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Merz Pharmaceuticals GmbH

Statistical Analysis Plan

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

Phase 3

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Date: 21-Jun-2019

Author: [redacted] (Statistician)

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/database close.

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
ATC	Anatomical Therapeutic Chemical
BDRM	Blind Data Review Meeting
BG	Blood Glucose
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BoNT	*Botulinum* neurotoxin
CI	Confidence interval
CP	Cerebral palsy
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	
DMC	Data Monitoring Committee
[redacted]	
eCRF	Electronic Case Report Form
EudraCT	European Union Drug Regulatoring Authorities Clinical Trials
FAS	Full Analysis Set
GICS	Global Impression of Change Scale
GMFCS	Gross Motor Function Classification System
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LS	Least square
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measurement
MP	Main Period
mTDS	Modified Teacher's Drooling Scale
OLEX	Open-Label Extension
PDF	Portable Document Format
PPS	Per Protocol Set
PT	Preferred Term
PVA	Polyvinyl Alcohol
SAE	Serious Adverse Event
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
TFLs	Tables / Figures / Listings
TEAE	Treatment Emergent Adverse Event
TEAESI	Treatment Emergent Adverse Event of Special Interest
TESAE	Treatment Emergent Serious Adverse Event
uSFR	Unstimulated Salivary Flow Rate
WHO-DD	World Health Organization Drug Dictionary

2 GENERAL AND TECHNICAL ASPECTS

The objective of this statistical analysis plan (SAP) is to specify the statistical analyses in more detail than stated in the clinical study protocol 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 1.0, dated 17-Jul-2014 and amendment no. 1 Version 2.0, dated 04-May-2015 which were consolidated in the clinical study protocol Version 2.0, dated 16-Jun-2016.

All programs will be written using SAS version 9.4. A font size of 10 points will be used for the tables and figures in section 14, corresponding to a linesize of 111 digits and a pagesize of 42 lines for an output in A4 format. For listings a standard font size of 10 points with the linesize and pagesize as defined above 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 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 for tables, figures and listings (TFLs) will be applied.

3 CLINICAL STUDY DESIGN AND OBJECTIVES

3.1 Clinical Study Design

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

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

The study consists of four injection cycles. The first injection cycle is the main period. The total duration of the main period is 15–22 weeks (comprising the screening period of up to 4 weeks before the first injection and the main treatment period of 16 ± 2 weeks). This first injection cycle is followed by three subsequent open-label injection cycles (16 ± 2 weeks each) for all subjects. The total treatment period thus lasts for 56–72 weeks after the first injection for those completing all four injection cycles. For the safety of subjects, a Data Monitoring Committee (DMC) assesses adverse events (AEs), including adverse events of

special interest (AESIs) and serious adverse events (SAEs) at regular intervals and after each group of 30 subjects has been fully recruited.

The treatment comprises four injections of NT 201 (parotid and submandibular glands, bilaterally); the dose is defined according to body weight (approximately 2 U/kg). At the end of the main period, subjects are assessed for eligibility to enter the extension period.

There will be one final analysis at the end of the study including MP and OLEX.

The study includes the following visits:

Table 1: Visit Schedule

Screening Visit (V1):	Day -28 to -7
Placebo-controlled main period (first injection cycle):	
Baseline injection visit (V2):	Day 1 of first injection cycle, randomization
Assessment visit (V3):	Week 4 ± 3 days
Assessment visit (V4):	Week 8 ± 7 days
Assessment visit (V5):	Week 12 ± 7 days
Final visit of main period (V6):	Week 16 ± 2 weeks
Open-label extension period (second, third and fourth injection cycle):	
Second injection cycle (16 ± 2 weeks after 1st injection):	
Injection visit (V6a)	Day 1 of second injection cycle
Assessment visit (V7)	Week 4 ± 3 days after the 2nd injection
Assessment visit (V8)	Week 8 ± 7 days after the 2nd injection
Assessment visit (V9)	Week 12 ± 7 days after the 2nd injection
End of cycle visit (V10)	Week 16 ± 2 weeks after 2nd injection
Third injection cycle (16 ± 2 weeks after 2nd injection):	
Injection visit (V10a)	Day 1 of 3rd injection
Assessment visit (V11)	Week 4 ± 3 days after 3rd injection

Assessment visit (V12)	Week 8 ± 7 days after 3rd injection
Assessment visit (V13)	Week 12 ± 7 days after 3rd injection
End of cycle visit (V14)	Week 16 ± 2 weeks after 3rd injection

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

Injection visit (V14a)	Day 1 of 4th injection cycle
Assessment visit (V15)	Week 4 ± 3 days after 4th injection
Assessment visit (V16)	Week 8 ± 7 days after 4th injection
Assessment visit (V17)	Week 12 ± 7 days after 4th injection
End of cycle/study visit (V18)	Week 16 ± 2 weeks after 4th injection

3.2 Clinical Study Objectives

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

4 DETERMINATION OF SAMPLE SIZE

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

[redacted]

4.1 Safety

Subjects in age group 6–17 years

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

Subjects in age group 2–5 years

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

4.2 Efficacy

Subjects in age group 6–17 years

[redacted]

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

Subjects in age group 2–5 years

Since the primary efficacy analysis is based on the population of subjects aged 6–17 years, no formal sample size estimation is necessary for the subjects in the youngest age group (2–5 years) who all receive active treatment. Additionally, only the co-primary efficacy variable 'GICS four weeks after injection' is assessed in this population. Power calculations with respect to the GICS four weeks after injection show that the sample size of 30 subjects is

sufficient to detect a GICS of ± 2.0 points as a statistically significant difference to a GICS of 0 points (no change) at Week 4 (V3) with a power of 95% by assuming a standard deviation of 2.94 points (two-sided t test, significance level $\alpha = 0.05$).

5 ANALYSIS SETS

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

Safety Evaluation Set MP

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

Full Analysis Set

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

Per Protocol Set

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

If subjects aged 6-17 years have erroneously not been treated according to the randomization list in the MP, in MP tables performed on the **SES** these subjects will be **analyzed as treated** and in MP tables performed on the **FAS or PPS** they will be **analyzed as randomized/ assigned** for the MP treatment group.

If subjects aged 2-5 years have erroneously not been treated with an NT 201 medication kit in the MP but with a main period medication kit containing placebo, then these subjects will be excluded from the MP analysis.

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

Safety Evaluation Set OLEX

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

If subjects have erroneously been treated with placebo during single OLEX cycles, no safety data in the respective cycle will be displayed. For summaries of safety data of the whole OLEX period or tables displaying changes between single cycles, for example shift tables, all subjects who received placebo in single OLEX cycles will be excluded. In case the OLEX period will be analyzed respective of MP treatment group, the actual treatment in MP will be used for safety data. For efficacy data subjects erroneously treated with placebo during single OLEX cycles will be included. Furthermore, the randomized/ assigned treatment in MP will be used for analysis respective of MP treatment group in chapter 14.1 and 14.2.

In the subject data listings, the treatment group of MP/OLEX will be listed as randomized/ assigned except for the section 16.2.7 and 16.2.8, here the actual treatment group of the respective cycle will be listed. All listings will be sorted by site, treatment group, subject and cycle.

