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-078
Drug Name:	Xeomin (NT 201)
Indication(s):	Lower limb (b) (4) spasticity in children/adolescents
Applicant:	Merz Pharmaceuticals
Date(s):	Submission date: 10/18/2019, PDUFA date: 08/18/2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Minjeong Park, Ph.D., Primary Reviewer
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Medical Division:	Division of Neurology I
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Keywords: ANCOVA, Mixed Models

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1 EXECUTIVE SUMMARY

Merz Pharmaceuticals submitted two phase 3 studies (referred to as Study 3070 and Study 3072 in this document) to support the claim of the efficacy (dose-response) and safety of Xeomin (incobotulinumtoxinA, NT 201) [redacted] subjects with upper limb (UL) spasticity [redacted] (Study 3072) [redacted]

In Study 3072, the NT 201 high dose group showed a statistically significant decrease in AS score of 0.22 (p-value=0.017) compared to the NT 201 low dose group. The NT 201 high dose group failed to show statistically significant improvement in investigator's GICS of the UL compared to the NT 201 low dose group. Subjects treated with the NT 201 mid dose failed to reach statistical significance in both AS scale and investigator's GICS of the UL compared to the NT 201 low dose.

2 INTRODUCTION

2.1 Overview

This application contains two phase 3 confirmatory studies. One is a prospective, multicenter, randomized, double-blind, parallel-group, dose-response study (MRZ60201_3070_1: referred to as "Study 3070" in this document) designed to evaluate dose-response and safety with three doses of Xeomin (NT 201 high [maximum total dose of 400 U], NT 201 mid [maximum total dose of 300 U] and NT 201 low dose [maximum total dose of 100 U]) in two injection cycles (each injection treatment will be followed by 12 to 36 weeks observation) in children and adolescents aged 2-17 years with lower limb (LL) spasticity due to cerebral palsy (CP). Another one is a prospective, multicenter, multi-national, randomized, double-blind, parallel-group, dose-response study (MRZ60201_3072_1: referred to as "Study 3072" in this document) designed to evaluate dose-response and safety with three doses of Xeomin (NT 201 high [maximum total dose of 200 U], NT 201 mid [maximum total dose of 150 U] and NT 201 low dose [maximum total dose of 50 U]) in one main period (MP) and a subsequent open-label extension (OLEX) period in children and adolescents aged 2-17 years with upper limb (UL) spasticity alone or with combined UL and LL spasticity due to CP.

Table 1. List of all studies included in analysis

Protocol No.	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
MRZ60201_3070_1	*Phase 3 – DB, R, PG, MC, DR trial*	*Dose-response (1st injection cycle): 12-36 weeks Dose-response (2nd injection cycle): 12-36 weeks*	*100 U NT 201: 78 300 U NT 201: 77 400 U NT 201:156*	*Subjects aged 2-17 years with LL spasticity due to CP. Subjects must have a clinical need for uni-or bilateral LL injections with BoNT for the treatment of spasticity, and subject must have an Ashworth scale [AS] score ≥2 in plantar flexors at least unilaterally at the time of 1st injection treatment visit, AS score ≥2 in both sides for bilateral treatment of pes equinus.*
MRZ60201_3072_1	*Phase 3 – DB, R, PG, MC, DR trial*	*DB main period: 12-16 weeks OLEX period: 3 injection cycles, 12-16 weeks for each cycle*	*50 U NT 201: 87 150 U NT 201: 87 200 U NT 201:176*	*Subjects aged 2-17 years with UL spasticity alone or with combined UL and LL spasticity due to CP. Subjects must have a clinical need for injection treatment in the UL at least unilaterally. Subject should*

				present an AS score ≥2 at least unilaterally in one or both of the main clinical target patterns of this study, flexed elbow and flexed wrist.

** DB: double-blind, R: randomized, PG: parallel group, MC: multi-center, DR: dose-response*

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\0341.

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.

(b) (4)

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3.3 Evaluation of Efficacy in Study 3072

