U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **BLA #:** | 125,360/S-086 |
| **Drug Name:** | Xeomin (NT 201) |
| **Indication(s):** | Chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury), and/or intellectual disability in children and adolescents aged 2–17 years |
| **Applicant:** | Merz Pharmaceuticals |
| **Date(s):** | Submission date: 06/18/2020, PDUFA date: 12/18/2020 |
| **Review Priority:** | Priority |
| **Biometrics Division:** | Division of Biometrics I |
| **Statistical Reviewer:** | Minjeong Park, Ph.D., Primary Reviewer |
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**Keywords:** ANCOVA, Mixed Models

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# 1 EXECUTIVE SUMMARY

Merz Pharmaceuticals submitted one phase 3 study (MRZ60201_3091_1) to support the claim of the efficacy and safety of NT 201 (incobotulinumtoxinA; Xeomin) in subjects aged 2-17 years with medical condition of chronic troublesome sialorrhea associated with neurological disorders and/or intellectual disability. In the primary analysis on the change in unstimulated salivary flow rate (uSFR) from baseline to Week 4, the least square (LS) mean difference between NT 201 versus placebo was statistically significant (-0.06, 95% CI: [-0.10, -0.03], p=0.0012). The result from co-primary analysis on carer's global impression of change scale (GICS) also showed a statistically significant difference in LS-Means between NT 201 and placebo (0.28, 95% CI: [0.02, 0.53], p=0.032). Sensitivity analyses yielded consistent results with the outcomes of the primary and co-primary analyses. Findings from efficacy evaluation in the phase 3 confirmatory study (MRZ60201_3091_1) with subjects aged 6-17 years support a greater treatment effect of NT 201 compared to the placebo in both uSFR and carer's GICS.

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# 2 INTRODUCTION

## 2.1 Overview

This application contains one phase 3 confirmatory study. It is a prospective, randomized, double-blind, placebo-controlled, parallel-group, multi-center study (MRZ60201_3091_1: hereinafter referred to as "Study 3091") designed to investigate the efficacy and safety of NT 201 (Xeomin) compared to the placebo for the treatment of chronic troublesome sialorrhea associated with neurological disorders (e.g. cerebral palsy, traumatic brain injury) and/or intellectual disability in children and adolescents aged 2-17 years and who are 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.

**Table 1. Summary of study included in analysis**

| Protocol No. | Phase and Design | Treatment Period | # of Subjects randomized per Arm | Study Population |
|---|---|---|---|---|
| Study 3091 | *Phase 3 – DB, R, PG, MC, PC trial* | *Main period: 15-22 weeks (screening up to 4 weeks and first injection cycle of 16±2 weeks)* | ***Subjects in age group 6-17 years*** *NT 201: 148 Placebo: 72* ***Subjects in age group 2-5 years*** *NT 201: 36* | *Subjects aged 2-17 years in medical condition of chronic troublesome sialorrhea associated with neurological disorders and/or intellectual disability for at least 3 months up to the screening, and mTDS of ≥6 (=severe drooling to the extent that clothing becomes damp occasionally) rated by the investigator.* |

*\* DB: double-blind, R: randomized, PG: parallel group, MC: multi-center, PC: placebo-controlled*

## 2.2 Data Sources

All documents reviewed for this supplement submission are in electronic form.
The electronic location of the submission is \\CDSESUB1\evsprod\BLA125360\0392 .

SDTM located at: \\CDSESUB1\evsprod\BLA125360\0392\m5\datasets\mrz-60201-3091-1\tabulations\sdtm
ADaM located at: \\CDSESUB1\evsprod\BLA125360\0392\m5\datasets\mrz-60201-3091-1\analysis\adam

# 3 STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

The sponsor submitted all necessary analysis datasets and SAS programs. This reviewer found the datasets acceptable. With these, this reviewer verified the analysis datasets and the primary results from the clinical study report.

## 3.2 Evaluation of Efficacy in Study 3091

### 3.2.1 Study Design and Endpoints

Study 3091 consisted 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 $16 \pm 2$ weeks). This first injection cycle will be followed by three subsequent open-label injection cycles ($16 \pm 2$ weeks each) for all subjects. The total treatment period will thus last for 56–72 weeks after the first injection for those completing all four injection cycles. For the safety of subjects, a DMC assessed AEs, including AESIs and SAEs, at regular intervals and after each group of 30 subjects had been fully recruited.

A total of 249 subjects were planned to be enrolled and that, of these, at least 219 in the age group 6–17 years (inclusive), formed the set of subjects for the primary analysis. At least 30 children in the youngest age group of 2–5 years (inclusive) were planned to be enrolled; these were to be treated with active treatment only. The group of older subjects was to be randomized in a randomization ratio of 2:1, i.e., 146 subjects were to be treated with NT 201 and 73 with placebo. Treatment was administered via intraparenchymal/intraglandular injections (percutaneously) into the parotid and submandibular glands bilaterally with a single injection site per gland per side. This international study was planned to be performed in eligible investigational sites in about 40 centers in and outside of the EU (e.g., Poland, Hungary, Romania, Georgia, Turkey, Serbia, Ukraine, and Russia).

The primary and co-primary variables for the subjects aged 6-17 years are the change in unstimulated salivary flow rate (uSFR) from baseline [V2] to Week 4 [V3] and the carer's/parent's global impression of change scale (GICS) at Week 4, respectively. The uSFR is measured by the swab method of direct saliva collection. 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: Salivary flow rate [mg/min] = Weight increase of swabs [mg]/ Time of collection [min]. The procedure will be repeated after 30 minutes ($\pm$ 5 minutes) and the average of the two results for flow rate will be calculated. The GICS rating is performed by the caregiver before the quantitative measurement of saliva production. The GICS is a 7-point Likert scale asking if changes in functioning are meaningful changes that the caregiver has noticed as a result of treatment (ranged from -3=very much worse to +3=very much improved).