6 VARIABLES FOR ANALYSIS

6.1 Efficacy Variables

6.1.1 Primary efficacy variables

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

- Change in mean unstimulated salivary flow rate (uSFR) from baseline (V2) to V3 (Week 4). The mean uSFR is calculated by averaging the two assessments at each visit.

- Global Impression of Change Scale (GICS) at V3 (Week 4) representing the functional improvement in drooling since baseline as assessed by the caregiver/parent(s).

Unstimulated Salivary Flow Rate (uSFR)

Unstimulated salivary flow rate (uSFR) is measured by the swab method of direct saliva collection.

The saliva collection method by absorbent swabs with safety threads are used instead of cotton rolls to prevent subjects from swallowing the swab. The used swab (made of polyvinyl alcohol (PVA)) has a size of 35 x 9 x 12 mm, with 15 cm safety thread, provided in double, sterile packaging. It is approved as medical device and used in clinical practice as nasal packs.

Two absorbent swabs (1 swab per side) are placed in the mouth, positioned between cheek and gums directly at the orifices of the salivary ducts of the glands, for 5 minutes. The flow rate can be calculated by the following formula:

$$\text{Salivary flow rate [g/min]} = \frac{\text{Weight increase of rolls [g]}}{\text{Time of collection [min]}}$$

The procedure is repeated after 30 minutes (± 5 minutes) and the average of the two results for flow rate is calculated. The assessments are performed under standardized conditions.

Global Impression of Change Scale (GICS)

The Global Impression of Change Scale (GICS) rating is performed by the caregiver before the quantitative measurement of saliva production.

The question of the GICS for the caregiver is: 'Compared to how the child was doing just before the last injection into his/her salivary gland, what is your overall impression of how he/she is functioning now as a result of this treatment?'

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:

Table 2: Possible responses on GICS rating

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

6.1.2 Secondary efficacy variables

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

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

6.2 Pharmacodynamic Variables

Not applicable

6.3 Pharmacokinetic Variables

Not applicable

6.4 Pharmacogenetic Variables

Not applicable

6.5 Safety Variables

As the analyses of all variables in this study will be shown separately for the two study periods, main period and extension period, the wording "overall and by injection cycle" in the following will be interpreted as "overall (MP and OLEX), per period (MP, OLEX) and by injection cycle" and analyzed as such.

6.5.1 Primary safety variable

Occurrence of treatment emergent AEs (TEAEs) overall and by injection cycle.

6.5.2 Secondary safety variables

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

6.5.3 Other safety variables

- Occurrence of non-treatment emergent AEs.
- Occurrence of non-serious TEAEs per period.
- Occurrence of TEAEs by worst intensity per period and injection cycle.
- Occurrence of TEAEs by worst causal relationship per period and injection cycle.

- Occurrence of related serious TEAEs per period and injection cycle.
- Occurrence of TEAEs by worst outcome per period and injection cycle.
- Listing of all serious TEAEs of subjects who died per period.
- Listing of TEAEs of standard MedDRA query suicide/self-injury and of TEAEs with possibly suicidal events, per period.
- Vital signs (blood pressure, heart rate, body temperature) at study baseline, V3 (week 4), V6 (week 16), during the main period, at injection visits in the extension period, at end of cycle visits in the extension period and at the end-of-study visit (V18) (Week 64).
- Body height and body mass index (BMI), calculated from body weight and height, at study baseline, final visit of the main period (V6) (Week 16), and end-of-study visit (V18) (Week 64).
- Body weight at study baseline, final visit of the main period (V6) (Week 16), at injection visits in the extension period, at end-of cycle visits in the extension period and end-of-study visit (V18) (Week 64).
- Clinical chemistry (including alkaline phosphatase (AP) and blood glucose (BG)) and hematology at study baseline, final visit of the main period V6 (Week 16), and end-of-study visit V18 (Week 64).
- Occurrence of antibodies against BoNT-A in subjects with ≥ 30 kg body weight.
- The number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during treatment based on the Columbia-Suicide Severity Rating Scale (C-SSRS).

Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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

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

1. Children's baseline / screening version

2. Children's since last visit version.

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

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.

6.6 Other Variables

The following additional variables will be analyzed:

- Subject dispositions (including number of subjects enrolled, number of discontinuations and reason for discontinuations)
- Incidence of protocol deviations
- Demographic data
- Gross Motor Function Classification System (GMFCS) level at baseline (V2) for CP subjects
- Medical history
- Medical history of sialorrhea
- Concomitant diseases
- Previous therapies, including medication and non-drug treatment
- Concomitant therapies, including medication and non-drug treatment
- Injection cycle length, period length and length of entire study period
- Extent of exposure
- Treatment compliance
- Method of administration of the injection

- Use of analgesics and/or sedatives during injection

Gross Motor Function Classification System (GMFCS)

The GMFCS is a 5-level classification system that is a standardized observational instrument for children with CP developed to measure change in gross motor function over time [Rosenbaum 2002]. It describes the gross motor function of children and adolescents with cerebral palsy (CP) on the basis of their self-initiated movement with particular emphasis on sitting, walking, and mobility. Distinctions between levels are based on functional abilities, the need for aids (e.g., walkers, crutches, and canes) or wheeled mobility, and quality of movement. The original version was developed in 1997 [Palisano 1997]. As of 2007, the expanded and revised version (GMFCS - E&R) further includes an age band for youth 12 to 18 years.

The GMFCS level will be determined at the Baseline Visit (V2)

7 STATISTICAL ANALYSIS METHODS

In most cases the end of cycle visit and the injection visit of the following cycle will be performed on the same date. In this case only end of cycle will be documented in the CRF and respective values will also be used for the analysis of the following injection visit. If the visits are not performed on the same date both visits will be documented for most parameters. Only the efficacy variable uSFR will be documented once. This value will be used for the analyses of the end of cycle visit and for the analyses of the injection visit.

7.1 Efficacy Variables

All efficacy analyses on data from the main period will be based primarily on the FAS and where deemed sensible additionally, to estimate another estimand, on the PPS. Analyses on data from the extension period are based on the SES only. If not stated otherwise, analyses are performed by all age groups and treatments, i.e. the analyses of the MP will be stratified by “Placebo (6-17 years)”, “NT 201 (6-17 years)”, “NT 201 (2-5 years)” and “Total NT 201 (2-17 years)”. For the OLEX, two sets of tables will be produced: one “respective of main period treatment” showing “NT 201 (MP=Placebo, 6-17 years)”, “NT 201 (MP=NT 201, 6-17 years)”, “NT 201 (MP=NT 201, 2-5 years)”, “NT 201 (MP=NT 201, 2-17 years)” and another set “irrespective of main period treatment” showing “NT 201 (6-17 years)”, NT 201 (2-5 years)” and “NT 201 (2-17 years)”. For the tables respective of main period treatment the randomized/ assigned treatment will be used.

For some variables, analyses by additional age groups and further subgroups will be performed (see Section 7.7.5).