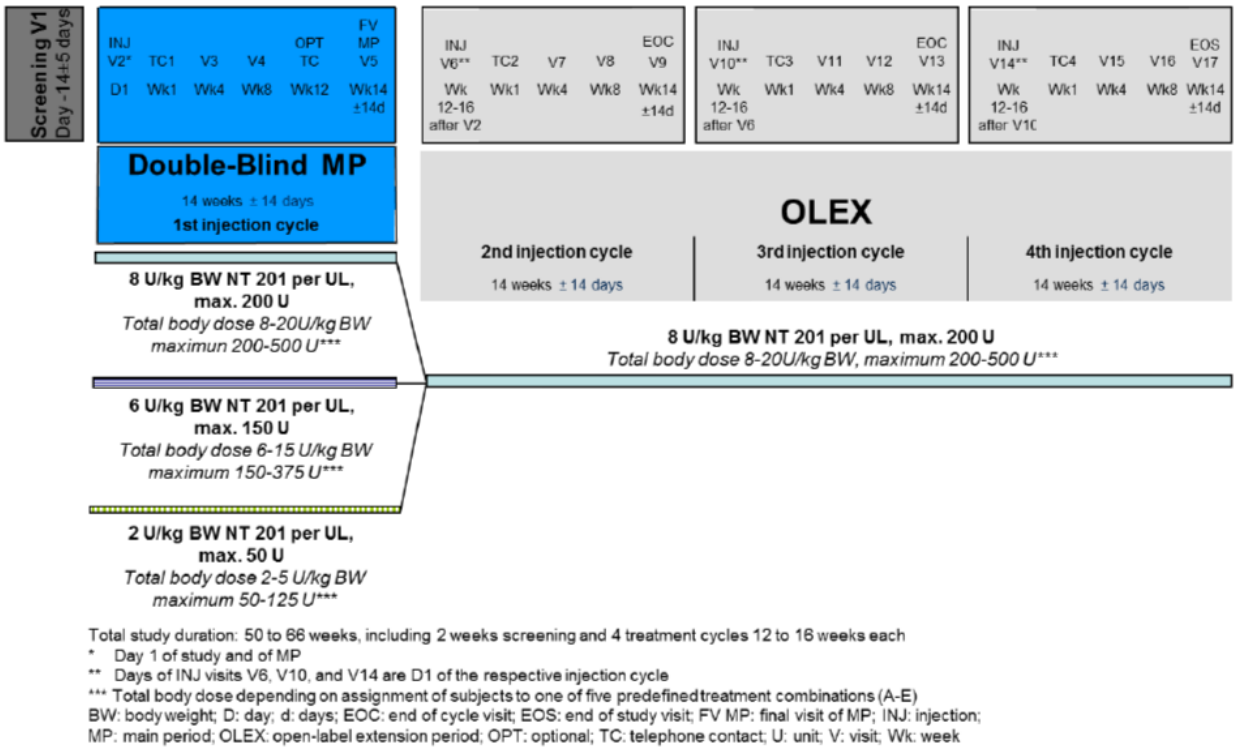
3.3.1 Study Design and Endpoints

Study 3072 consisted of a screening period of 2 weeks and a total of 4 observation periods of 12 to 16 weeks, i.e. 14 weeks ± 14 days, after 1 double-blind injection treatment in double-blind treatment cycle (MP: Main Period) and after 3 open-label injection treatments in open-label treatment cycles (OLEX) with one of three doses: high dose group 8 U/kg BW NT 201 per UL with a maximum total dose of 200 U for subjects ≥25 kg BW, mid dose group 6 U/kg BW per UL with a maximum total dose of 150 U, and low dose group 2 U/kg BW per UL with a maximum total dose of 50 U.

The study design is presented in Figure 4. A total of 344 subjects were to be enrolled with at least 172 subjects randomized to the high dose group, at least 86 subjects to the mid dose group and at least 86 subjects to the low dose group (2:1:1 ratio). This international study was planned to be performed in eligible investigational sites worldwide. Overall, 28 sites actively recruited, the number of sites per country was: 1 actively recruiting in Argentina, 6 in Mexico, 7 in Poland, 4 in Russia, 4 in the Ukraine, and 6 in USA.

The primary endpoint is the change from baseline in the Ashworth Scale (AS) score in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at Day 29 (Week 4) of MP. An interactive voice (web) response system (IV/WRS) will be used for selection and randomization to treatment groups in MP, if two main clinical target patterns would qualify for primary analysis based on (a) clinical need for investigational product (IP) injection in combination with (b) an AS score of ≥ 2. The co-primary efficacy endpoint is the Investigator's Global Impression of Change Scale [GICS] at Day 29 (Week 4) of MP. Key secondary efficacy variables are (1) change from baseline in AS score of the other treated main clinical target pattern (i.e. of elbow flexors or wrist flexor, if treated) at Day 29 (Week 4) of MP (this analysis was performed in case two target patterns would qualify as main clinical target pattern for the main clinical target pattern not analyzed as primary efficacy variable. For subjects with bilateral upper limb (UL) treatment body side to be analyzed was decided by investigator at screening); (2) change from baseline in AS score of treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Day 29 (Week 4) of MP (For subjects with bilateral UL treatment body side to be analyzed was decided by investigator at screening). In addition to these key secondary efficacy variables, a responder rate, which is defined as a proportion of subjects who showed at least 1-point improvement from baseline to Day 29 (Week 4) in the AS score, was also considered as another important secondary efficacy variable.

Figure 4. Study 3072: Study design



Source: Figure 1 on page 69 of Clinical Study Report.

3.3.2 Statistical Methodologies

Sponsor's Methods

The sample size estimation for the primary efficacy variable "change from baseline in AS in the primary clinical target pattern, i.e. elbow flexors or wrist flexors, at day 29 (Week 4)" was based on data of a study with BoNT/A (onabotulinumotoxinA) in the treatment of post-stroke UL SP in adults. With consideration of 3% missing rates, the sponsor assumed the group mean change of -0.68 in NT 201 low dose group and -0.98 in NT 201 high and mid dose group with common standard deviation of 0.6. An estimated total number of 258 (with randomization ratio of 2:1) subjects was to provide 96.5% power to show a statistically significant difference between the NT 201 high dose group (172 subjects) and the NT 201 low dose group (86 subjects) at a significance level of 0.05. And an estimated total number of 172 subjects (with randomization ratio of 1:1) was to provide 90.3% power to show a statistically significant difference between the NT 201 mid dose group (86 subjects) and the NT 201 low dose group (86 subjects) at a significance level of 0.05. The sample size estimation for co-primary efficacy variable "Investigator's GICS 4 weeks after injection" was also based on the same published study above. After consideration of 3% missing rates, an estimated total number of 258 (with randomization ratio of 2:1) subjects for the treatment comparison of the primary efficacy variable, a mean treatment response difference of 0.582 points with a pooled common standard deviation of 1

would provide 99.2% power to show statistically significant superiority in the co-primary variable in favor of NT 201 high dose vs. low dose group, and an estimated total number of 172 subjects (with randomization ratio of 1:1) was to provide 96.7% power to show a statistically significant difference between the NT 201 mid dose group and the NT 201 low dose group at a significance level of 0.05. It was estimated that the sample size of 344 subjects was to provide 95.7% power (product of the single power calculations for both the primary and the co-primary efficacy variable for the high vs. low dose treatment comparison) to show a statistically significant difference between NT 201 high dose and NT 201 low dose group. A power of 87.3% was provided based on the estimated sample size for the treatment comparison of the mid versus the low dose in both primary and co-primary efficacy variables.
Testing of the primary, co-primary efficacy and key-secondary efficacy variables of the MP was performed in a 4-step approach using hierarchical test procedure as described below:

Step 1: Primary and co-primary efficacy variables for NT 201 high dose vs. NT 201 low dose.
Step 2: First key-secondary efficacy variable and co-primary efficacy on subpopulation variables for NT 201 high dose vs. NT 201 low dose.
Step 3: Second key-secondary efficacy variable for NT 201 high dose vs. NT 201 low dose.
Step 4: Primary and co-primary efficacy variables for NT 201 mid dose vs. NT 201 low dose.