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**Figure 1. Study design**
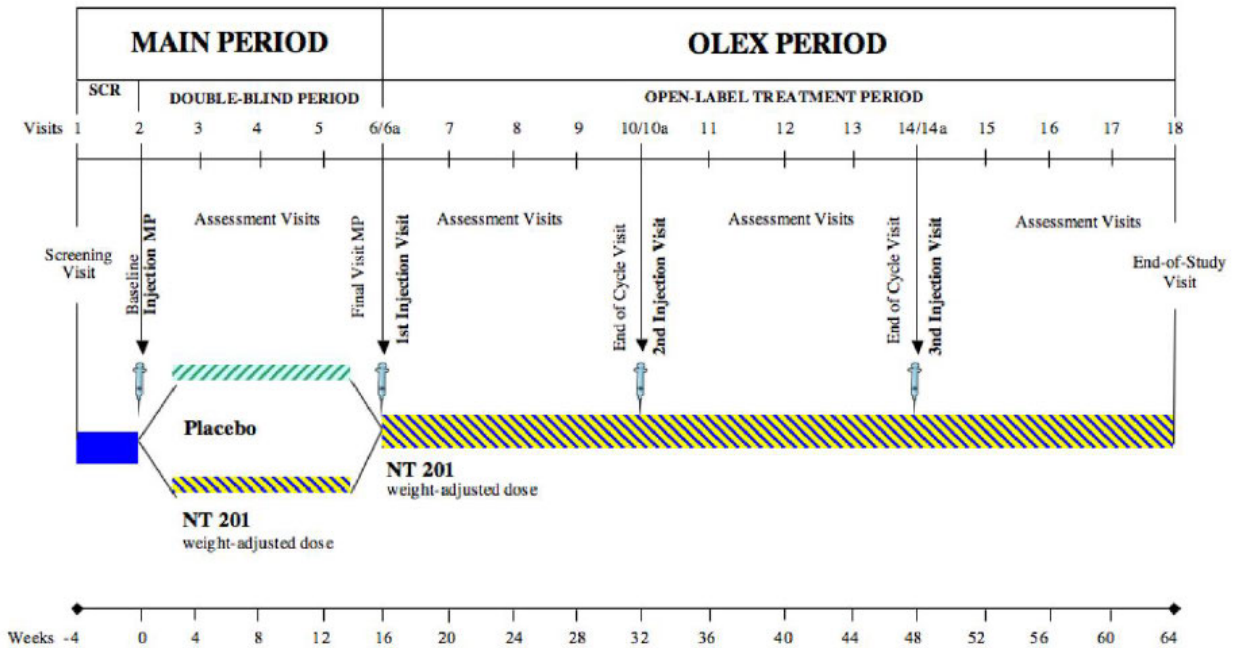


*Note: for children aged 2-5 years, only the NT 201 arm was applicable.*
*Source: Figure 1 on page 45 of Clinical Study Report.*

### 3.2.2 Statistical Methodologies

<u>Sponsor's Methods</u>

*Subjects in age group 6–17 years*

The sample size consideration for the primary efficacy variable 'change in uSFR from baseline to four weeks thereafter' is based on data from a study with Botulinum neurotoxin type A in children with sialorrhea. In this study, a mean change ($\pm$ SD) for BoNT-A in the uSFR of -0.16 $\pm$ 0.19 ml/min from baseline to Week 4 was observed (as the specific gravity of saliva is 1.0 g/ml, the results were expressed by Jongerius et al. in milliliters per minute; the figure is the same as for g/min). These values include a 'missing' rate of approximately 23% with missing values imputed using last observation carried forward (LOCF). For the placebo group, no reliable data were available. As a conservative estimate, a mean change ($\pm$ SD) of -0.05 $\pm$ 0.22 g/min was assumed for the sample size consideration. On the basis of these assumptions and a 2:1 randomization ratio, it is estimated that 146 subjects in the NT 201 treatment group and 73 subjects in the placebo group will provide 95% power to show a statistically significant difference between active treatment-treated and placebo-treated subjects by a two-sided t-test at a significance level of $\alpha = 0.05$. This yields an overall sample size of 219 subjects for the age group 6–17 years. For the co-primary efficacy variable 'GICS four weeks after injection' no data were available. 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

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placebo-treated subjects with a standard deviation of 1.93 points (two-sided t test, significance level α = 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 α = 0.05).

In this study, the safety evaluation set (SES) of the main period includes all subjects who received study medication (NT 201 or placebo) during the main period of the study, the full analysis set (FAS) is identical to the subset of subjects in the SES, and the per protocol set (PPS) is the subset of subjects in the FAS aged 6-17 years without major deviations from the protocol. 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.

The primary and co-primary estimands are the difference in mean uSFR change from baseline to week 4 and mean GICS at week 4 between NT 201 and placebo, respectively. The main analytic approach or primary confirmatory analysis of the co-primary estimands is a mixed model repeated measurement analysis (MMRM, 2-sided, significance level α =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 independent variables were defined as treatment group, pooled investigation sites and age groups (6-9, 10-12 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 modified Teacher's Drooling Scale (mTDS) rated by the parent(s)/carer is used as covariate in the MMRM model for the GICS. Only if both co-primary efficacy variables show a statistically significant difference compared to placebo the superiority of NT 201 over placebo are considered to be proven. Therefore, no α-adjustment for multiple testing is necessary. In addition to the MMRM, an analysis of covariance (ANCOVA) model was 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" as sensitivity analyses.

For the GICS, a logistic regression was performed as sensitivity analysis to the distribution assumption. The responder rate was determined as minimally improved (all subjects with GICS entry of at least +1). This analysis was performed on the FAS (6-17 years) without imputation of missing values and by imputing subjects with missing GICS entries as non-responder. When using the imputation approach, percentages were based on all subjects with observed or imputed values at the respective visit.