Statistical tests will be two-sided hypothesis tests for between-treatment differences in general. Continuous variables (values and changes from baseline) will be summarized by the number of observed values (n obs), the number of missing or imputed values (n miss/ n imp),

mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (n, %) and, if applicable, shift tables will be displayed. Confidence limits and descriptive p-values will be given, where appropriate.

P-values will be reported to four decimal places (e.g. p=0.0375). P-values below 0.0001 will be presented as '<0.0001'.

Mean, standard deviation, Q1, median and Q3 will be reported to one decimal place greater than the data were collected, for derived data an adequate number of decimals has to be chosen. Percentages will be calculated using the denominator of all subjects in a specified population or treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary. Percentages will be reported to one decimal place.

In general values measured at the baseline injection visit (V2) will be used as study baseline value. If data is missing for this visit the last valid value before first injection will be used instead. If e.g. the uSFR is not measured at Visit 2 (Baseline) and the last valid value before first injection is the uSFR value at screening then this value will be used as study baseline value in all analyses described below.

For all MP and OLEX tables the treatment groups will be analyzed as randomized/ assigned in the respective study period. For all OLEX tables, which are stratified by visit/cycle, only subjects with injection in the respective cycle are included; for the end-of-study visit all subjects with at least one injection in the OLEX are included (irrespective of regular or premature discontinuation). Additional to "End of Study" visit "Cycle 4 Week 16" visit will be analyzed. For "Cycle 4 Week 16" only subjects regularly completing cycle 4 are included. In general, percentages will be based on all subjects treated in the respective cycle.

7.1.1 Primary/Co-primary Efficacy Variable

The main co-primary estimands will be defined as follows:

Objective	Evaluate whether treatment with NT 201 is superior to treatment with placebo with respect to reducing sialorrhea
Population	Subjects treated
Variable(s)	uSFR and GICS, evaluated at 4 weeks after treatment in comparison to baseline
Handling of intercurrent events	To be defined during the BDRM
Population-level summary of the variable(s)	Difference in mean uSFR change from baseline to week 4 / mean GICS at week 4 between NT 201 and placebo

The main analytic approach or primary confirmatory analysis of the co-primary estimands will be a mixed model repeated measurement analysis (MMRM, 2-sided, significance level alpha=0.05) with comparison of least square means between NT 201 and placebo performed on the group of subjects within the FAS aged 6-17 years.

The dependent variables will be the change in uSFR from baseline (V2) to V3 (Week 4) (ΔuSFR) and the carer's/parent's GICS at V3 (Week 4), respectively.

The independent variables are defined as treatment group, pooled investigation sites (see section 7.7.6) and age groups (6-9 years, 10-12 years and 13-17 years) as fixed factors, visit*treatment as interaction term, and visit as repeated factor. To adjust for the baseline status, the MMRM of the uSFR change additionally includes the baseline score of the uSFR as covariate. Since no baseline assessment of the GICS is available, the baseline mTDS rated by the parent(s)/carer is used as covariate in the MMRM model for the GICS.

The following SAS code will be used:

```
proc mixed data = dataset;
   class treatment pooled_site age_group subject visit;
   model ΔuSFR (GICS) = treatment pooled_site age_group uSFR_baseline
         (mTDS) visit visit*treatment /solution ddfm=kr;
   repeated visit / subject = subject type = un grp = treatment
   LSMeans visit*treatment pooled_site age_group / pdiff CL alpha =
0.05;
run;
```

where:

treatment	=	treatment group (NT 201 (6-17 years) and Placebo (6-17 years))
pooled_site	=	pooled investigation sites
age_group	=	age group (6-9 years, 10-12 years and 13-17 years)
uSFR_baseline	=	Value of uSFR at Visit 2 (Baseline)
mTDS	=	Value of mTDS at Visit 2 (Baseline)

Only if both co-primary efficacy variables show a statistically significant difference compared to placebo the superiority of NT 201 over placebo will be considered to be proven. Therefore, no α-adjustment for multiple testing is necessary.

Intercurrent events with potential bias on the co-primary endpoints will be identified prior to or during the BDRM. In case these events are judged as relevantly biasing the co-primary endpoints, conservative sensitivity analyses on the MMRM model will be specified during the BDRM.

In addition to the MMRM, an analysis of covariance (ANCOVA) model will be performed on the FAS (age 6-17 years) using observed cases as well as using the baseline observation carried forward approach (BOCF, no effect) for uSFR and imputing missing GICS entries as “no change”. The ANCOVA models will be performed by use of the following SAS code:

```
proc mixed data = dataset;
   class treatment pooled_site age_group;
   model ΔuSFR (GICS) = treatment pooled_site age_group uSFR_baseline
         (mTDS)/solution ddfm=kr;
   LSMeans treatment pooled_site age_group / pdiff CL alpha = 0.05;
   where visit = V3;
run;
```

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

```
proc npar1way data=dataset wilcoxon;
 class treatment;
 var ΔuSFR;
run;
```

For the GICS, a logistic regression will be performed as sensitivity analysis to the distribution assumption. The responder rate will be determined, i.e. all subjects with GICS entry of at least +1 (Minimally improved).

Treatment arm comparisons with respect to responders based on the GICS entries will be performed analogously to the primary efficacy analysis, but based on estimates of logistic regression models. The dependent variable of these models will be the response to treatment. Treatment group, pooled investigation site and age group will be included as factors into the models. Baseline adjustment will be done by including the baseline values of the mTDS as covariate. The following SAS code will be used for estimation:

```
proc logistic data=dataset desc order=formatted;
    class treatment pooled_site age_group;
    model resp(GICS) = treatment pooled_site age_group mTDS;
   where visit = V3;
run;
```

The comparison with respect to treatment group will be performed by use of the Odds Ratios and their corresponding 95% Wald confidence intervals (CI).

This analysis will be performed on the FAS (6-17 years) without imputation of missing values and by imputing subjects with missing GICS entries as non-responder. In the observed case analysis, percentages will be based on subjects with values at the respective visit. When using the imputation approach, percentages will be based on all subjects with observed or imputed values at the respective visit. For the response rate frequencies, including 95% confidence limits and descriptive p-values for NT201 (6-17 years) vs. placebo (6-17 years) (based on Fisher's exact test or or χ^2-test as appropriate as appropriate) will be given.

If one of the logistic regression models is not estimable due to a too small amount of responders or non-responders, this analysis will be replaced by descriptive summary statistics.

In addition, descriptive summary statistics and frequency tables (for GICS only) of values and changes from baseline (uSFR only) will be given for the primary and co-primary efficacy variables overall and by age groups and further subgroups (observed case and imputed values). A frequency table will also be given for the GICS responder/non-responder.

