TEAEs of the MP and the OLEX period will be displayed together in total.

Only TEAEs will be analyzed. Non-TEAEs will only be listed.

If an AE worsens between start and end of this AE it will be considered as new AE starting with the date of the worsening. In this case the imputation of end dates within episodes of the

same AE will be done by setting the end date/end time to start date/start time of the consecutive worsening record.

In detail missing or partially missing start and stop dates of an AE will be imputed as follows for the calculation of the duration of an AE:

- if start time is missing and start date is given and not equal to date of an injection visit, set start time to 00:00, else if start date is equal to date of an injection visit set start time to time of injection, if given (else 00:00)
- if start date/time is completely missing and end date is before first exposure in the MP: no imputation
- if start date/time is (partially) missing and end date after or equal first exposure in the MP or missing:
  - only start day is missing, but start month and start year same as an injection visit: set start day and start time to day and time of this injection visit, else set start day to 1 and start time to 00:00
  - start day and start month are missing, but start year is the same as year of first exposure in the MP: set start day, start month, start time to day, month, time of first exposure in the MP, else set start day and start month to 1 and start time to 00:00
  - start date/time completely missing and end date/time not before date/time of first exposure in the MP, set start date/time to date/time of first exposure in the MP
  - if AE end date and time are missing set end date to study end date (i.e. last contact or last visit of the study) and end time to 23:59
  - if AE end date/time is partially missing, set end day to last day of the given month or end day/month to 31/12 of the given end year and missing end time to 23:59
  - if AE end time is missing set time to 23:59.

Imputation rules for multiple records in case of AE worsening:

- For missing AE start date/time the imputation strategies as defined above will be applied to all records of the same AE.
- For missing TEAE end date/time the imputation strategies as defined above will be applied to the last record of the same TEAE.

Calculation of time to onset/duration of AEs [days]:

- Time to onset of an AE is defined as start date of AE - date of most recent administration of study drug [+ 1 for AE starting after start of treatment]
- The duration will be calculated as stop date - onset date + 1 for each episode of worsening.

Incidences will be calculated for TEAEs overall (MP+OLEX), overall OLEX and by injection cycle on the system organ class (SOC) level and on the preferred term (PT) level (i.e., total, by worst intensity, by worst relationship, and by worst outcome). Listings and, if applicable, tables displaying incidences for TEAEs leading to discontinuation, serious TEAEs, related serious TEAEs, TEAEs of special interest, and deaths will also be provided. Additionally the number and percentage of subjects with at least one non-serious TEAE with incidence ≥ 5%

in any MP treatment group or in the OLEX Period and number of non-serious TEAE will be displayed by SOC level and PT level. Time to onset and duration of AEs will be listed. Time to onset and duration of AEs will be listed.

For any missing data of adverse events, a worst case strategy will be applied for all analysis tables. The intensity will be imputed by the worst intensity “severe”, the causal relationship will be imputed by the worst relationship “drug related”. Missing data of the worst outcome will be imputed by “unknown”. If a subject has more than one outcome within a preferred term (PT) only the worst outcome will be used in the frequency tables. Also on subject level only the worst outcome category per subject will be counted in the frequency table. The worst outcome is defined in the following order:

- recovered/resolved
- recovered/resolved with sequelae
- recovering/resolving
- not recovered/not resolved
- unknown
- fatal

TEAESIs are defined as TEAEs that are thought to possibly indicate toxin spread. A list of adverse events of special interest possibly indicating toxin spread is given in **Table 1: List of Adverse Events of Special Interest Possibly Indicating Toxin Spread.**

Table 1: List of Adverse Events of Special Interest Possibly Indicating Toxin Spread

MedDRA PT	**MedDRA PT**
Accommodation disorder	IIIrd nerve paresis
Areflexia	Ileus paralytic
Aspiration	IVth nerve paresis
Botulism	Monoparesis
Bradycardia	Muscular weakness
Bulbar palsy	Paralysis
Constipation	Paraparesis
Cranial nerve palsies multiple	Paresis
Cranial nerve paralysis	Paresis cranial nerve
Diaphragmatic paralysis	Peripheral nerve palsy
Diplopia	Peripheral paralysis
Dry mouth	Pelvic floor muscle weakness
Dysarthria	Pneumonia aspiration
Dysphagia	Pupillary reflex impaired
Dysphonia	Quadriparesis
Dyspnoea	Respiratory arrest
Extraocular muscle paresis	Respiratory depression
Eyelid function disorder	Respiratory failure
Eyelid ptosis	Speech disorder
Facial paralysis	Trigeminal nerve paresis
Facial paresis	Urinary retention
Hemiparesis	Vision blurred
Hypoglossal nerve paresis	Vocal cord paralysis
Hyporeflexia	Vocal cord paresis
Hypotonia	
Wording of PTs is according to MedDRA version 21.0	