### 3.2.3 Patient Disposition, Demographic

A total of 281 subjects were screened, 256 of whom were randomized/assigned to treatment in the main period (MP). One subject assigned to the NT 201 (2-5 years) group discontinued the study before being treated. The remaining 255 subjects received the treatment to which they had been randomized/assigned: 72 subjects in the placebo (6-17 years) group, 148 subjects in the NT 201 (6-17 years) group, and 35 subjects in the NT 201 (2-5 years) group. After receiving treatment in the MP, two subjects in both the placebo (6-17 years) group and the NT 201 (6-17 years) group and one subject in the NT 201 (2-5 years) group discontinued the study (Table 2).

**Table 2. Study disposition during the MP**

| | Placebo (6-17 years) | | NT 201 (6-17 years) | | NT 201 (2-5 years) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | % |
| Randomized/assigned | 72 | (100.0) | 148 | (100.0) | 36 | (100.0) |
| Randomized/assigned and treated in MP as randomized/assigned | 72 | (100.0) | 148 | (100.0) | 35 | (97.2) |
| SES MP | 72 | (100.0) | 148 | (100.0) | 35 | (97.2) |
| FAS MP | 72 | (100.0) | 148 | (100.0) | 35 | (97.2) |
| PPS MP | 65 | (90.3) | 138 | (93.2) | | |
| Completed MP | 70 | (97.2) | 146 | (98.6) | 34 | (94.4) |
| Discontinued MP | 2 | (2.8) | 2 | (1.4) | 2 | (5.6) |
| Reason for discontinuation of MP [a] | | | | | | |
| AE(s) | 0 | (0.0) | 1 | (0.7) | 1 | (2.8) |
| Withdrawal by subject | 2 | (2.8) | 0 | (0.0) | 1 | (2.8) |
| Physician decision | 0 | (0.0) | 0 | (0.0) | 1 | (2.8) |
| Lost to follow-up | 0 | (0.0) | 1 | (0.7) | 0 | (0.0) |
| Main reason for discontinuation of MP [b] | | | | | | |
| AE(s) | 0 | (0.0) | 1 | (0.7) | 1 | (2.8) |
| Withdrawal by subject | 2 | (2.8) | 0 | (0.0) | 1 | (2.8) |
| Lost to follow-up | 0 | (0.0) | 1 | (0.7) | 0 | (0.0) |

*100% base = N = number of subjects randomized/assigned to respective treatment group.*
*a: Multiple entries possible.*
*b: Main reason derived from multiple entries according to the above given order of reasons, e.g., AE(s) plus Lack of efficacy leads to main reason AE(s).*
*AE: adverse event; MP: main period; n: number of subjects.*
*FAS: full analysis set; MP: main period; n: number of subjects; PPS: per protocol set; SES: safety evaluation set.*
*Source: Table 8, Table 9 on page 113 of Clinical Study Report, verified by the reviewer using sponsor's data (ds.xpt).*

The demographic results for the SES and the FAS are shown in Table 3, as the two analysis sets were identical. In SES/FAS population, approximately 63% of subjects were male across all arms and all subjects were white. The mean and median age were similar in two treatment groups with subjects aged 6-17 years.

**Table 3. Demographics (SES/FAS)**

|  | Placebo (6-17 years) (N = 72) | NT 201 (6-17 years) (N = 148) | NT 201 (2-5 years) (N = 35) |
|---|---|---|---|
| Sex (n (%)) | | | |
| Male | 45 (62.5) | 93 (62.8) | 22 (62.9) |
| Female | 27 (37.5) | 55 (37.2) | 13 (37.1) |
| Missing | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Age [years] | | | |
| n | 72 | 148 | 35 |
| Mean (SD) | 10.3 (3.25) | 10.4 (3.17) | 3.9 (0.91) |
| Median | 10.0 | 10.0 | 4.0 |
| Min, max | 6, 17 | 6, 17 | 2, 5 |
| Ethnic origin/race (n (%)) | | | |
| White | 72 (100.0) | 148 (100.0) | 35 (100.0) |
| Height [cm] | | | |
| n | 72 | 148 | 35 |
| Mean (SD) | 135.3 (16.92) | 132.8 (17.15) | 101.1 (8.09) |
| Median | 132.5 | 131.5 | 101.0 |
| Min, max | 99, 170 | 93, 170 | 81, 124 |
| Weight [kg] | | | |
| n | 72 | 148 | 35 |
| Mean (SD) | 30.8 (11.67) | 28.8 (11.48) | 15.7 (3.00) |
| Median | 27.5 | 26.5 | 15.2 |
| Min, max | 15, 69 | 12, 74 | 12, 25 |
| BMI [kg/m$^2$] | | | |
| n | 72 | 148 | 35 |
| Mean (SD) | 16.4 (3.65) | 15.8 (3.25) | 15.3 (1.85) |
| Median | 16.1 | 15.1 | 15.1 |
| Min, max | 10, 32 | 10, 28 | 12, 19 |

Age as documented in the eCRF
100% base = N = number of subjects in respective treatment group
BMI: body mass index; eCRF: electronic case report form; FAS: full analysis set; MP: main period; n: number of subjects; SD: standard deviation; SES: safety evaluation set
Source: Table 13 on page 118 of Clinical Study Report, verified by the reviewer using sponsor's data (adsl.xpt).