All analyses stated above will also be performed on the PPS. This addresses a different estimand, namely:

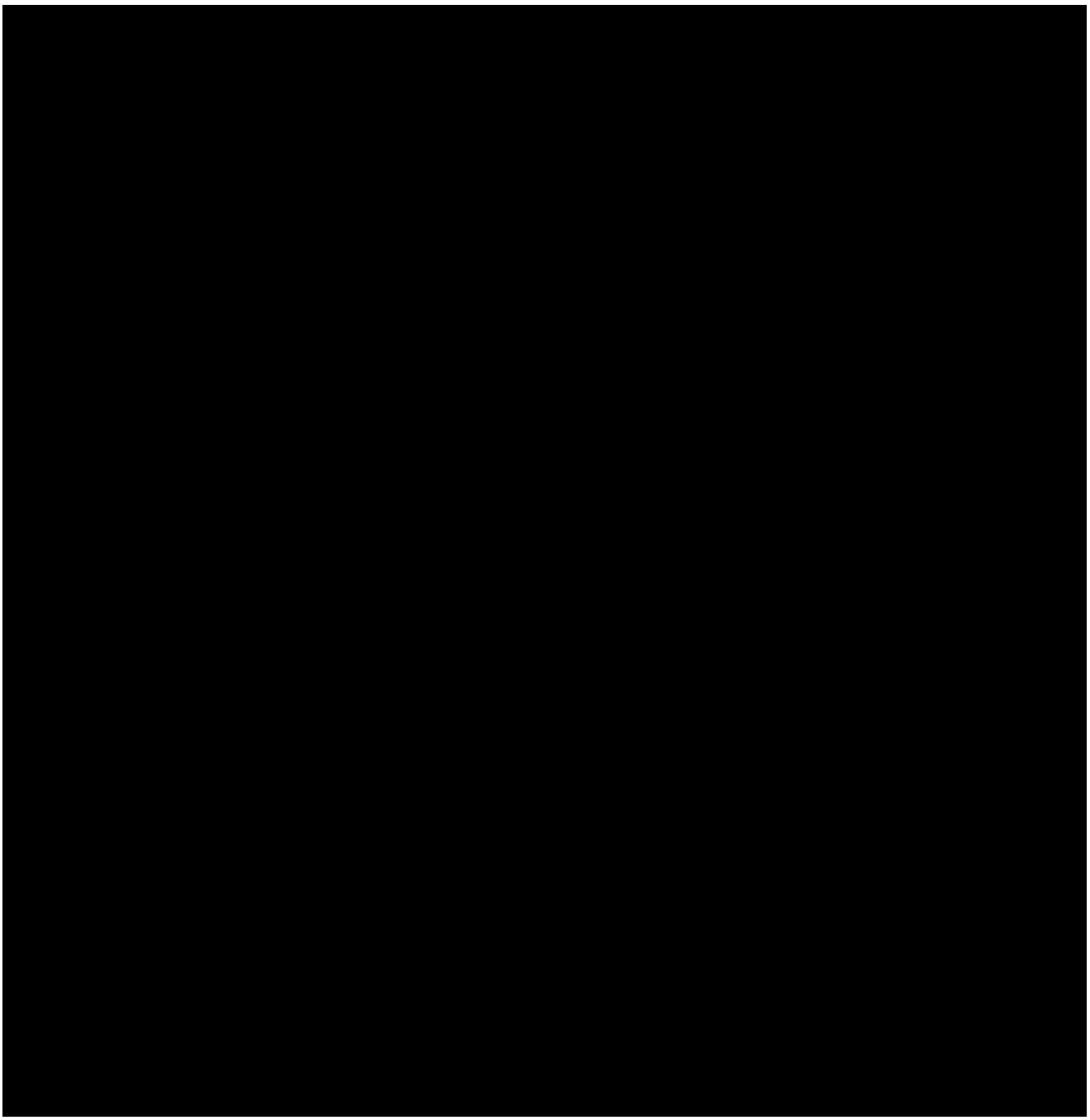
Objective	Evaluate whether treatment with NT 201 is superior to treatment with placebo with respect to reducing sialorrhea when applied as specified in the protocol
Population	Subjects who are treated and follow the procedures in the protocol related to the treatment or the observation of its effect (i.e. e.g. do not take prohibited medication)
Variable(s)	uSFR and GICS, evaluated at 4 weeks after treatment in comparison to baseline
Handling of intercurrent events	To be defined during the BDRM
Population-level summary of the variable(s)	Difference in mean uSFR change from baseline to week 4 / mean GICS at week 4 between NT 201 and placebo

7.1.2 Secondary Efficacy Variables

The analyses of the secondary efficacy variables are also based on the subjects aged within the FAS 6–17 years.

The changes in uSFR from baseline (V2) to V4 and V5 (Week 8 and 12, respectively) and the GICS at V4 and V5 (Week 8 and 12, respectively) are analyzed analogously to the primary efficacy variables by means of a MMRM, ANCOVA and Wilcoxon rank-sum test with the analysis sets and methods to handle missing values as described in Section 7.1.1. Furthermore, the logistic regression will be performed for the GICS at V4 and V5.

Although these are "other" and not "secondary" efficacy variables, the uSFR change from baseline to V6 (Week 16) and the GICS at V6 will be included in the MMRM, ANCOVA and Wilcoxon rank-sum tables to give a complete picture over the main period. Furthermore, the logistic regression will be performed for the GICS at V6.



7.2 Pharmacodynamic Variables

Not applicable.

7.3 Pharmacokinetic Variables

Not applicable.

7.4 Pharmacogenetic Variables

Not applicable.

7.5 Safety Variables

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

All analyses will be performed by age groups and treatment and additionally for the group of subjects of all ages (2-17) who received NT 201 in the respective treatment period (main or extension period), i.e. all analyses of the MP will be stratified by “Placebo (6-17 years)”, “NT 201 (6-17 years)”, “NT 201 (2-5 years)”, “Total NT 201 (2-17 years)”. For the OLEX, two sets of tables will be produced: one “respective of main period treatment” showing “NT 201 (MP=Placebo, 6-17 years)”, “NT 201 (MP=NT 201, 6-17 years)”, “NT 201 (MP=NT 201, 2-5 years”) and another set “irrespective of main period treatment” showing “NT 201 (6-17 years)”, “NT 201 (2-5 years)” and “NT 201 (2-17 years)”. OLEX tables for non-serious TEAEs with incidence ≥ 5%, C-SSRS and Botulinum toxin antibody results will only be presented irrespective of main period treatment.

For all OLEX tables which are stratified by visit/cycle, only subjects with injection in the respective cycle are included. For End of Study all subjects from SES (OLEX) will be included and the results from V18 will be used. Visit “Cycle 4 Week 16” will not be analyzed.

Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (version in effect when the database is closed).

TEAEs of MP are defined as AEs with onset or worsening after the first injection of NT 201 or Placebo up to and before first injection of the extension period or – in case of discontinuation before second injection – up to and including 16 weeks after first injection of NT 201 or Placebo or date of last study visit, whichever is later. AEs starting in the MP and not having resolved at the final visit of MP (V6) will be followed and further documented in the extension period.

TEAEs of OLEX are defined as AEs with onset or worsening after the first injection of OLEX up to and including 16 weeks after last injection or the date of last study visit, whichever is later.