To fulfill FDA requirements, TEAE data will be screened for suicidal events. The MedDRA PTs of all TEAEs will be checked using standard MedDRA query (SMQ) „Suicide/self-injury“. Resulting TEAE findings will be listed in a separate listing. A list of the MedDRA PTs of the SMQ „Suicide/self-injury is given in Table 2.

Table 2: List of Adverse Events of Standard MedDRA Query „Suicide/self-injury“

MedDRA PT:	MedDRA PT:
Columbia suicide severity rating scale abnormal	Self injurious behaviour
Completed suicide	Self-injurious ideation
Depression suicidal	Suicidal behaviour
Intentional overdose	Suicidal ideation
Intentional self-injury	Suicide attempt
Poisoning deliberate	Suicide threat

In addition all comment fields of the case report form (CRF) and all investigator reported terms of TEAEs will be screened for the following terms or term elements (‘strings’) and listed in a separate listing:

Table 3: List of Search Terms and Search Strings of Possibly Suicidal Events

Term:	Term:
attempt	self inflict
cut	self injur
gas	self-damage
hang	self-harm
hung	self-inflict
jump	self-injur
mutilate	shoot
overdos	slash
self damage	suic
self harm	

Obvious false positive findings will be excluded from the listing (e.g., “gas” in “gastrointestinal” or “cut” in “acute” or in “cutaneous”).

7.5.3 Other Safety Variables

Laboratory evaluations, vital signs, BMI, body 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. Results of the C-SSRS will be summarized descriptively.

The following analyses will be performed for the MP data:

C-SSRS

Additionally, to fulfill FDA requirements, prospective monitoring of suicidality with the C-SSRS should be considered the most important (but not the only) source of information concerning suicidality.

These C-SSRS assessments will be done in the subpopulation of subjects enrolled after amendment 1.0 approval only.

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

Following versions of the C-SSRS are to be applied only for subjects enrolled after amendment approval:

1. Children's baseline / screening version

2. Children's since last visit version.

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

The C-SSRS is based on the research and development at the Columbia University by Posner et al. [Posner 2007a (3)] supported by Columbia-Classification Algorithm for Suicide Assessment (C-CASA) developed by the same group [Posner 2007b (4)]. It is a semi-structured clinical interview consisting of domains of suicidal ideation, suicidal behavior and non-suicidal self-injurious behavior, and details of actual and potential lethality. It is designed for personal interview administration. Subjects or Parents/Caregivers are asked directly by a trained clinical assessor. Clinical assessment questions are presented, and subjects provide their responses. These responses enable the interviewer to branch to the appropriate follow up questions, faithfully adhering to C-SSRS probing specifications and potential positive responses. This approach provides consistent assessment and documentation.

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

For the sub-population of subjects enrolled after amendment approval and of respective age and cognitive state the following analysis will be performed. Descriptive frequency tables will be displayed for total sub-population and by treatment group. The number of subjects who experience any suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at least once at any post-baseline visit of the Main Period will be tabulated. Statistical evaluation of the data will be performed according to Table 1 of the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0 (Finalized February 2013) [Nilsson 2013 (5)]. Baseline data and further C-SSRS data such as intensity of ideation and lethality data will only be listed.

Laboratory data

Descriptive statistics for absolute values at Screening V1 will be given for continuous variables. No categorical laboratory variables will be collected. Laboratory parameters will be sorted by predefined categories (e.g., hematology, differential count, and chemistry).

Laboratory data, unscheduled and doubly performed laboratory data will be listed individually. For additionally performed laboratory measurements of certain subjects on other visit dates or of other laboratory parameters than planned no descriptive statistics will be created.