### 3.2.4  Efficacy Results

#### 3.2.4.1  Primary/Co-Primary Endpoints

*Change in uSFR from baseline to Week 4*

The confirmatory analyses of the primary and co-primary endpoints were determined as a MMRM analysis (2-sided, significance level alpha=0.05) with comparison of LS-Means between NT 201 and placebo performed on the group of subjects within the FAS aged 6-17 years. At baseline, mean uSFR in the FAS was slightly higher in the placebo (6-17 years) group than in the NT 201 (6-17 years) group, and it was opposite for the median values (Table 4). At Week 4, mean and median uSFR values were lower for subjects in the NT 201 (6-17 years) group than for subjects in the placebo (6-17 years) group. Mean changes in uSFR from baseline to Week 4, median changes as well as LS-Mean changes from an MMRM model, including treatment, pooled site, age group as factors and uSFR at baseline as a covariate, indicated a reduction in uSFR in both groups. A greater improvement was observed in the NT 201 (6-17 years) group (LS-Mean [95% CI]: -0.14 [-0.16; -0.11] g/min) than in the placebo (6-17 years) group (-0.07 [-0.10; -0.04] g/min). Based on the primary confirmatory analysis, the LS-Mean difference between the NT 201 (6-17 years) group and the placebo (6-17 years) group (-0.06 [95% CI: -0.10; -0.03] g/min) was statistically significant (p=0.0012) (Table 4). Figure 2 displays the density curves of changes in uSFR from baseline to Week 4 by treatment group. It shows that the density of NT 201 (6-17 years) group is skewed to the left compared to that of placebo (6-17 years) group which means that the treatment effect of NT 201 is greater than the placebo.

**Table 4. Change in uSFR from baseline to Week 4 – MP (FAS, MMRM)**

|  |  | Placebo (6-17 years) (N = 72) | NT 201 (6-17 years) (N = 148) |
|---|---|---|---|
| Baseline | Mean (SD) | 0.60 (0.25) | 0.57 (0.25) |
|  | Median (IQR) | 0.55 (0.45; 0.73) | 0.57 (0.40; 0.70) |
| Week 4 | Mean (SD) | 0.52 (0.21) | 0.45 (0.21) |
|  | Median (IQR) | 0.49 (0.38; 0.60) | 0.43 (0.32; 0.54) |
| Change | Mean (SD) | -0.07 (0.15) | -0.13 (0.17) |
|  | Median (IQR) | -0.05 (-0.14; 0.01) | -0.10 (-0.22; -0.01) |
|  | LS-Mean (SE) (95% CI) | -0.07 (0.015) (-0.10; -0.04) | -0.14 (0.012) (-0.16; -0.11) |
| LS-Mean difference versus placebo |  |  | -0.06 (0.019) (-0.10; -0.03) |
|  | p-value |  | 0.0012 |

*uSFR is given in g/min*
*LS-Means are from model with treatment, pooled site, and age group included as (fixed) factors and uSFR at baseline included as covariate. visit\*treatment is interaction term and visit is repeated factor.*
*CI: confidence interval; FAS: full analysis set; IQR: interquartile range; LS: least square; MMRM: mixed model repeated measurement; MP: main period; N: number of subjects in the respective group and analysis set; SD: standard deviation; SE: standard error; uSFR: unstimulated salivary flow rate*
*Source: Table 21 on page 133 of Clinical Study Report, verified by the reviewer using sponsors data (adfa.xpt).*

**Figure 2. Distribution of Changes in uSFR from baseline to Week 4 by treatment arm –
MP (FAS)**
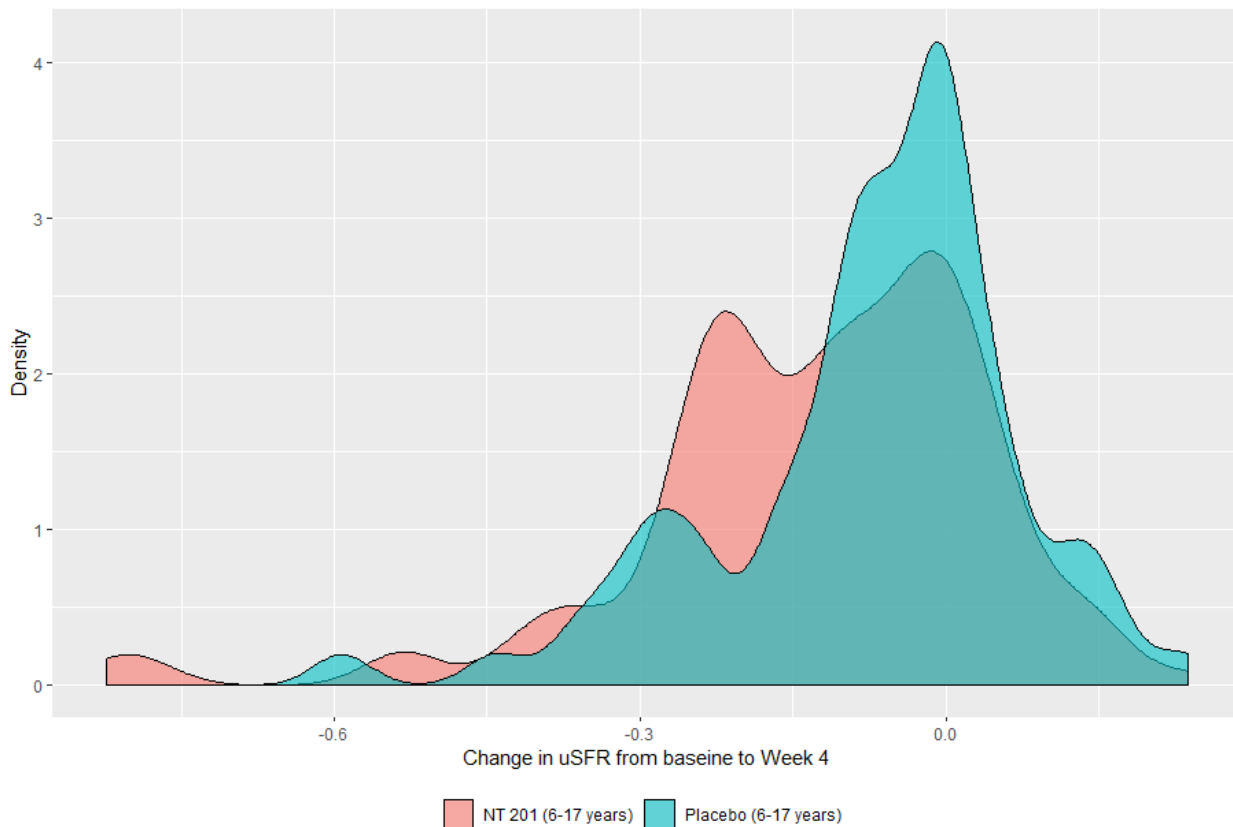