A detailed description of the rules to be used for the classification of TEAEs can be found in Appendix 1. 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 date is given and not equal to first exposure date in MP or OLEX, set time to 00:00, else if date is equal to first exposure date in MP or OLEX set time to time of first exposure in MP or OLEX, if given (else 00:00), respectively
- if start time is missing and date is given and equal to the subsequent exposure date in OLEX (e.g. 2nd injection in OLEX), set time to time of the subsequent exposure, if given (else 00:00)
- if start date/time is completely missing and end date is not after or equal to first exposure of MP: no imputation.
- if start date/time is (partially) missing and end date is after or equal first exposure in MP or missing:
  - only start day is missing, but month and year same as first exposure in MP or OLEX: set day and time to day and time of first exposure, else set day to 1 and time to 00:00
  - Start day and month are missing, but year is the same as year of first exposure in the MP (which is ≠ year of first exposure in OLEX): set day, month, time to day, month, time of first exposure in the MP
  - Start day and month are missing, but year is the same as year of first exposure in the OLEX (which might be the same as year of first exposure in MP): set day, month, time to day, month, time of first exposure in OLEX
  - Start day and month are missing and year is not the same as year of first exposure in the MP or OLEX: else set day and month to 1 and time to 00:00
- if start date/time is completely missing and end date/time is at or after date/time of first exposure in the MP and before date/time of first exposure in OLEX, set start date/time to date/time of first exposure in the MP (e.g. AE start missing, AE end date 1OCT2014, first injection MP: 1AUG2014).
- if start date/time is completely missing and end date/time is at or after date/time of first exposure in the OLEX, set start date/time to date/time of first exposure in the OLEX
- if AE end date and time are missing and date and time of study end (i.e. last contact or last visit of the study) are not missing, set end date/time to study end date/time, else set end date to study end date and time to 23:59.
- if AE end date/time is partially missing and given information on date is not equal to study end, set day to last day of the given month or day/month to 31/12 of the given year and missing time to 23:59.
- if AE end date/time is partially missing and year or year and month are equal to year or year and month of study end, set analysis end date/time to the date/time study end and missing time to 23:59.
- if AE end time is missing time will be set to 23:59
- if start date and end date is completely missing, set end date to study end date and time to 23:59. Estimate then missing start date as described above

In the following case a special rule will be applied:

If it is not clear in which OLEX cycle the AE starts, incomplete AE start dates/times will be replaced in such a way that the AE is assigned to the earliest possible cycle:

- if start time is missing but date is given and equal to any exposure date in OLEX and AE is assigned to the later cycle, time will be set to start of the later cycle. If AE is assigned to the previous cycle, time will be set to 0:00.

- If day and time are missing, but month and year are given and equal to any exposure date (month and year) in OLEX and AE is assigned to the later cycle, day and time will be set to start day and time of the later cycle. If AE is assigned to the previous cycle, day will be set to 1 and time to 00:00.

- If month, day and time are missing, but year is given and covering several OLEX cycles and the earliest possible OLEX cycle for assignment starts in the year before the AE start (but ends in the year of the AE start), month and day will be set to 1 and time to 00:00. If the earliest possible OLEX cycle for assignment starts in the year of the AE start, month/day/time will be set to month/day/time of the respective cycle start.

Calculation of time to duration of AEs [days]:

- The duration will be calculated as stop date - onset date + 1 for each episode of worsening of AE.

An overview summary table will be created for TEAEs and non-TEAEs displaying the frequencies and percentages of the following categories: “Any TEAE”, “Any TEAE related to treatment”, “Any TEAE of special interest”, “Any TEAE of special interest related to treatment”, “Any serious TEAE”, “Any serious TEAE related to treatment”, “Any TEAE leading to discontinuation”, “Any TEAE leading to discontinuation related to treatment”, “Any fatal TEAE” and “Any fatal TEAE related to treatment” for TEAEs and “Any non-TEAE”, “Any non-TEAE of special interest”, “Any serious non-TEAE”, “Any non-TEAE leading to discontinuation” and “Any fatal non-TEAE” for non-TEAEs.

Incidences will be calculated for TEAEs, treatment-related TEAEs, serious TEAEs, related serious TEAEs, TEAEs leading to discontinuation, TEAEs of special interest at the system organ class level and at the preferred term level and will be presented by treatment, by injection cycle and overall (i.e. per period). TEAEs will also be presented by preferred term level, by treatment, injection cycle and overall. Additionally, TEAEs will be analyzed by worst intensity, by worst causal relationship and by worst outcome.

The number and percentage of subjects with at least one non-serious TEAE with incidence ≥= 5% will be displayed by system organ class level and preferred term level.

In general, all safety analyses for OLEX will be performed overall and for the 2nd, 3rd and 4th injection cycle. Only the number and percentage of subjects with at least one non-serious TEAE with incidence ≥= 5% will be performed overall only.

Listings displaying incidences for TEAEs leading to discontinuation, serious TEAEs and TEAEs of special interest will also be provided.

Listings will be created for subjects who died, subjects with TEAEs of standard MedDRA query suicide/self-injury and for subjects with possibly suicidal events.

TEAEs for the 2nd injection cycle are defined as adverse events with onset or worsening at or after date of 2nd injection and before date of 3rd injection. TEAEs for the 3rd injection cycle are defined as adverse events with onset or worsening at or after date of 3rd injection and before date of 4th injection. TEAEs for the 4th injection cycle are defined as TEAEs with onset or worsening at or after 4th injection.

Duration of AEs will be listed only. Imputed values will be flagged as such.

In case of missing intensity or missing causal relationship of an AE the worst case principle will be applied, i.e. a missing intensity will be set to "severe" and a missing causal relationship will be set to "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.

For any missing data on seriousness a worst case strategy will be applied for all analysis tables. The AE will be regarded as 'serious'.

TEAESIs are defined as adverse events occurring after treatment that are thought to possibly indicate toxin spread. The list of adverse events of special interest possibly indicating toxin spread based on MedDRA version 22.0 (version in effect at database closure) is given in Table 4.

Table 4: List of Adverse Events of Special Interest Possibly Indicating Toxin Spread

MedDRA Preferred Term (MedDRA version 22.0)	
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: only when severe, serious, or outcome is not recovered, fatal or unknown	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 preferred terms is according to MedDRA version 22.0	

To fulfill FDA requirements, TEAE data will be screened for suicidal events. The MedDRA Preferred Terms 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 Preferred Terms of the SMQ ‘Suicide/self-injury’ based on MedDRA version 22.0 is given in Table 5 (version in effect at database closure).

Table 5: List of Adverse Events of Standard MedDRA Query 'Suicide/self-injury'

MedDRA Preferred Term:	MedDRA Preferred Term:
Assisted suicide	Self-injurious ideation
Columbia suicide severity rating scale abnormal	Suicidal behaviour
Completed suicide	Suicidal ideation
Depression suicidal	Suicide attempt
Intentional overdose	Suicide threat
Intentional self-injury	Suspected suicide
Poisoning deliberate	Suspected suicide attempt
Wording of preferred terms is according to MedDRA version 22.0	

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 6: 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').

Vital signs, body weight, and BMI

The individual blood pressure, heart rate, body temperature, body weight, height and BMI data will be listed. Vital signs, body height and weight and BMI will be summarized (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) to all post-baseline visits.