Due to the hierarchical testing strategy of (co-)primary and key-secondary efficacy variables and the two dose group comparisons (high vs. low and mid vs. low), this 4-step hierarchical testing procedure ensured the overall type I level of 5% for the confirmatory tests. If 1 of 4 hierarchical tests did not yield a statistically significant result, the consecutive tests were still performed but considered to be only descriptive.
All efficacy analyses were based primarily on the full analysis set (FAS) and additionally in the MP, for sensitivity purposes, on the per protocol set (PPS). The FAS of the MP was the subset in the safety evaluation set (SES) of the MP for whom the primary efficacy variable or the co-primary efficacy variable was available.
The primary efficacy analysis was performed by using a mixed model repeated measurement analysis (MMRM) with comparison of least square means (LS-means) where the independent variables were defined as treatment group, pooled sites, BoNT/A pre-treatment status as fixed factors, visit*treatment as interaction term, visit as repeated factor, baseline AS score of the primary clinical target pattern and the GMFCS-E&R level at screening as covariates. The co-primary efficacy analysis was performed by using analysis of covariance (ANCOVA) with comparison of LS-Means in analogy to the primary efficacy analysis where independent variables were defined as treatment group, pooled sites, BoNT/A pre-treatment status as fixed factors, the maximum AS score of the 2 possible primary target clinical patterns flexed elbow or flexed wrist at baseline and GMFCS-E&R level at screening as covariates.
Sensitivity analyses were performed on the PPS as well as on the FAS of the MP using the last observation carried forward (LOCF) principle and without missing replacement (OC: observed case analysis). For this purpose, ANCOVA based on LOCF and OC was used without visit*treatment interaction and visit as repeated factor. Sensitivity analyses for the co-primary efficacy variable were performed on the PPS as well as on the FAS of the MP and PPS without missing replacement (OC analysis).

3.3.3 Patient Disposition, Demographic

A total of 351 subjects randomized in this study, 176 subjects to the NT 201 high dose, 88 to the NT 201 mid dose and 87 to the NT 201 low dose group. One subject who randomized to the mid dose group discontinued the study prematurely without being treated. Hence, a total of 350 subjects were randomized and treated in this study. The SES comprised 350 subjects, the FAS was identical to the SES and the PPS comprised 309 subjects (high dose:156, mid dose: 74, low dose: 79). A total discontinuation rate in the MP was 5.7% (n=20), and it was similar across arms. A total of 331 subjects who completed the MP continued treatment in the OLEX (81 from low dose, 82 from mid dose, 168 from high dose). Out of 331 subjects entering and treated in the OLEX, 281 (84.9%) completed the OLEX. (b) (4)

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Table 16. Study 3072: Study disposition - MP (randomized subjects)

	NT 201 Low dose (N=87)		NT 201 Mid dose (N=88)		NT 201 High dose (N=176)		Total (N=351)	
	n	(%)	n	(%)	n	(%)	n	(%)
Completed MP	81	(93.1)	82	(93.2)	168	(95.5)	331	(94.3)
Discontinued MP	6	(6.9)	6	(6.8)	8	(4.5)	20	(5.7)
Reason for discontinuation*								
Adverse event(s)	0	(0.0)	1	(1.1)	1	(0.6)	2	(0.6)
Withdrawal by subject	6	(6.9)	2	(2.3)	2	(1.1)	10	(2.8)
Physician decision	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.3)
Lost to follow-up	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.6)
Other	1	(1.1)	3	(3.4)	3	(1.7)	7	(2.0)
Main reason for discontinuation**								
Adverse event(s)	0	(0.0)	1	(1.1)	1	(0.6)	2	(0.6)
Withdrawal by subject	6	(6.9)	2	(2.3)	2	(1.1)	10	(2.8)
Physician decision	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Lost to follow-up	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.6)
Other	0	(0.0)	3	(3.4)	3	(1.7)	6	(1.7)

100% base = number of subjects randomized
** Multiple entries possible*
*** Main reason derived from multiple entries according to the above given order of reasons, e.g. Adverse event(s) plus Withdrawal by subject leads to main reason Adverse event(s).*
MP: main period
Source: Table 19 on page 175 of Clinical Study Report

Table 17. Study 3072: Demographics – MP (SES/FAS)

	NT 201 Low dose (N=87)	NT 201 Mid dose (N=87)	NT 201 High dose (N=176)	Total (N=350)
Sex (n [%])				
Male	49 (56.3)	57 (65.5)	114 (64.8)	220 (62.9)
Female	38 (43.7)	30 (34.5)	62 (35.2)	130 (37.1)
Age [years]				
n	87	87	176	350
Mean (SD)	7.2 (4.70)	7.5 (4.15)	7.3 (4.40)	7.3 (4.40)
Median	6.0	6.0	7.0	6.5
Min, max	2, 17	2, 17	2, 17	2, 17
Age group (n [%])				
2-5 years	41 (47.1)	39 (44.8)	73 (41.5)	153 (43.7)
6-11 years	23 (26.4)	31 (35.6)	63 (35.8)	117 (33.4)
12-17 years	23 (26.4)	17 (19.5)	40 (22.7)	80 (22.9)
Race (n [%])				
White	81 (93.1)	74 (85.1)	160 (90.9)	315 (90.0)
Black or African American	3 (3.4)	2 (2.3)	2 (1.1)	7 (2.0)
Other	3 (3.4)	11 (12.6)	14 (8.0)	28 (8.0)
Ethnicity (n [%])				
Hispanic or Latino	16 (18.4)	25 (28.7)	45 (25.6)	86 (24.6)
Not Hispanic or Latino	71 (81.6)	62 (71.3)	131 (74.4)	264 (75.4)
Height [cm]				
n	87	87	176	350
Mean (SD)	118.8 (26.80)	121.0 (24.79)	118.3 (25.16)	119.1 (25.44)
Median	112.0	117.0	116.0	116.0
Min, max	75, 173	80, 180	76, 178	75, 180
Weight [kg]				
n	87	87	176	350
Mean (SD)	24.8 (15.38)	26.6 (17.19)	24.3 (13.66)	25.0 (15.02)
Median	18.3	20.4	19.7	19.7
Min, max	10, 91	9, 99	7, 68	7, 99
Weight group (n [%])				
<25 kg	55 (63.2)	55 (63.2)	112 (63.6)	222 (63.4)
≥25 kg	32 (36.8)	32 (36.8)	64 (36.4)	128 (36.6)
BMI [kg/m^2]				
n	87	87	176	350
Mean (SD)	16.2 (3.73)	16.7 (4.24)	16.2 (3.24)	16.3 (3.63)
Median	15.4	15.8	15.3	15.5
Min, max	9, 31	11, 32	11, 30	9, 32