*Source: Reviewer using sponsor's data (adfa.xpt)*

### *GICS at Week 4 since baseline as assessed by the carer*

At Week 4, the most frequent rating of carer's GICS in the placebo (6-17 years) group was 0 'no
change in function', reported for over half of the subjects, while the most frequent rating of
carer's GICS in the NT 201 (6-17 years) group was +1 'minimally improved', reported for nearly
half of the subjects. Accordingly, the total proportion of subjects whose function was rated by
the carer to have at least +1 'minimally improved', i.e., subjects defined as responders, was much
higher in the NT 201 (6-17 years) group (105 subjects [70.9%]) than in the placebo (6-17 years)
group (33 subjects [45.8%]) (Table 5). Mean GICS ratings as well as LS-Mean GICS ratings
from an MMRM model including pooled site, age group, and mTDS at baseline as further
variables at Week 4 showed an improvement in function in both groups in the FAS, but greater
improvement in the NT 201 (6-17 years) group (LS-Mean of 0.91 [95% CI: 0.76; 1.06]) than in
the placebo (6-17 years) group (LS-Mean of 0.63 [0.43; 0.84]). Based on the co-primary
confirmatory analysis, the LS-Mean difference between the NT 201 (6-17 years) group and the
placebo (6-17 years) group (0.28 [95% CI: 0.02; 0.53]) was statistically significant (p=0.0320)
(Table 6).

**Table 5. Frequency of Carer's GICS at Week 4 – MP (FAS)**

|  | Placebo (6-17 years) (N = 72) | NT 201 (6-17 years) (N = 148) |
|---|---|---|
| n (%) | | |
| -3 = Very much worse | 0 (0.0) | 1 (0.7) |
| -2 = Much worse | 0 (0.0) | 0 (0.0) |
| -1 = Minimally worse | 1 (1.4) | 3 (2.0) |
| 0 = No change | 38 (52.8) | 39 (26.4) |
| +1 = Minimally improved | 21 (29.2) | 72 (48.6) |
| +2 = Much improved | 9 (12.5) | 27 (18.2) |
| +3 = Very much improved | 3 (4.2) | 6 (4.1) |

Carer: caregiver/parent(s); FAS: full analysis set; GICS: global impression of change scale; MP: main period; n: number of subjects with respective rating; N: number of subjects in the respective group and analysis set.
Source: Table 23 on page 135 of Clinical Study Report, verified by the reviewer using sponsor's data (adqsef.xpt).

**Table 6. Carer's GICS ratings at Week 4 – MP (FAS, MMRM)**

|  |  | Placebo (6-17 years) (N = 72) | NT 201 (6-17 years) (N = 148) |
|---|---|---|---|
| Week 4 | Mean (SD) | 0.7 (0.9) | 0.9 (0.9) |
|  | LS-Mean (SE) (95% CI) | 0.63 (0.104) (0.43; 0.84) | 0.91 (0.075) (0.76; 1.06) |
| LS-Mean difference versus placebo |  |  | 0.28 (0.127) (0.02; 0.53) |
|  | p-value |  | 0.0320 |

LS-Means are from model with treatment, pooled site, and age group included as (fixed) factors and mTDS at baseline included as covariate. visit*treatment is interaction term and visit is repeated factor.
Carer: caregiver/parent(s); CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; LS: least square; MMRM: mixed model repeated measurement; MP: main period; mTDS: modified Teacher's Drooling Scale; N: number of subjects in the respective group and analysis set; SD: standard deviation; SE: standard error
Source: Table 23 on page 135 of Clinical Study Report, verified by the reviewer using sponsor's data (adqsef.xpt).

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### 3.2.4.2  Sensitivity Analysis

#### *Change in uSFR from baseline to Week 4*

Sensitivity analyses on the FAS included ANCOVA models using the BOCF approach and observation cases (OC), in addition to the MMRM on the PPS (Table 7). All sensitivity analysis results were consistent with the outcome of the primary analysis. The ANCOVA results in the same analysis set population were identical regardless of the imputation approach (BOCF or OC) since there was no early discontinued subject up to Week 4.

**Table 7. Sensitivity analysis for primary efficacy analysis on change in uSFR from baseline to Week 4 – MP**

| | NT 201 (6-17 years) vs. Placebo (6-17 years) | |
|---|---|---|
| **Analysis method** <br> Analysis set | **LS-Mean Difference** <br> **(95% CI)** | **p-value** |
| **MMRM** | | |
| PPS | -0.056 (-0.096, -0.017) | 0.0059 |
| **ANCOVA** | | |
| FAS, BOCF/OC | -0.062 (-0.101, -0.024) | 0.0018 |
| PPS, BOCF/OC | -0.056 (-0.097, -0.016) | 0.0071 |

*MMRM: mixed model with repeated measurement, ANCOVA: analysis of covariance, FAS: full analysis set, PPS: per protocol set, MP: main period, CI: confidence intervals, uSFR: unstimulated salivary flow rate, LS: least square, BOCF: baseline observation carried forward, OC: observation case only.*
*Source: reviewer using sponsor's data (adfa.xpt)*

#### *GICS at Week 4 since baseline as assessed by the carer*

Sensitivity analyses on the FAS included ANCOVA models using the imputation of no change approach (INC) and OC in addition to the MMRM on the PPS (Table 8). For the GICS, a logistic regression was performed as a sensitivity analysis to the distribution assumption using response rates which is defined as subjects with GICS entry of at least +1 (Minimally Improved) at Week 4 (Table 9). The results from logistic regression analysis were consistent with the outcome of co-primary efficacy analyses in both FAS and PPS population. The analysis results in the same analysis set were identical regardless of the imputation approach (INC or OC) since there was no early discontinued subject at Week 4.