If subjects have additional laboratory examinations during screening examination, only the last sample before application of study medication will be used for final analysis tables. No post-baseline laboratory data is planned for the MP.

Vital signs, body weight, height, and BMI

The individual blood pressure, heart rate, body weight, height, and BMI data will be listed and summarised (n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum) at each time point. Descriptive statistics will be given for absolute values and changes from baseline V2.

Frequencies of subjects with lowered, normal, or raised values will be displayed as shift tables from Baseline V2 vs. Control Visits V3, V4, and Final Visit V5.

High and low values are defined as given in Table 4.

Table 4: High and Low Values of Vital Signs

Vital Sign Variable	Flag	Observed Value
Systolic Blood Pressure (mmHg)	High	≥ 180
	Low	≤ 90
Diastolic Blood Pressure (mmHg)	High	≥ 105

Vital Sign Variable	Flag	Observed Value
	Low	≤ 55
Heart rate (bpm)	High	≥ 110
	Low	≤ 50
Height (cm)	High	Not applicable
	Low	Not applicable
Weight (kg)	High	Not applicable
	Low	Not applicable
BMI (kg/cm^2)	High	≥ 30
	Low	≤ 18.5

A value is considered as high/low if it meets the criterion for observed values

Botulinum Toxin Antibodies

For the subset of subjects with body weight greater or equal to 21 kg, frequency tables will be presented for Screening V1 by category (Fluorescence Immuno Assay for antibodies (FIA-AB)/Hemi diaphragm assay (HDA)), treatment group, pre-treatment status (treatment-naïve/pre-treated, i.e. pre-treatment with any BTX for any indication).

Investigator's Global Assessment of Tolerability

Frequency tables and descriptive statistics will be generated for the data collected at Final Visit V5 of the Main Period.

The following analyses will be performed for the OLEX data:

C-SSRS

For the sub-population of subjects enrolled after amendment 1.0 approval and of respective age and cognitive state the following analysis will be performed. Descriptive frequency tables will be displayed for total sub-population and by MP treatment group. The number of subjects who experience any suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at least once at any visit of the OLEX will be tabulated. Statistical evaluation of the data will be performed according to Table 1 of the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0 (Finalized February 2013) [Nilsson 2013 (5)]. Further C-SSRS data such as intensity of ideation and lethality data will only be listed.

Laboratory data

Descriptive statistics for absolute values at the Injection Visit V6 and the End of Study Visit (V17) and changes from Screening V1 to V6 and to V17 will be given for continuous variables.

The number of subjects with lowered, normal, or raised values compared to normal range as shift tables from Screening V1 vs. V6 and V1 vs. V17. Laboratory parameters will be sorted by predefined categories (e.g., hematology, differential count, and chemistry).

Laboratory data, unscheduled and doubly performed laboratory data will be listed individually. For additionally performed laboratory measurements of certain subjects on other visit dates or of other laboratory parameters than planned no descriptive statistics will be created. If subjects have additional laboratory examinations during screening examination, only the last sample before treatment start will be used. The first valid value for a post-baseline visit is analyzed.

Vital signs, body weight, height, and BMI

The individual blood pressure, heart rate, body weight, height, and BMI data will be listed and summarised (n, mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum) at each time point. Descriptive statistics will be given for absolute values and changes from baseline V2.

Frequencies of subjects with lowered, normal, or raised values will be displayed as shift tables from Baseline V2 vs. all available OLEX period visits.

Botulinum Toxin Antibodies

For the subset of subjects with body weight greater or equal to 21 kg, frequency tables and shift tables for Screening vs. End of Study Visit (V17) will be presented by category (Fluorescence Immuno Assay for antibodies (FIA-AB)/Hemi diaphragm assay (HDA)), treatment group, pre-treatment status (treatment-naïve/pre-treated, i.e. pre-treatment with any BTX for any indication).

Investigator's Global Assessment of Tolerability

Frequency tables and descriptive statistics will be generated for the data collected at Day 99 (Week 14) of all OLEX cycles.