Table 17. Study 3072: Demographics – MP (SES/FAS) – continued

	NT 201 Low dose (N=87)	NT 201 Mid dose (N=87)	NT 201 High dose (N=176)	Total (N=350)
GMFCS -E&R (n [%])				
Level I	14 (16.1)	28 (32.2)	23 (13.1)	65 (18.6)
Level II	19 (21.8)	26 (29.9)	54 (30.7)	99 (28.3)
Level III	17 (19.5)	17 (19.5)	44 (25.0)	78 (22.3)
Level IV	18 (20.7)	9 (10.3)	22 (12.5)	49 (14.0)
Level V	19 (21.8)	7 (8.0)	33 (18.8)	59 (16.9)
AS score [points][1]				
n	85	87	173	345
Mean (SD)	2.6 (0.52)	2.7 (0.48)	2.7 (0.56)	2.6 (0.53)
Median	3.0	3.0	3.0	3.0
Min, max	2, 4	2, 3	1, 4	1, 4

[1] *AS score in UL primary clinical target pattern, primary body side at Baseline Visit (V2), observed cases.*
100% base = number of subjects randomized
Age as documented in the CRF
GMFCS-E&R level: I = Walks without limitations, II = Walks with limitations, III = Walks using a hand-held mobility device, IV = Self-mobility with limitations; may use powered mobile, V = Transported in a manual wheelchair
AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
AS: Ashworth scale; BMI: body mass index; CRF: case report form; FAS: full analysis set; GMFCS-E&R: gross motor function classification system expanded and revised; MP: main period; SD: standard deviation; SES: safety evaluation set; V: visit
Source: Table 23 on page 180-182 of Clinical Study Report

The demographic results for the SES/FAS in the MP are shown in Table 17. In the SES/FAS population, 62.9% of subjects were male and median age was 6.5 years old. More than 70% of subjects in all dose groups were in age under 11 years old. Majority of subjects were White, and it was similar across arms. Subjects in NT 201 mid dose group have higher percentage (81.6%) of Level I – III of GMFCS-E&R compared to other two dose groups (high dose:68.8%, low dose: 57.4%).

3.3.4 Efficacy Results

3.3.4.1 Primary/Key-Secondary Endpoints

Step 1*: Primary and co-primary efficacy variables for NT 201 high dose vs. NT 201 low dose.*

The primary clinical target pattern was set to missing for subjects whose primary clinical target pattern was not treated in the MP. This was the case in 5 subjects who were randomized to flexed wrist as primary clinical target pattern, but not treated accordingly by mistake. As consequence,

these subjects did not have a value for the primary efficacy variable "Change from baseline in AS in the primary clinical target pattern at Week 4".
Analysis of the primary efficacy variable (AS score) was performed on the FAS-MP, applying the MMRM approach with comparisons of LS-Means using a 4-step hierarchical test procedure. In the first step, high dose vs. low dose treatment differences were analyzed for both primary and the co-primary efficacy variables. First, the MMRM model was performed to analyze NT 201 high dose vs. NT 201 low dose, and the results are shown in Table 18. The LS-Mean (SE, 95% confidence interval [CI] change was -1.15 (0.056, 95% CI: -1.26, -1.04) in the high dose and -0.93 (0.078, 95% CI: -1.08, -0.78) in the low dose group. The LS-Mean difference between these two dose groups was -0.22 (0.091; 95% CI: -0.40, -0.04) with a p-value of 0.017.

For the co-primary efficacy variable, ANCOVA models with comparison of LS-Means were used for testing. Similar to the analysis of the primary efficacy variable, the model was performed to analyze high dose vs. low dose treatment difference in the first step. The results are shown in Table 19. In the analysis of high vs. low dose, the LS-Mean (SE, 95% CI) change was 1.64 (0.062, 95% CI: 1.52, 1.76) in the high dose and 1.55 (0.083, 95% CI: 1.38, 1.71) in the low dose group. The LS-Mean difference for the high vs. low dose analysis was 0.09 (0.094, 95% CI: -0.10, 0.28) resulting in a p-value of 0.340. Since the statistical significance in the primary efficacy variable was not achieved, the hierarchical testing procedure was stopped and the following step analyses were performed in an explorative manner only. All efficacy analysis results were verified by the reviewer.

Table 18. Study 3072: Change from baseline (V2) in AS in the primary clinical target pattern at Week 4 (V3) – MP (FAS, MMRM), step 1 (NT 201 high vs. low dose group)

			NT 201		NT 201
		n	High dose	n	Low dose
Baseline (V2)	Mean (SD)*	173	2.7 (0.56)	85	2.6 (0.52)
Week 4 (V3)	Mean (SD)*	172	1.5 (0.83)	85	1.7 (0.74)
Change	Mean (SD)*	172	-1.2 (0.71)	85	-0.9 (0.69)
	LS-Mean (SE), (95% CI)	172	-1.15 (0.056); (-1.26; -1.04)	85	-0.93 (0.078); (-1.08; -0.78)
LS-Mean difference versus NT 201 low			-0.22 (0.091); (-0.40; -0.04)		-
	p-value		0.017		-

** observed cases*
AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
*LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline as well as GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term and visit is repeated factor.*
AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MMRM: mixed model repeated measures; MP: main period; SD: standard deviation; SE: standard error; V: visit
Source: Table 33 on page 202 of Clinical Study Report

Table 19. Study 3072: Investigator's GICS of the UL at Week 4 (V3) - MP (FAS, ANCOVA, no change imputation), step 1 (NT 201 high vs. low dose group)

		n	NT 201 High dose	n	NT 201 Low dose
GICS (V3)	Mean (SD)	176	1.7 (0.7)	87	1.6 (0.7)
	LS-Mean (SE); (95% CI)	176	1.64 (0.062); (1.52; 1.76)	87	1.55 (0.083); (1.38; 1.71)
LS-Mean difference versus NT 201 low			0.09 (0.094); (-0.10; 0.28)		-
	p-value		0.340		-

GICS: -3 = Very much worse, -2 = Much worse, -1 = Minimally worse, 0 = No change, +1 = Minimally improved, +2 = Much improved, +3 = Very much improved
No change imputation = missing values are set to '0' (no change)
LS-Means are from ANCOVA with treatment group, pooled site and pre-treatment status included as fixed factors and maximum AS score of the 2 possible primary target patterns flexed elbow or flexed wrist at baseline as well as GMFCS-E&R level at screening included as covariates.
ANCOVA: analysis of covariance; AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MP: main period; SD: standard deviation; SE: standard error; UL: upper limb; V: visit
system (expanded and revised version); LS: least square; n: number of non-missing observations; SD: standard deviation; SE: standard error; V: visit
Source: Table 35 on page 205 of Clinical Study Report

***Step 2**: First key-secondary efficacy variable and co-primary efficacy on subpopulation variables for NT 201 high dose vs. NT 201 low dose.*

The "Change from baseline in AS score of the other treated main clinical target pattern (i.e. of elbow flexors and wrist flexors, if treated) at Day 29 (Week 4) of the MP" was analyzed as the first key-secondary efficacy variable for high dose vs. low dose on the FAS-MP, applying the MMRM approach with comparisons of LS-Means. In addition, the investigator's GICS of the UL was analyzed for subjects having 2 main clinical target patterns for high dose vs. low dose on the FAS-MP, applying the ANCOVA approach (no change imputation) with comparisons of LS-Means. The results are shown in Table 20 and Table 21.