**Table 8. Sensitivity analysis for co-primary efficacy analysis on Carer's GICS at Week 4 – MP**

| | NT 201 (6-17 years) vs. Placebo (6-17 years) | |
|---|---|---|
| **Analysis method** <br> Analysis set | **LS-Mean Difference** <br> **(95% CI)** | **p-value** |
| **MMRM** | | |
| PPS | 0.268 (0.004, 0.532) | 0.0465 |

|  | **NT 201 (6-17 years) vs. Placebo (6-17 years)** | |
| --- | --- | --- |
| **Analysis method** Analysis set | **LS-Mean Difference** **(95% CI)** | **p-value** |
| **ANCOVA** | | |
| FAS, INC/OC | 0.280 (0.0272, 0.533) | 0.0301 |
| PPS, INC/OC | 0.271 (0.007, 0.535) | 0.0446 |

*MMRM: mixed model with repeated measurement, ANCOVA: analysis of covariance, FAS: full analysis set, PPS: per protocol set, MP: main period, CI: confidence intervals, GICS: global impression of change scale, LS: least square, INC: imputation with no change, OC: observation case only.*
*Source: reviewer using sponsor's data (adqsef.xpt)*

**Table 9. Sensitivity analysis for co-primary efficacy analysis on response rates defined as subjects with GICS entry of at least +1 (Minimally Improved) at Week 4 – MP**

|  | **NT 201 (6-17 years) vs. Placebo (6-17 years)** | |
| --- | --- | --- |
| **Analysis method** Analysis set | **Odds Ratios** **(95% CI)** | **p-value** |
| **Logistic regression** | | |
| FAS, INC/OC | 3.031 (1.651, 5.564) | 0.0003 |
| PPS, INC/OC | 3.021 (1.603, 5.693) | 0.0006 |

*FAS: full analysis set, PPS: per protocol set, MP: main period, CI: confidence intervals, GICS: global impression of change scale, LS: least square, INC: imputation with no change, OC: observation case only.*
*Source: reviewer using sponsor's data (adqsef.xpt)*

## 3.3  Evaluation of Safety

This review does not evaluate safety.  Please refer to the clinical review for an evaluation of safety.

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# 4   FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the results of reviewer's subgroup analyses. Each subgroup analysis was conducted by including subgroup interaction term in the primary MMRM on change in uSFR from baseline to Week 4 and ANCOVA on carer's GICS in the full analysis set.

**Geographic Regions, Gender and Age**

**uSFR/ Carer's GICS :** All subgroup analyses results presented in Table 10 and Table 11 show consistent results with the outcomes of the primary/co-primary efficacy analyses in the full analysis set population. There was no evidently noticeable subgroup effect of NT 201 compared to the placebo either on the change in uSFR from baseline to Week 4 or carer's GICS at Week 4.

**Table 10. Subgroup analysis for uSFR – summary statistics by subgroup and MMRM with subgroup interaction term – MP (FAS, MMRM)**
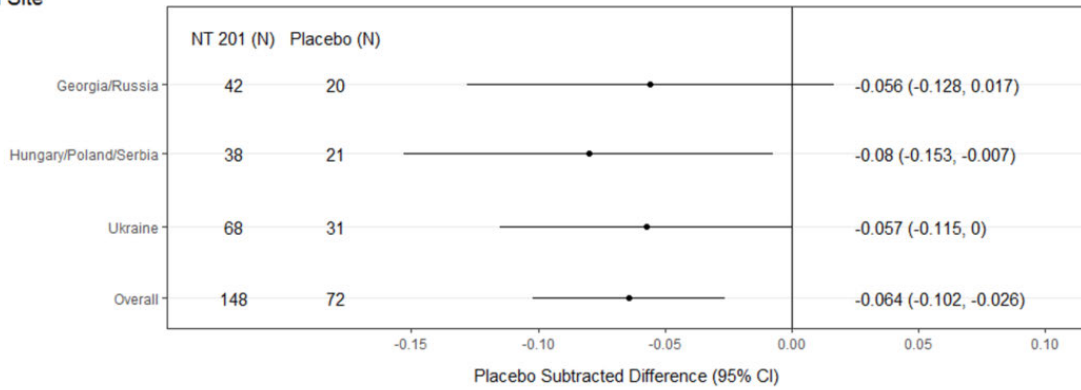
| Subgroup | | Treatment Arm | Sample Size (N) | Baseline Mean (SD) | LS Mean Difference from Baseline to Week 4 (SE) | LS Mean Difference from Placebo (95% CI) |
|---|---|---|---|---|---|---|
| Pooled site | Georgia /Russia | NT 201 | 42 | 0.53 (0.21) | -0.14 (0.02) | -0.056 (-0.128, 0.017) |
| | | Placebo | 20 | 0.54 (0.20) | -0.08 (0.03) | -- |
| | Hungary /Poland /Serbia | NT 201 | 38 | 0.66 (0.38) | -0.17 (0.02) | -0.080 (-0.153, -0.007) |
| | | Placebo | 21 | 0.61 (0.36) | -0.09 (0.03) | -- |
| | Ukraine | NT 201 | 68 | 0.55 (0.16) | -0.11 (0.02) | -0.057 (-0.115, 0.000) |
| | | Placebo | 31 | 0.63 (0.18) | -0.05 (0.02) | -- |
| Age group | 6-9 years | NT 201 | 60 | 0.57 (0.16) | -0.15 (0.02) | -0.062 (-0.122, -0.002) |
| | | Placebo | 30 | 0.56 (0.21) | -0.09 (0.02) | -- |
| | 10-12 years | NT 201 | 50 | 0.59 (0.31) | -0.13 (0.02) | -0.064 (-0.130, 0.002) |
| | | Placebo | 24 | 0.59 (0.20) | -0.07 (0.03) | -- |
| | 13-17 years | NT 201 | 38 | 0.56 (0.29) | -0.12 (0.02) | -0.067 (-0.143, 0.009) |
| | | Placebo | 18 | 0.67 (0.36) | -0.06 (0.03) | -- |
| Gender | Female | NT 201 | 55 | 0.63 (0.22) | -0.14 (0.02) | -0.082 (-0.145, -0.020) |
| | | Placebo | 27 | 0.56 (0.23) | -0.06 (0.02) | -- |
| | Male | NT 201 | 93 | 0.54 (0.26) | -0.13 (0.02) | -0.052 (-0.10, -0.004) |
| | | Placebo | 45 | 0.62 (0.26) | -0.08 (0.02) | |