Frequencies of subjects with lowered, normal, or raised values will be displayed as shift tables from baseline (V2) to all post-baseline visits.

High and low values are defined as given in **Table 7**.

Table 7: High and Low Values of Vital Signs

Vital Sign Variable	**Flag**	**Observed Value**[1]
Systolic Blood Pressure (mmHg)	High	≥ 180
	Low	≤ 90
Diastolic Blood Pressure (mmHg)	High	≥ 105
	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/m^2)	High	> 30.0
	Low	≤ 18.5
Temperature (°C)	High	> 37.5
	Low	< 36.5

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

Laboratory data

Descriptive summary statistics for original values and for the changes from study baseline will be displayed for each parameter.

Furthermore, the number of subjects with lowered, normal, or raised values compared to normal range will be displayed as shift tables from Screening to final visit of main period V6 and end-of-study visit V18. Laboratory parameters will be sorted by predefined categories (Hematology and clinical chemistry).

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 shift tables or descriptive statistics will be created.

The first valid value will be analyzed for all post-baseline visits. In case no exact value is given (<x.x, >x.x) the respective higher/ lower value will be used, e.g. >1.24 will be changed to 1.241 and <0.5 will be changed to 0.49.

Antibodies against BoNT-A

Occurrence of antibodies against BoNT-A in subjects with ≥ 30 kg BW will be analyzed descriptively (frequency tables by category and shift tables from baseline (V2) to end-of-study visit V18) and screened for individual notable values and/or changes. In case blood sample is taken at V17 instead of V18 these values are used for analyses.

C-SSRS

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

Questions which were documented between one day after start of MP and up to start of OLEX will be assigned to MP. For subjects who discontinued during MP, all questions which were documented at least one day after start of MP will be assigned to MP. Questions which were documented at least one day after start of OLEX will be assigned to OLEX.

The following outcomes are C-SSRS categories and have binary responses (yes/no).

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5 – Active Suicidal Ideation with Specific Plan and Intent
Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt
Category 8 – Interrupted Attempt
Category 9 – Actual Attempt (non-fatal)
Category 10 – Completed Suicide

The following composite endpoints will be calculated:

1. Suicidal ideation (MP): A “yes” answer during MP to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS.

2. Suicidal behavior (MP): A “yes” answer during MP to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS.

3. Suicidal ideation or behavior (MP): A “yes” answer during MP to any one of the ten suicidal ideation and behavior questions (categories 1-10) on the C-SSRS.

4. Suicidal ideation (OLEX): A “yes” answer during OLEX to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.

5. Suicidal behavior (OLEX): A “yes” answer during OLEX to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

6. Suicidal ideation or behavior (OLEX): A “yes” answer during OLEX to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Frequency tables for the composite endpoints and for the single questions for these time periods will be created. All subjects who filled out at least one questionnaire during the respective period will be used for the denominator whereby only questions which are referring to the time period since last visit are regarded. Furthermore, information on C-SSRS will be listed for subjects with at least one post-baseline suicide-finding during MP (including V6) and for subjects with at least one post-baseline suicide-finding after V6. In case the questionnaire was not filled out on a visit date the previous visit will be assigned in the listing.

7.6 Other Variables

Disposition, demographic and other baseline data

Subject dispositions, demographic data, and baseline characteristics (including height, weight and BMI at screening V1) will be presented using standard descriptive statistics; no homogeneity tests will be performed. Demographic data will be summarized for screening failures, the SES of MP (actual treatment will be displayed), the FAS (planned treatment will be displayed), the PPS and the SES of OLEX. The analyses of the MP will be stratified by “Placebo (6-17 years)”, “NT 201 (6-17 years)”, “NT 201 (2-5 years)” and “Total NT 201 (2-17 years)”. For tables including all enrolled/randomized subjects, the additional “Total” column will be displayed. For the OLEX, two sets of tables will be produced: one “respective of main period treatment” showing “NT 201 (MP=Placebo, 6-17 years)”, “NT 201 (MP=NT

201, 6-17 years)", "NT 201 (MP=NT 201, 2-5 years)", "NT 201 (MP=NT 201, 2-17 years)" and another set "irrespective of main period treatment" showing "NT 201 (6-17 years)", "NT 201 (2-5 years)" and "NT 201 (2-17 years)".

A table given the absolute and relative frequencies for the following European Union Drug Regulatoring Authorities Clinical Trials (EudraCT) age categories will be generated:

- 2-11 years
- 12-17 years.

Furthermore, the absolute and relative frequencies for the following age categories will be generated:

- 2-5 years
- 6-9 years
- 10-12 years
- 13-17 years.

The weight at baseline will be classified in the following categories:

- >= 12 kg and <15 kg
- >= 15 kg and <19 kg
- >= 19 kg and <23 kg
- >= 23 kg and <27 kg
- >= 27 kg and <30 kg
- >= 30 kg.

A table giving the absolute and relative frequencies for subject's reason for premature study discontinuation will be generated giving all reasons as documented in the CRF. The analysis will be based on all randomized/ assigned subjects of MP and on all subjects entered OLEX for OLEX. The randomized/ assigned treatment group will be displayed. For the extension period the reason will be summarized overall and for each cycle. The following subjects are regarded as completers for MP:

- Subjects who are included in SES OLEX or
- Subjects who performed last visit at day 95 or later

Additionally, the reason will be summarized for the complete study for randomized/ assigned subjects. Further, for MP and OLEX, 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 deviation
8. Lost to follow-up
9. Other.

GMFCS level

A frequency table for GMFCS level at baseline (V2) for CP subjects will be displayed for SES and FAS of MP and SES of OLEX.

Protocol deviations

Protocol deviations will be classified into minor and major violations during the BDRM. Major protocol deviations (deviations leading to exclusion from per protocol set) will be summarized for all randomized/ assigned subjects of the MP and all subjects that entered the OLEX using a frequency table.

All protocol deviations will be listed, including their classification.

Diseases specific and general medical history and concomitant diseases

Medical history and concomitant diseases will be coded according to the MedDRA and displayed with respect to System Organ Class and preferred terms for SES of MP and FAS. Concomitant diseases will also be tabulated for the SES of OLEX; medical history will be tabulated for the MP only. A detailed description of the rules to be used to classify medical history and concomitant diseases can be found in Appendix 1.

The following data on the medical history of sialorrhea will be analyzed descriptively for MP (SES and FAS) and for OLEX (SES):

- Primary reason (frequency table).
- Duration since first diagnosis of sialorrhea in months: (date of baseline injection visit in the main period – date of start of sialorrhea + 1)/30.5 (summary statistics).
- Intellectual disability (frequency table).

In case of missing days (but month given) for the start of sialorrhea, 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 left as missing.

Previous and concomitant therapies

Previous therapies are defined as therapies for which the stop date is before the date of the first injection of NT 201 or Placebo.

For concomitant therapies of MP (and not OLEX) the following conditions have to be fulfilled:

- stop date is at or after start of first injection of MP.
- start date is not after start of treatment of the OLEX.
- not ongoing at the end of MP.