Table 20. Study 3072: Change from baseline (V2) in AS score of the other treated UL main clinical target pattern at Week 4(V3), primary body side – MP (FAS, MMRM), step 2 (NT 201 high vs. low dose group)

	n	NT 201 High dose	n	NT 201 Low dose
LS-Mean (SE); (95% CI)	143	-1.13 (0.061); (-1.25, -1.01)	67	-1.03 (0.083); (-1.19, -0.87)
LS-Mean difference vs. NT 201 low dose		-0.10 (0.097); (-0.29, 0.09)		--
p-value		0.30		--

AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
*LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline as well as GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term and visit is repeated factor.*

AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MMRM: mixed model repeated measures; MP: main period; SE: standard error; UL: Upper limb; V: visit
Source: Table 38 on page 210 of Clinical Study Report

Table 21. Study 3072: Investigator's GICS of the UL at Week 4 (V3) for subjects having 2 main target patterns – MP (FAS, ANCOVA, no change imputation), step 2 (NT 201 high vs. low dose group)

	n	NT 201 High dose	n	NT 201 Low dose
LS-Mean (SE); (95% CI)	142	1.64 (0.075); (1.49, 1.79)	65	1.59 (0.101); (1.39, 1.79)
LS-Mean difference vs. NT 201 low dose		0.05 (0.111); (-0.17, 0.27)		--
p-value		0.657		--

GICS: -3=Very much worse, -2=Much worse, -1=Minimally worse, 0=No change, +1=Minimally improved, +2=Much improved, +3=Very much improved.
No change imputation=missing values are set to '0' (no change)
LS-Means are from ANCOVA with treatment group, pooled site and pre-treatment status included as fixed factors and maximum AS score of the 2 possible primary target patterns flexed elbow or flexed wrist at baseline as well as GMFCS-E&R level at screening included as covariates.
ANCOVA: analysis of covariance; AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MP: main period; SD: standard deviation; SE: standard error; UL: upper limb; V: visit
Source: Table 37 on page 208 of Clinical Study Report

***Step 3**: Second Key-secondary efficacy variable for NT 201 high dose vs. NT 201 low dose.*

The second key-secondary efficacy variable "Change from baseline in AS score of the treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Day 29 (Week 4) of the MP" was analyzed on the FAS-MP, applying the MMRM approach with comparisons of LS-Means. The results are presented in Table 22.

Table 22. Study 3072: Change from baseline (V2) in AS score of the treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Week 4 (V3), primary body side – MP (FAS, MMRM), step 3 (NT 201 high vs. low dose group)

	n	NT 201 High dose	n	NT 201 Low dose
LS-Mean (SE); (95% CI)	45	-1.0 (0.133); (-1.27, -0.74)	18	-0.53 (0.212); (-0.95, -0.10)
LS-Mean difference vs. NT 201 low dose		-0.47 (0.224); (-0.92, -0.03)		--
p-value		0.038		--

AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
*LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline as well as GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term and visit is repeated factor.*
AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MMRM: mixed model repeated measures; MP: main period; SE: standard error; UL: Upper limb; V: visit
Source: Table 39 on page 213 of Clinical Study Report

***Step 4**: Primary and co-primary efficacy variables for NT 201 mid dose vs. NT 201 low dose.*

Table 23. Study 3072: Change from baseline (V2) in AS in the primary clinical target pattern at Week 4 (V3) – MP (FAS, MMRM), step 4 (NT 201 mid vs. low dose group)

		n	NT 201 Mid dose	n	NT 201 Low dose
Baseline (V2)	Mean (SD)*	87	2.7 (0.48)	85	2.6 (0.52)
Week 4 (V3)	Mean (SD)*	86	1.6 (0.82)	85	1.7 (0.74)
Change	Mean (SD)*	86	-1.1 (0.79)	85	-0.9 (0.69)
	LS-Mean (SE); (95% CI)	86	-1.02 (0.082); (-1.19; -0.86)	85	-0.96 (0.082); (-1.12; -0.80)
LS-Mean difference versus NT 201 low			-0.07 (0.112); (-0.29; 0.15)		-
	p-value		0.546		-

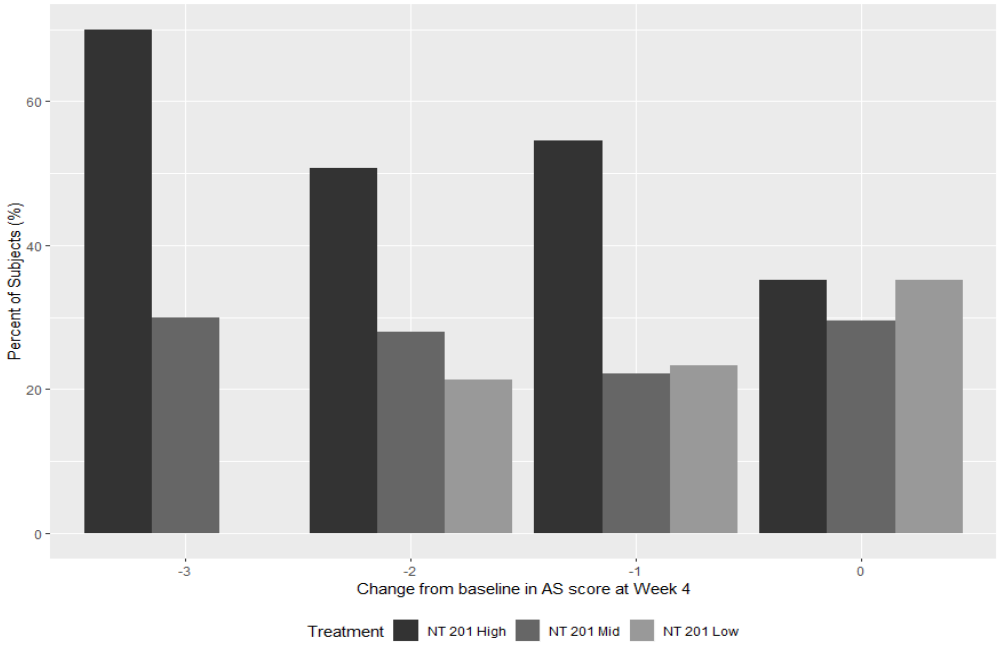
** observed cases*
AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
*LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline as well as GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term and visit is repeated factor.*
AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MMRM: mixed model repeated measures; MP: main period; SD: standard deviation; SE: standard error; V: visit
Source: Table 34 on page 203 of Clinical Study Report