*uSFR: unstimulated salivary flow rate, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, SD: standard deviation, SE: standard error, CI: confidence interval, LS: least square. Source: reviewer using sponsor's data (adfa.xpt)*
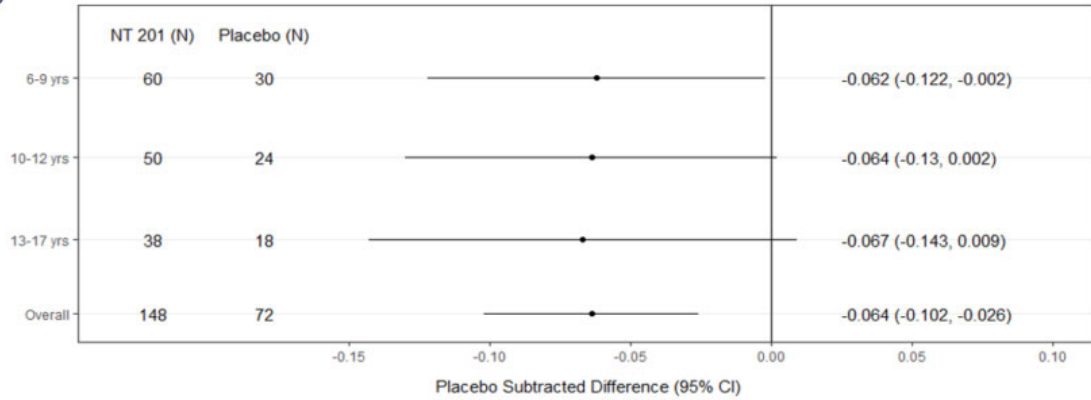
**Figure 2. Subgroup analysis for uSFR – LS means difference between NT 201 and placebo at Week 4 – MP (FAS, MMRM)**
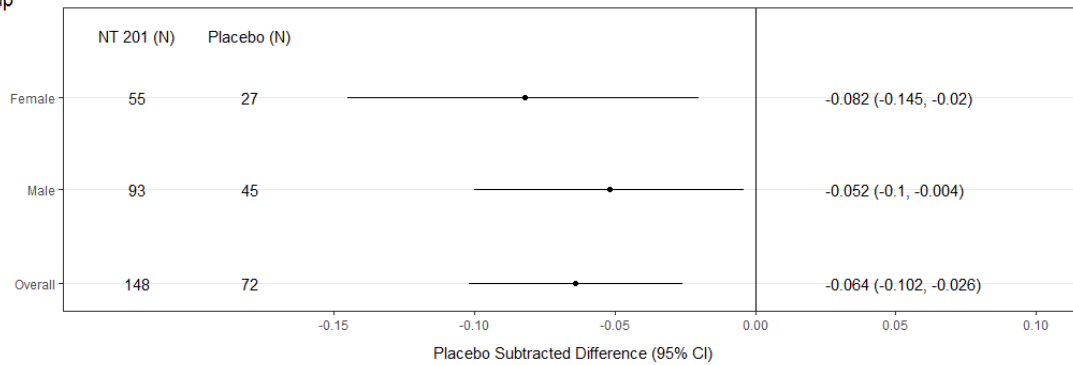