7.6 Other Variables

The analysis will be performed by MP treatment group (high, mid, low) and in total. Tables for the SES will be created according to the actual treatment group and tables for the FAS will be created for the MP treatment group as randomized. Subject dispositions, demographic data, GMFCS-E&R level at Screening, and baseline characteristics will be presented using standard descriptive statistics; no homogeneity tests will be performed. Demographic data, GMFCS-E&R level at Screening and treatment compliance will be summarized for the SES of the MP, the FAS of the MP, the PPS of the MP, the SES of the OLEX, and the FAS of the OLEX. Demographic data and GMFCS-E&R level at Screening will be given for all randomized subjects in addition. The remaining baseline data such as CP history (including main cause for cerebral palsy, affected limbs, duration since first diagnosis of spasticity, and duration since the first diagnosis of cerebral palsy), primary clinical pattern, planned treatment of spasticity, BoNT-A pre-treatment status at screening and use of local anesthesia/analgosedation for injection treatments will be summarized descriptively only for the FAS of the MP, the PPS of the MP, and the FAS of the OLEX (AS scores at baseline will be displayed in the efficacy section 14.2.). The information, if monitoring was done during sedation of subjects will be listed. Injection guidance technique will be listed for each treated clinical pattern.

The absolute and relative frequencies for subject's reason for premature study discontinuation will be tabulated. Further, the main reason will be tabulated by using the following approach for identification: chose from the reasons that are documented for a subject that one that occurs first in the list as main reason. The list is as follows:

1. Death
2. Pregnancy
3. Adverse Event(s)
4. Lack of efficacy
5. Withdrawal by subject
6. Physician decision
7. Protocol violation
8. Lost to follow-up
9. Other

The analysis of BoNT-A pre-treatment status includes frequency tables for:

- number pre-treated/naïve subjects
- Botulinum Toxin preparations used since first treatment
- Botulinum Toxin preparation used at most recent injection session
- specification of limbs and body side of the most recent pre-treatment

and descriptive summary statistics for:

- number of pre-treatments

- duration since first treatment with Botulinum Toxin
- duration since most recent injection session prior to study entry
- total body dose of Botulinum Toxin at most recent injection session

With respect to pre-treatment with Botulinum Toxin the following durations will be calculated:

- Duration since first treatment with Botulinum Toxin [months] = (date of first injection (V2) – date of first treatment with Botulinum Toxin) + 1 / 30.5

- Duration since most recent injection session prior to study entry [months] = (date of first injection (V2) – date of most recent injection session prior to study entry) + 1 / 30.5

In case of missing days, the date will be set to the first day of the respective month. In case the month is also missing, no imputation will be done and the duration will be defined as missing.

The duration since the first diagnosis of spasticity and the duration since the first diagnosis of cerebral palsy in months will be calculated as follows:

- Duration since diagnosis [months] = (data of first injection (V2) - date of first diagnosis) + 1/ 30.5

In case of missing days, the date will be set to the first day of the respective month. In case the month is also missing, no imputation will be done and the duration will be defined as missing.

Regarding planned treatment of spasticity frequency tables will be created for treatment combinations A, B, C, D, and E, limbs planned to be treated (lower limb right, lower limb left, upper limb right, and upper limb left), and primary body side chosen for analyses.

Treatment compliance for each injection visit (V2, V6, V10, and V14) will be calculated as follows:

- Total Compliance per injection cycle [%] = 100 * Total volume injected in all 4 limbs [mL]/ Total planned volume for all 4 limbs according to treatment combinations A, B, C, D, and E and body weight.

- Compliance per injection cycle and per limb [%] = 100 * Total volume injected in limb [mL]/ Total planned volume for limb according to treatment combinations A, B, C, D, and E and body weight.#

For the overall OLEX Period the following is calculated in addition:

- Total compliance of the OLEX Period is calculated as mean compliance per subject for all performed injection cycles of this subject in the OLEX Period.

Treatment compliance will be displayed using descriptive summary statistics and frequency table for classified compliance per injection visit, primary body/non-primary body side, upper/lower limb(s) in total for these categories. Separate listings will be given for all subjects with total treatment compliance per cycle >100% for the SES of the MP and for the SES of the OLEX period.