Table 24. Study 3072: Investigator's GICS of the UL at Week 4 (V3) - MP (FAS, ANCOVA, no change imputation), step 4 (NT 201 mid vs. low dose group)

		n	NT 201 Mid dose	n	NT 201 Low dose
GICS (V3)	Mean ± SD	87	1.6 (0.8)	87	1.6 (0.7)
	LS-Mean (SE) (95% CI)	87	1.44 (0.092); (1.26; 1.63)	87	1.57 (0.089); (1.39; 1.75)
LS-Mean difference versus NT 201 low			-0.12 (0.118); (-0.36; 0.11)		-
	p-value		0.297		-

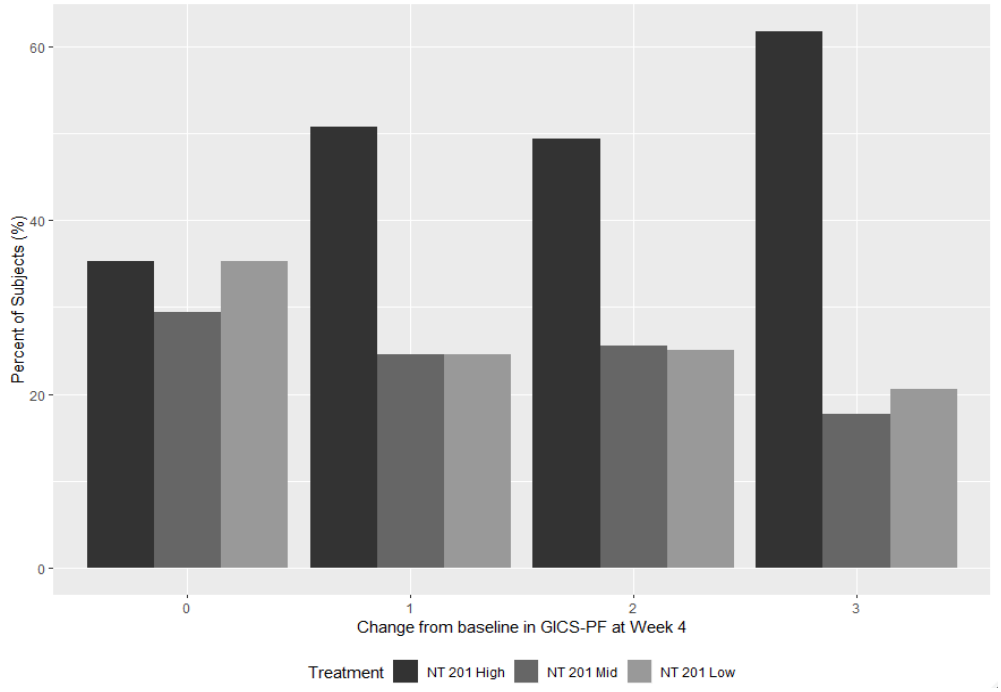
GICS: -3 = Very much worse, -2 = Much worse, -1 = Minimally worse, 0 = No change, +1 = Minimally improved, +2 = Much improved, +3 = Very much improved
No change imputation = missing values are set to '0' (no change)
LS-Means are from ANCOVA with treatment group, pooled site and pre-treatment status included as fixed factors and maximum AS score of the 2 possible primary target patterns flexed elbow or flexed wrist at baseline as well as GMFCS-E&R level at screening included as covariates.
ANCOVA: analysis of covariance; AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MP: main period; SD: standard deviation; SE: standard error; UL: upper limb; V: visit
Source: Table 36 on page 206 of Clinical Study Report

Figure 5. Study 3072: Percentage of subjects with a specified magnitude of change from baseline (V2) in AS in the primary clinical target pattern at Week 4 (V3) (FAS-MP, observed case only)



Source: Reviewer

Figure 6. Study 3072: Percentage of subjects with a specified magnitude of Investigator's GICS of the UL at Week 4 (V3) (FAS-MP, observed case only)



Source: Reviewer

Figure 5 and Figure 6 summarized the response distribution of subjects to NT 201 treatment by displaying the percentage of patients with specified magnitude of change from baseline in AS score and investigator's GICS of the UL at week 4, respectively. These response distributions show greater quantitative improvement in NT 201 high dose group compared to either NT 201 mid or low dose group. For the investigator's GICS of the UL, there was only one subject who assigned to the NT 201 mid dose group and answered '-1: minimally worse' which was not included in the Figure 6.

Another Important Secondary Efficacy Variable

Responder rate based on the AS score

In this report, a responder is defined as a subject with at least 1-point improvement from baseline to Day 29 (Week 4) in the AS score. Table 25 and Table 26 show a summary of the number and proportion of responders and analysis results using the logistic regression analysis where the dependent variable is the responder and the independent variables are treatment group, country, BoNT/A pre-treatment status, baseline AS score and GMFCS-E&R level at screening in the FAS and PPS population, respectively. In Table 27, the responder rate in NT 201 high (86.0%) and mid (76.7%) dose group were higher compared to the NT 201 low dose group (70.6%). The results from logistic regression analysis show that the difference of response rate between NT 201 high dose and NT 201 low dose groups are statistically significant, however, no significant difference between NT 201 mid dose and NT 201 low dose group. Adjusted p-values for multiple comparisons were calculated by using Dunnett's test. The responder rates and logistic regression analysis results in the PPS population were analogous to ones in the FAS population.