*uSFR: unstimulated salivary flow rate, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, CI: confidence interval, LS: least square.*
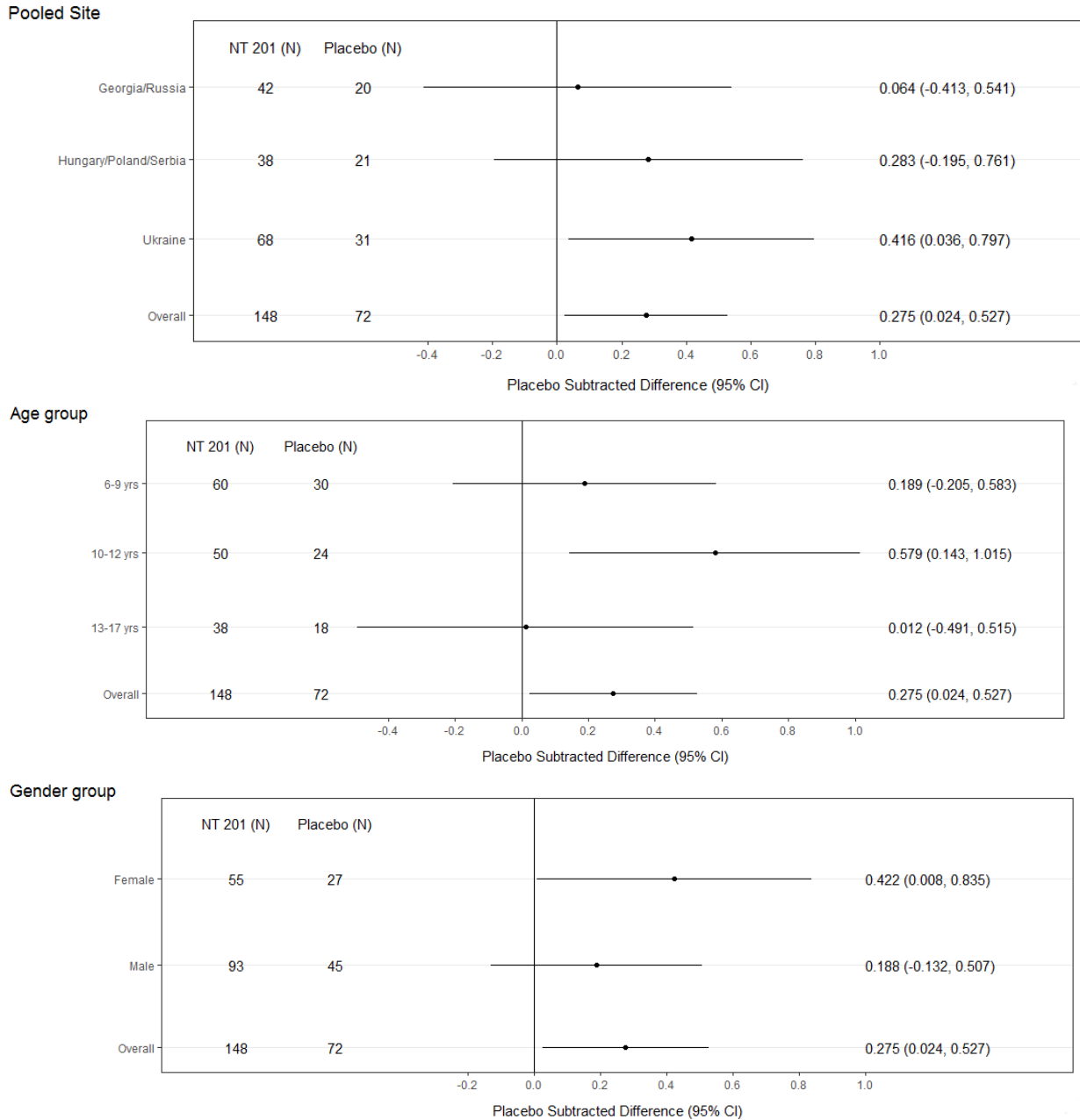*Source: reviewer using sponsor's data (adfa.xpt)*

**Table 11. Subgroup analysis for Carer's GICS – summary statistics by subgroup and MMRM with subgroup interaction term – MP (FAS, MMRM)**

| Subgroup | | Treatment Arm | Sample Size (N) | LS Mean at Week 4 (SE) | LS Mean Difference from Placebo (95% CI) |
|---|---|---|---|---|---|
| Pooled site | Georgia/Russia | NT 201 | 42 | 0.80 (0.14) | 0.064 (-0.413, 0.541) |
| | | Placebo | 20 | 0.73 (0.20) | -- |
| | Hungary/Poland /Serbia | NT 201 | 38 | 0.99 (0.15) | 0.283 (-0.195, 0.761) |
| | | Placebo | 21 | 0.71 (0.19) | -- |
| | Ukraine | NT 201 | 68 | 0.98 (0.11) | 0.416 (0.036, 0.797) |
| | | Placebo | 31 | 0.56 (0.16) | -- |
| Age group | 6-9 years | NT 201 | 60 | 0.91 (0.12) | 0.189 (-0.205, 0.583) |
| | | Placebo | 30 | 0.72 (0.16) | -- |
| | 10-12 years | NT 201 | 50 | 1.05 (0.13) | 0.579 (0.143, 1.015) |
| | | Placebo | 24 | 0.47 (0.18) | -- |
| | 13-17 years | NT 201 | 38 | 0.76 (0.15) | 0.012 (-0.491, 0.515) |
| | | Placebo | 18 | 0.75 (0.21) | -- |
| Gender | Female | NT 201 | 55 | 0.98 (0.12) | 0.422 (0.008, 0.835) |
| | | Placebo | 27 | 0.56 (0.17) | -- |
| | Male | NT 201 | 93 | 0.86 (0.10) | 0.188 (-0.132, 0.507) |
| | | Placebo | 45 | 0.67 (0.13) | |

*GICS: global impression of change scale, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, SE: standard error, CI: confidence interval, LS: least square.*
*Source: reviewer using sponsor's data (adqsef.xpt)*

**Figure 3. Subgroup analysis for Carer's GICS – LS means difference between NT 201 and placebo at Week 4 – MP (FAS, MMRM)**



*GICS: global impression of change scale, MP: main period, FAS: full analysis set, MMRM: mixed model with repeated measurement, N: number, SE: standard error, CI: confidence interval, LS: least square.*
*Source: reviewer using sponsor's data (adqsef.xpt)*

# 5    SUMMARY AND CONCLUSIONS

## 5.1    Statistical Issues

No statistical issue affected the primary and co-primary endpoints.

## 5.2    Collective Evidence

Study 3091 showed statistically significant differences between NT 201 and placebo in both primary (uSFR) and co-primary (carer's GICS rating) endpoints.

## 5.3    Conclusions and Recommendations

There are findings to support a significant treatment effect of NT 201 compared to the placebo in subjects aged 6-17 years in medical condition of chronic troublesome sialorrhea associated with neurological disorders and/or intellectual disability, measured by uSFR and carer's GICS rating.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MINJEONG PARK
12/11/2020 03:15:03 PM

KUN JIN
12/11/2020 03:34:20 PM
I concur with the review.

HSIEN MING J HUNG
12/11/2020 04:13:45 PM