Frequencies of previous and concomitant treatments of the MP will be given based on different Anatomical Therapeutic Chemical classification (ATC) code levels of the World Health Organization (WHO) dictionary version MAR 2018 as well as by generic name for the SES of the MP, the FAS of the MP, and the PPS of the MP. Frequencies of concomitant treatments of the OLEX period will be given based on different ATC code levels as well as by generic name for the SES of the OLEX and the FAS of the OLEX. Indications for previous and concomitant therapies will not be coded and will only be listed. Medical history and concomitant diseases well as non-drug treatment of the MP will be described based on MedDRA SOC and PT levels for the SES of the MP. Concomitant diseases well as non-drug treatment of the OLEX period will be described based on MedDRA SOC and PT levels for the SES of the OLEX.

The analysis of extent of exposure, length of injection cycles and total observation period as described below will be performed for the SES of the MP or the SES of the OLEX period, respectively.

Descriptive statistics will be generated for injected volume and injected units, number of injected sites. The analysis will be done per body side, clinical pattern, primary clinical target pattern, and per muscle including ‘total’ for each of these categories.

Frequency tables will be given for treated limbs at each injection visit V2, V6, V10 and V14 (lower limb right, lower limb left, upper limb right, and upper limb left). The number and percentage of subjects with unilateral treatment and with bilateral treatment for upper limbs and for lower limbs will be tabulated.

Descriptive statistics will be generated for length of injection cycle, and the total observation period in weeks over the entire study, for MP and for OLEX period. Frequency tables will be given for classified injection cycle length by injection cycle. The following classes will be used:

- < 12 weeks
- 12 – 16 weeks
- > 16 weeks

The injection visit will be regarded as start of a cycle and the day before the next injection (or the last available visit in case of a discontinued cycle or the last cycle) will be regarded as end of cycle. Length of injection cycle and observation period in weeks will be calculated as follows:

- Total observation period in weeks over the entire study will be calculated as date of last available study visit (e.g. V17 for completers) - date of baseline visit V2 **+1 day**.

- Observational period of the MP in weeks will be calculated as:

  Date of first injection in the OLEX V6 - date of baseline visit V2, if V6 is available.

  Date of last available visit of the MP (e.g. V5 for completers of the MP) - date of baseline visit V2 **+1 day**, if V6 is not available.

- Observational period of the OLEX in weeks will be calculated as date of last available visit of the OLEX (e.g. V17 for completers) - date of first injection in the OLEX V6 **+1 day**.

- The injection cycle length of injection cycle (x) in weeks will be calculated as
  - Date of injection cycle (x+1) - date of injection (x) **or**
  - Date of last available visit – date of injection (x) **+1** day in case of last or discontinued cycle

If injection cycle was not performed length of injection cycle will be missing.

7.7 Special Statistical/Analytical Issues

7.7.1 Discontinuations and Missing Data

Discontinued subjects will not be replaced.

The primary and secondary efficacy variables of the Ashworth scale score will be analyzed on the FAS and PPS of the MP using MMRM for accounting for missing data. The model will be based on the observed cases data without imputing missing values. 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 principle will be followed on the FAS and PPS of the MP, i.e., the last observation (including baseline) will be carried forward to Week 4 and 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.

As the GICS is only measured at Control Visit V3, it is not possible to apply a model based analysis like mixed model repeated measurement. Therefore, only 'no change replacement' and observed case analysis as sensitivity analysis will be performed.

For the secondary efficacy variable 'Questionnaire on Pain caused by Spasticity' LOCF and observed case analyses will be performed on the FAS and the PPS. For the secondary efficacy variable 'Global Impression of Change Scales' missing values will be replace by "0" (no change) and an observed case analyses will be performed on the FAS and the PPS.

For child's/adolescent's GICS and QPS the observed case analysis is the main analysis of interest, and the 'no change replacement' (GICS) and the LOCF (QPS) are the respective sensitivity analyses.

[redacted]

Missing assessments except for primary or co-primary efficacy variable will not be listed as protocol deviations.

Observe case analysis will be performed for all efficacy data of the OLEX period, i.e. missing data of the OLEX will not be replaced.

7.7.2 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.

7.7.3 Data Monitoring Committee

An independent data monitoring committee (DMC) will be assigned to monitor subject's safety throughout the clinical course of the study. 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 the subject. The DMC provides a mean to rapidly note an unexpected hazard that may lead to study termination.

On a regular basis the DMC will evaluate safety data of this study to ascertain protection of subject's safety. The DMC will be kept informed by a DMC office manager who is not involved in this study and located at a contract research organization. The DMC will convene at regular intervals to discuss and decide upon safety issues.