Table 25. Study 3072: Responder rates based on the AS score at Week 4 (FAS-MP, observed cases only)

Characteristic	Statistic	NT 201 High dose (N=173)	NT 201 Mid dose (N=87)	NT 201 Low dose (N=85)
AS score reduction				
Responders	n (%)	148 (86.0%)	66 (76.7%)	60 (70.6%)
Non-responders	n (%)	24 (14.0%)	20 (23.3%)	25 (29.4%)
Missing	n	1	1	0
Logistic regression analysis	p-value*	0.0099	0.9125	--

** Adjusted p-value for multiple comparisons was calculated by using Dunnett's test*
Source: Reviewer

Table 26. Study 3072: Responder rates based on the AS score at Week 4 (PPS-MP, observed cases only)

Characteristic	Statistic	NT 201 High dose (N=156)	NT 201 Mid dose (N=74)	NT 201 Low dose (N=79)
AS score reduction				
Responders	n (%)	137 (87.8%)	59 (79.7%)	54 (68.4%)
Non-responders	n (%)	19 (12.2%)	15 (20.3%)	25 (31.6%)
Missing	n	0	0	0
Logistic regression analysis	p-value*	0.0008	0.4948	--

** Adjusted p-value for multiple comparisons was calculated by using Dunnett's test*
Source: Reviewer

3.3.4.2 Sensitivity Analysis

For the primary efficacy analysis, sensitivity analyses based on the MMRM in the PPS-MP were in line with the confirmatory analysis on the FAS-MP. Also, further sensitivity analyses were performed on the ANCOVA model for both FAS and PPS using LOCF imputation and OC on the FAS-MP and the PPS-MP. Decreases in LS-Mean AS scores of the primary clinical target pattern, indicating clinically meaningful improvements, were seen in all 3 dose groups. In the analysis of high versus low dose for the PPS population, the LS-Mean difference between the dose groups was -0.29 (0.093, 95% CI: -0.47; -0.10) with a p-value of 0.002. Using LOCF imputation and OC on the FAS-MP and the PPS-MP yielded similar results (Table 27). All sensitivity analysis results for primary and co-primary efficacy variables were verified by the reviewer.

Table 27. Study 3072: Sensitivity analysis for primary efficacy analysis on change from baseline (V2) in AS in the primary clinical target pattern at Week 4 (V3)

	NT 201 High vs. NT 201 Low		NT 201 Mid vs. NT 201 Low	
Analysis method Analysis set	**LS-Mean Difference (95% CI)**	**p-value**	**LS-Mean Difference (95% CI)**	**p-value**
MMRM				
FAS	-0.22 (-0.40, -0.04)	0.017	-0.07 (-0.29, 0.15)	0.546
PPS	-0.29 (-0.47, -0.10)	0.002	-0.19 (-0.41, 0.03)	0.095
ANCOVA				
FAS, LOCF	-0.23 (-0.41, -0.06)	0.009	-0.07 (-0.29, 0.15)	0.507
PPS, LOCF	-0.29 (-0.47, -0.11)	0.001	-0.15 (-0.36, 0.06)	0.166
FAS, OC	-0.24 (-0.41, -0.07)	0.006	-0.09 (-0.31, 0.13)	0.416
PPS, OC	-0.29 (-0.47, -0.11)	0.001	-0.15 (-0.36, 0.06)	0.166

Source: Sponsor (End-of-text table 14.2.1.1, End-of-text table 14.2.1.2)

For the co-primary efficacy analysis, sensitivity analyses based on the ANCOVA model for the PPS were in line with the confirmatory analysis on the FAS. The LS-Mean difference for the high versus low dose analysis was 0.09 (0.096, 95% CI: -0.10; 0.28) resulting in a p-value of 0.331 and the LS-Mean difference for the mid versus low dose analysis was -0.04 (0.113, 95% CI: -0.26; 0.18) with a p-value of 0.724 (Table 28).

Table 28. Study 3072: Sensitivity analysis for co-primary efficacy analysis on Investigator's GICS of the UL at Week 4 (V3) – MP

	NT 201 High vs. NT 201 Low		NT 201 Mid vs. NT 201 Low	
Analysis method Analysis set	**LS Mean Diff (95% CI)**	**p-value**	**LS Mean Diff (95% CI)**	**p-value**
ANCOVA				
FAS	0.09 (-0.10, 0.28)	0.340	-0.12 (-0.36, 0.11)	0.297
PPS	0.09 (-0.10, 0.28)	0.331	-0.04 (-0.26, 0.18)	0.724

Source: Sponsor (End-of-text table 14.2.19.1, End-of-text table 14.2.19.2)

Reviewer's Comments:

1. The reviewer recommends using the term "last available value approach" instead of "last observation carried forward (LOCF)".

2. The sponsor defined the FAS as the subset of subjects in the SES of the MP for whom the primary efficacy variable or co-primary efficacy variable was available (i.e., all subjects who had at least either an AS score in the clinical pattern flexed elbow or flexed wrist at baseline [Day 1] or the investigator's GICS for UL at Day 29 [Week 4]). However, the reviewer recommends using the modified intention-to-treat (mITT) population which is defined as all subjects who randomized, treated with at least 1 dose of investigational medicinal product [IMP] after randomization and with at least 1 post baseline assessment in neurology studies.