For concomitant therapies of MP and OLEX the following conditions have to be fulfilled:

- stop date is at or after start of first injection of OLEX or ongoing at MP/ OLEX.
- start date is not after start of treatment of the OLEX.

For concomitant therapies of OLEX (and not MP) the following conditions have to be fulfilled:

- stop date is at or after start of first injection of OLEX or ongoing at OLEX.
- start date is after start of treatment of the OLEX.

A detailed description of the rules to be used to classify previous therapies and concomitant therapies can be found in Appendix 1. Classes of non-drug treatments are derived from the observed data before database close in order to display frequencies of non-drug treatments. Indications for previous and concomitant therapies will not be coded and will only be listed.
Frequencies of previous and concomitant treatments will be given based on different Anatomical Therapeutic Chemical (ATC) code levels of the World Health Organization (WHO) (dictionary version in effect at database closure) as well as by generic names. Previous therapies will not be tabulated for the OLEX, only for the MP. Previous medication will be tabulated for SES of MP and FAS and previous non-drug treatment only for SES of

MP. Concomitant therapies for the MP will be analyzed for the SES of the MP and FAS. Concomitant therapies for the OLEX will be analyzed for SES of the OLEX.

Duration of exposure

The injection cycle length will be determined for each injection cycle. 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. Furthermore, the period length for OLEX and the length of the entire study period will be analyzed.

The injection cycle length in weeks will be summarized descriptively for each cycle (SES of MP, FAS, SES of OLEX):

- Injection cycle length of 1st injection cycle in weeks:
  if 1st cycle is the last cycle: (date of last visit – date of 1st injection V2 + 1)/7
  else: (date of 2nd injection – date of 1st injection V2)/7 (rounded to one decimal).

- Injection cycle length of2nd injection cycle in weeks:
  if 2nd cycle is the last cycle: (date of last visit – date of 2nd injection V6a + 1)/7
  else: (date of 3rd injection – date of 2nd injection V6a)/7 (rounded to one decimal).

- Injection cycle length of3rd injection cycle in weeks:
  if 3rd cycle is the last cycle: (date of last visit – date of 3rd injection V10a + 1)/7
  else: (date of 4th injection – date of 3rd injection V10a)/7 (rounded to one decimal).

- Injection cycle length of4th injection cycle in weeks:
  (date of last visit – date of 4th injection V14a + 1)/7 (rounded to one decimal).

In case a cycle is omitted, the day before date of next available injection will be used as end date for the calculation of the injection cycle length.

Furthermore, frequency tables for the injection cycle length will be displayed for SES of MP, FAS and SES of OLEX) (< 14 weeks, 14-18 weeks and >18 weeks).

The length of entire study period is defined as the sum of the duration of all injection cycles and will be summarized descriptively (SES of MP, FAS).

The period length of the OLEX period is defined as the sum of the duration of all injection cycles of the OLEX and will be summarized descriptively (SES of OLEX).

Extent of exposure

The extent of exposure will be determined for each injection cycle. For each subject and injection the total injected NT 201 units per injection (which will be zero for subjects treated with placebo) will be divided by the subject's body weight at the corresponding injection visit. This ratio will be classified into the following categories: 0 U/kg,]0,1.5[U/kg, [1.5, 1.8[U/kg, [1.8, 2.2[U/kg, [2.2, 2.5] U/kg and >2.5 U/kg.

A frequency table will display the number and percentage of subjects per (above given) categories of injected NT 201 units/{kg body weight at respective injection} per injection. Furthermore, the total injected NT201 units per injection will be analyzed for the following classes: <25 U, [15, 50[U, [50,75[U, 75 U, >75 U. Numbers will be based on the SES/ FAS of the MP for the first injection and on the SES of the OLEX for the injections within the OLEX.

OLEX tables for extent of exposure will only be presented irrespective of main period treatment.

Subjects with dose reduction or with differences in actual/ randomized treatment will be listed.

Treatment compliance, method of administration of injection and use of analgesics and/or sedatives during injection

For the NT 201 group dosages will be given according to the predefined volumes of fixed total doses defined for each of the six body-weight classes (see Table 8 below).

In general for subjects with a body weight of 12–30 kg the total dose is approximately 2 U/kg. Subjects with a body weight ≥ 30 kg will receive a fixed total dose of 75 U. Due to the unitary concentration of the NT 201 solution the dose adjustment will be performed by adapting the injection volumes for each dose group (see Table 8).

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

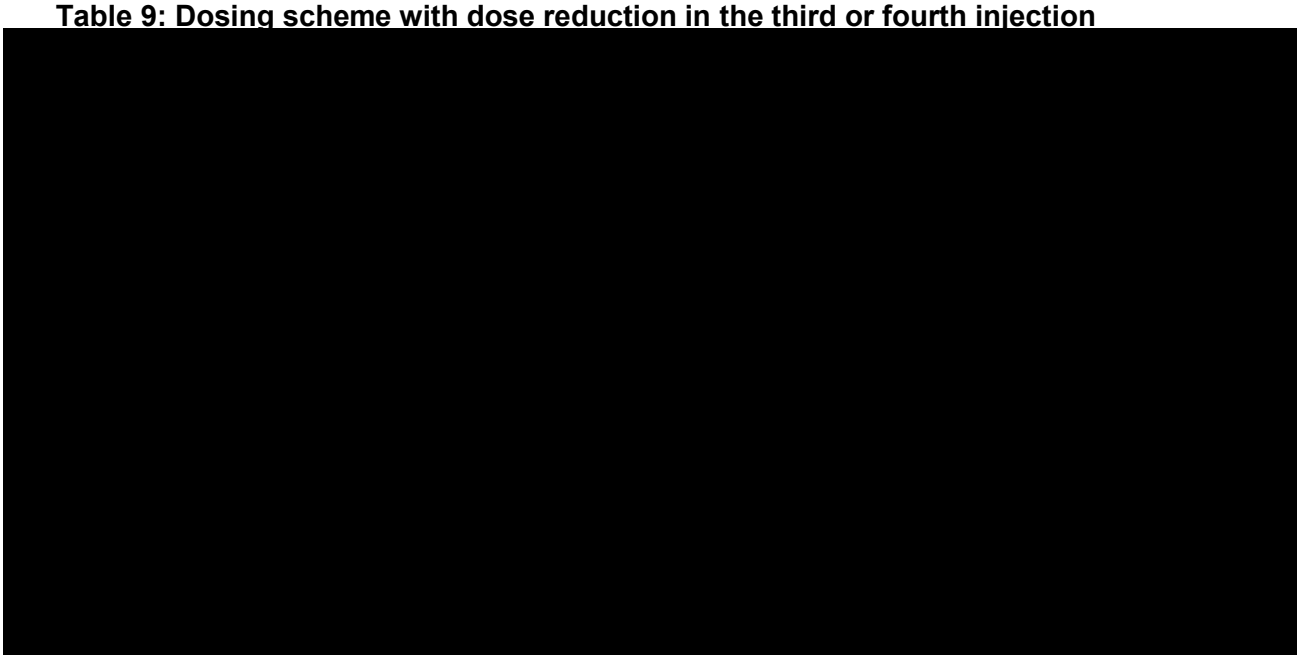
In the placebo group (only during MP), subjects will receive the respective volume of placebo solution (0.9% sodium chloride, sucrose and human serum albumin) as in the NT 201 treatment group according to their bodyweight classification.