Safety data will be evaluated without knowledge of efficacy data. 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.

If indicated, the DMC will advise Merz and make recommendations regarding e.g., subject's withdrawals and/or study measures. Details on responsibilities and procedures to be followed by the DMC will be laid down in the DMC Charter.

7.7.4 Multiple Comparisons/Multiplicity

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 section 7.1.1 and 7.1.2. If one of the 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. Whenever two variables are tested in one step (step 1, 2, and 4), both variables have to show statistically significant treatment differences in order to prove superiority over low dose treatment in this step. For this reason no α-adjustment for multiplicity is necessary in these combined tests of two variables. This four step hierarchical testing procedure ensures the overall type I level of 5% for the confirmatory tests.

7.7.5 Examination of Subgroups

Subgroup analyses will be performed for the AS regarding treatment group, pooled sites, BoNT-A pre-treatment status, GMFCS-E&R level groups at Screening, AS baseline value, age (2-5, 6-11, 12-17 years), weight group at baseline (<25 kg, ≥ 25 kg), use of local anesthetics and/or analgosedation and unilateral versus bilateral treatment. Shift tables and frequency tables of changes will not be presented for subgroup analyses.

Subgroup analysis for TEAEs, related TEAEs, serious TEAEs and TEAEs of special interest by SOC and PT will be perform for the following subgroups: GMFCS-E&R level groups, age (2-5, 6-11, 12-17 years), weight group at baseline (<25 kg, ≥ 25 kg), and use of local anesthesia/analgosedation for injection treatment.

The following TEAESIs will be analyzed by UL treated, LL treated, not applicable (not located at any treated limb):

- Muscular weakness

- Monoparesis
- Hemiparesis
- Paralysis
- Paralysis flaccid
- Paraparesis
- Paresis
- Peripheral nerve palsy
- Peripheral paralysis
- Quadriparesis

For this analysis "UL treated" means that the AE is located at an upper limb, which was treated. "LL treated" means that the AE is located at a lower limb, which was treated. "Not applicable" means that the AE is not located at any treated limb.

For the subgroup analysis 'use of local anesthetics and/or analgosedation' the two following subgroups will be analyzed:

- Subjects with use analgesics and/or sedatives been used during corresponding injection
- Subjects without use analgesics and/or sedatives been used during corresponding injection

For the subgroup analysis regarding 'unilateral versus bilateral treatment' the following subgroups will be defined for analysis of the AS score of the ULs:

- Unilateral treatment of the upper limbs (Treatment combination A if unilateral, B, C and D)
- Bilateral treatment of the upper limbs (Treatment combination A if bilateral and E)

For analysis of the AS score of the LLs the following subgroups will be analyzed:

- Unilateral treatment of the lower limbs (Treatment combination B)
- Bilateral treatment of the lower limbs (Treatment combination C, D and E)

7.7.6 Pooling of sites

For the purpose of the analyses sites will be pooled according to the country the site is located.

8 CHANGES IN THE PLANNED ANALYSES

The definition of the FAS of the MP and of the OLEX was changed from the CSP in the SAP. In the CSP the FAS of the MP 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)). "for upper limb" was forgotten in the CSP, so the definition was changed to: The FAS of the MP 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 either an AS score in the clinical pattern flexed elbow or flexed wrist at baseline (Day 1), or the Investigator's GICS **for upper limb** at Day 29 (Week 4). This means who have only an Investigator's GICS for lower limb at Day 29 and no Investigator's GICS for upper limb at Day 29 and no AS score in the primary clinical pattern at baseline will be excluded from the FAS, since Investigator's GICS for lower limb is no co-primary efficacy variable.

The definition of the FAS of the OLEX was in the CSP 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. This was changed to: The FAS is the subset of subjects in the SES of the OLEX for whom at least one **post-baseline value of any efficacy variable** in the OLEX is available. These means subjects without a value of the AS score in the OLEX for the primary clinical pattern, but who have other efficacy data in the OLEX will be included in the FAS of the OLEX.

In the SAP it was added how subjects will be analyzed who were not treated according to the randomization list or who have been treated with MP medication in the OLEX (see section 5).