Table 8: Dosing scheme

The treatment compliance will be calculated for each cycle in percentage by (100 * Total volume injected [mL]/Total volume planned [mL]). For MP the compliance will be displayed using descriptive summary statistics for SES of MP and FAS. For OLEX the total compliance (2^{nd}, 3^{rd} and 4^{th} injection cycle together) and the compliance per injection cycle will be displayed using descriptive summary statistics for the SES of the OLEX. The total compliance is calculated as the mean compliance per subject for all performed injections of OLEX.

If a dose reduction is documented for a subject then the reduced planned dose will be used for calculation of the compliance in the next cycle. E.g. if a subject had an adverse event with action taken = 'dose reduced' in cycle 3 then it will be assumed that for the subject the reduced dose was documented in cycle 4. The dosing scheme with dose reduction is given in Table 9.

Table 9: Dosing scheme with dose reduction in the third or fourth injection



If in the third cycle the dose is reduced, then the fourth cycle dose will likewise be determined by reference to Table 9, using the subject's current body weight.

In the event of a subject's gaining weight such that he/she would progress from one dose level to a higher dose level according to Table 8, while at the same time requiring dose reduction because of a relevant adverse event, the subject will remain at the previous dose level.

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

A frequency table for the method of administration of the injection per cycle will be displayed (ultrasound and other) for SES and FAS of MP and SES of OLEX.

A frequency table for the use of analgesics and/or sedatives during injection will be displayed (yes and no) for SES and FAS of MP and SES of OLEX.

7.7 Special Statistical/Analytical Issues

7.7.1 Discontinuations and Missing Data

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

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

In general, values measured at the baseline injection visit (V2) will be used as study baseline value. If data is missing for this visit the last valid value before first injection will be used instead.

7.7.2 Interim Analyses

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

7.7.3 Data Monitoring Committee

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

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

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

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

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

For each DMC meeting, minutes are taken by the responsible DMC coordinator/administrator of the Contract research organization (CRO) and reviewed by the DMC members before finalization.

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

A list of members of the committee and a copy of the committee's charter are provided separately and is reviewed by the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB).

7.7.4 Multiple Comparisons/Multiplicity

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

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

7.7.5 Examination of Subgroups

All subgroup analyses will be performed on an explorative level.

Tables with descriptive statistics for uSFR, GICS, GICS response and mTDS will be repeated for the following subgroups:

- Age group:
  - 6-9 years,
  - 10-12 years
  - 13-17 years.
- Pooled investigational sites (where pooling will be the same as used for the MMRM and ANCOVA models).
- Etiology (cerebral palsy, traumatic brain injury and other)
- Gender
- Weight group (rounded to one decimal place):
  -]0, 30 kg[and ≥ 37.5kg (corresponds to a planned NT201 exposure of ≤ 2U/kg)
  - [30, 37.5kg[(corresponds to a planned NT 201 exposure of > 2U/kg)
- Baseline disease severity:
  - uSFR at baseline ≤ median of uSFR at baseline
  - uSFR at baseline > median of uSFR at baseline

These analyses will be performed for FAS, PPS and SES OLEX for uSFR and GICS. Tables for mTDS will be created for FAS and SES OLEX. The analysis by age group will be performed for FAS (6-17 years) instead of FAS.

In addition, the following uSFR and GICS MMRM models will be built:

1. MMRM model with treatment, pooled site and age group included as (fixed) factors and uSFR at baseline (or mTDS at baseline) included as covariate, visit*treatment and subgroup*visit*treatment as interaction terms and visit as repeated factors. I.e. two different models will be calculated (pooled site as interaction term and age group as interaction term).

2. Primary endpoint MMRM model based on subjects with uSFR at baseline ≤ median of uSFR at baseline, only.

3. Primary endpoint MMRM model based on subjects with uSFR at baseline > median of uSFR at baseline, only.

4. MMRM model with treatment, pooled site, age group, etiology, gender, weight group included as (fixed) factors and uSFR at baseline (or mTDS at baseline) included as covariate, visit*treatment and subgroup*visit*treatment as interaction terms and visit as repeated factors. I.e. five different models will be calculated (pooled site as interaction term, age group as interaction term, etiology as interaction term, gender as interaction term and weight group as interaction term).

For each subgroup level of age group and pooled site, the LS-Mean for difference between NT201 and placebo at week 4 will be selected from Model 1) and presented in a table and forest plot.

For the first (second) subgroup level of baseline disease severity, the LS-Mean for difference between NT201 and placebo at week 4 will be selected from Model 2) (3) and presented in the same table and forest plot as mentioned above.

For each subgroup level of etiology, gender and weight group, the LS-Mean for difference between NT201 and placebo at week 4 will be selected from Model 4) and also presented in the above mentioned table and forest plot.

These analyses will be performed for FAS (6-17 years).

7.7.6 Pooling of Sites

During the blind data review meeting (BDRM) it will be decided if for the purpose of the analyses sites or countries will be pooled.

7.7.7 Definition of Study Baseline and Cycle Baseline

Study baseline is defined as the last measurement before first injection.

Cycle baseline is defined as the measurement on the corresponding injection visit. If an injection visit is performed on the same day as the end-of-cycle visit of the previous cycle, the measurements of the end-of-cycle visit will be used for the cycle baseline.

7.7.8 Definition of Study End

Study end is defined as the last documented date in the CRF (including AE end date). Incomplete dates will not be used for the calculation.

8 CHANGES IN THE PLANNED ANALYSES

Additionally to the planned analysis for the GICS a logistic regression of GICS response rates (observed and worst cases for FAS only) will be done.

Vital signs, body height and weight at screening, BMI, clinical chemistry and occurrence of antibodies against BoNT-A, which were defined as other variable in the CSP were added to other safety variables. Treatment compliance, injection cycle length, period length, length of entire study period, method of administration of the injection and use of analgesics and/or sedatives for injection visits were added to other variables.

Tabulation of occurrences of TEAEs by worst intensity, worst causal relationship and by worst outcome is a standard analysis. Therefore these other safety variables were added to section 6.5.3 and corresponding analysis was added to the section of TEAE analyses (7.5).

For the same reason, non-TEAEs will also be analyzed.

For coding of AEs the Medical Dictionary for Regulatory Activities (MedDRA) (version in effect when the database is closed) is used instead of (version in effect when the study is initiated).

Unstimulated salivary flow rate was measured in g units instead of mg units. This deviation from the CSP description was corrected in the current version of the SAP.

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Appendix 1: List of Tables, Figures, and Listings

See MRZ60201_3091_1-sap-appendix-1-final v1.0-2019-06-21.pdf

Any changes that become necessary after generation of SAP version ‘Final Draft’ do not necessarily need to be reflected. Changes which are not only editorial but indicate changes in analyses should at least be covered in the SAP text part or may also be implemented in the mock tables.

Appendix 2: List of Programmed In-text Tables, Figures, and Listings

Not applicable.