AS:

The definition of the secondary efficacy variable 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 was made more precise in the SAP. "etc." was changed to "pronated forearm and thumb in palm" to make it more clear that all treated upper limb patterns are meant.

AS score of each treated LL pattern will be analysis using descriptive summary statistics for absolute values and changes from baseline only, since the LL patterns will be treated with a different dose for all subjects. One-sample t-test and one-sample Wilcoxon signed-rank test have been added to the planned analysis of the AS score of the OLEX Period.

GICS:

The definition of the co-primary efficacy variable was changed in the SAP compared to the CSP. In the CSP the co-primary efficacy variable was the Investigator's GICS at Day 29 (Week 4) of MP.

However, it was never intended to use the Investigator's GICS for lower limb at Day 29 (Week4) of MP as co-primary variable because a) the first primary variable refers to upper limb only and b) not all subjects will be treated for lower limb. The definition of the co-primary variable was therefore corrected to refer to the Investigator's GICS of the upper limb only. Analogously in the secondary efficacy variable Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) of MP "**for upper limb**" was also added in the SAP. Furthermore as a consequence the Investigator's, Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS at Day 29 (Week 4) of MP were added as other efficacy variables in the SAP and will be analyzed in an exploratory manner. For the OLEX period the other efficacy variable Investigator's, Child'/Adolescent's and Parent's/Caregiver's GICS at Week 4 of each OLEX treatment cycle was changed to Investigator's, Child'/Adolescent's and Parent's/Caregiver's GICS **for upper limb and for lower limb** at Week 4 of each OLEX treatment cycle, i.e. at Ctrl. Visits (V7, V11, and V15) to make the definition more precise.

As the GICS of the MP is measured only at Control Visit V3, it is not possible to apply a model based analysis like mixed model repeated measurement. Therefore, only 'no change replacement' and the observed cases analysis will be performed (see section 7.1.1 for details).

The primary clinical target pattern will be set to missing for subjects whose primary clinical target pattern was not treated in the MP by mistake. As a consequence these subjects will not have the primary efficacy variable "change from baseline in AS in the primary clinical target pattern". If these subjects have a measurement for the Investigator's GICS for upper limb at Day 29 these subject still belong to the FAS of the MP. According to the definition of the FAS of the OLEX from the CSP, subjects without primary clinical target pattern will be excluded from the FAS of the OLEX. But it is more reasonable to evaluate all subjects for the OLEX for whom at least one post-baseline value of any efficacy variable in the OLEX is available. In agreement with the intention-to-treat principle the Full Analysis Set of the OLEX should be as "full" as possible. For this reason the definition of the FAS of the OLEX will be changed to the following definition: The FAS of the OLEX is the subset of subjects in the SES of the OLEX for whom at least one post-baseline value of any efficacy variable in the OLEX is available. As a consequence subjects without primary clinical target pattern will no longer be excluded from the OLEX.

Investigator's, Child's/Adolescent's (if applicable) and Parent's/Caregiver's GICS [redacted] will be analyzed by descriptive summary statistics and frequency tables [redacted] instead of analysis of covariance (ANCOVA) for the OLEX Period. An ANCOVA is not appropriate for the OLEX period since all subjects receive the same treatment and no treatment differences can be estimated.

Other efficacy variables:

For other efficacy variables in the SAP the visit numbers were added and the variables were given in more detail than in the protocol.

Further other variables:

Planned treatment of spasticity, treatment compliance, monitoring during sedation, injection guidance technique, length of injection cycle, and extent of exposure were added to other variables.

Safety variables:

The secondary efficacy variable occurrence of TEAEs by final outcome in the CSP was changed to occurrence of TEAEs by worst outcome in the SAP. Usually final outcome is the same was worst outcome. But it may occur that a subject has two different TEAE at two different time points, which are coded with the same PT (e.g. left leg broken and right leg broken). Then it is more important to know the worst outcome of both TEAEs than only the outcome of the second TEAE.

TEAE data and all CRF comments will be screened for possibly suicidal events. For this purpose to additional listing will be generated (see section 7.5.2).

Additionally, to fulfill FDA requirements, only for subjects of respective age and cognitive state enrolled after amendment 1 approval, prospective assessments for suicidality using the C-SSRS assessments have to be applied.

9 REFERENCES

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