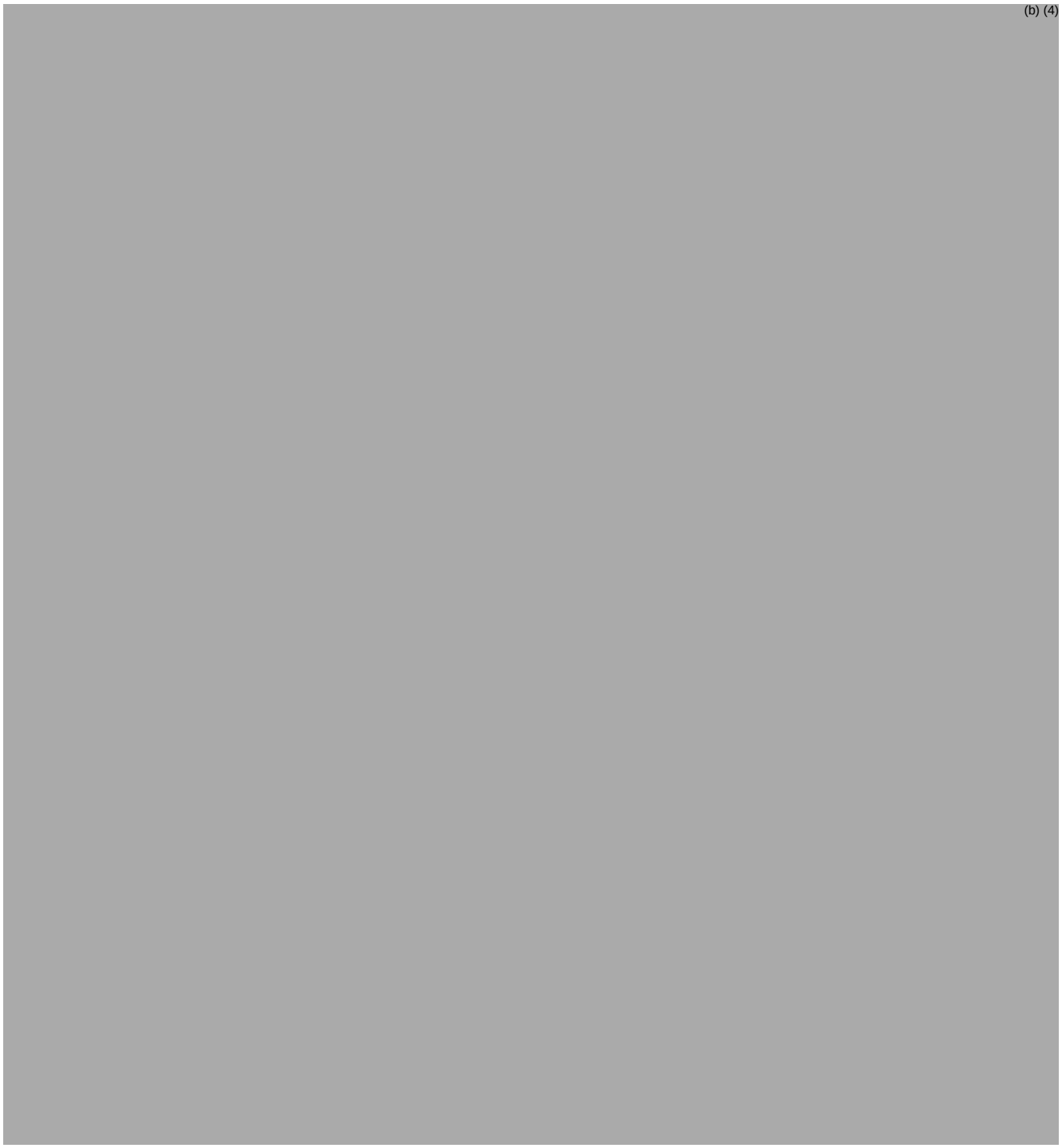
3.4 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section contains the results of reviewer's subgroup analyses. Each subgroup analysis was conducted by running the primary MMRM on change in AS score and ANCOVA on (b) (4) Investigator's GICS of the UL (Study 3072) in the full analysis set.

(b) (4)



Study 3072

Table 31. Study 3072: Subgroup Analysis – Change from baseline (V2) in AS in the primary clinical target pattern at Week 4 (V3) (FAS, MMRM)

Subgroup		Treatment Arm	Sample Size	Baseline Mean (SD)	LS Mean Difference from Baseline (SE)	LS Mean Difference from NT 201 Low (95% CI)
Country	Argentina	High/Low	9/ 3	2.8 (0.7)/ 2.7 (0.6)	-0.67 (0.17)/ -0.33 (0.30)	-0.33 (-1.10, 0.43)
		Mid/Low*	7/ 3	2.4 (0.5)/ 2.7 (0.6)	-0.4 (0.8)/ -0.3 (0.6)	--
	Mexico	High/Low	32/ 11	2.6 (0.7)/ 2.4 (0.5)	-1.03 (0.13)/ -0.73 (0.22)	-0.30 (-0.81, 0.20)
		Mid/Low	18/ 11	2.6 (0.5)/ 2.4 (0.5)	-1.17 (0.20)/ -0.73 (0.25)	-0.44 (-1.09, 0.21)
	Poland	High/Low	39/ 26	2.5 (0.5)/ 2.5 (0.5)	-1.0 (0.08)/ -0.65 (0.10)	-0.35 (-0.60, -0.09)
		Mid/Low	18/ 26	2.6 (0.5)/ 2.5 (0.5)	-0.89 (0.13)/ -0.65 (0.11)	-0.24 (-0.59, 0.12)
	Russia	High/Low	18/ 10	2.4 (0.7)/ 2.2 (0.4)	-0.89 (0.13)/ -0.80 (0.17)	-0.09 (-0.52, 0.34)
		Mid/Low	8/ 10	2.4 (0.5)/ 2.4 (0.4)	-1.0 (0.21)/ -0.80 (0.19)	-0.20 (-0.79, 0.39)
	Ukraine	High/Low	59/ 28	2.9 (0.4)/ 2.9 (0.5)	-1.41 (0.10)/ -1.25 (0.15)	-0.16 (-0.51, 0.20)
		Mid/Low	32/ 28	2.8 (0.4)/ 2.9 (0.5)	-1.32 (0.14)/ -1.25 (0.15)	-0.07 (-0.48, 0.33)
	USA	High/Low	16/ 7	2.6 (0.5)/ 2.7 (0.5)	-1.53 (0.18)/ -1.0 (0.26)	-0.53 (-1.20, 0.13)
		Mid/Low	4/ 7	3.0 (0.0)/ 2.7 (0.5)	-1.0 (0.8)/ -1.0 (0.6)	--*
Age group	2-5 years	High/Low	71/ 39	2.7 (0.5)/ 2.6 (0.5)	-1.28 (0.09)/ -0.95 (0.12)	-0.33 (-0.63, -0.03)
		Mid/Low	39/ 39	2.6 (0.5)/ 2.6 (0.5)	-1.0 (0.13)/ -0.95 (0.13)	-0.05 (-0.41, 0.30)
	6-11 years	High/Low	63/ 23	2.5 (0.6)/ 2.6 (0.5)	-1.10 (0.07)/ -0.87 (0.12)	-0.23 (-0.50, 0.04)
		Mid/Low	31/ 23	2.7 (0.4)/ 2.6 (0.5)	-1.19 (0.13)/ -0.87 (0.15)	-0.32 (-0.71, 0.06)
	12-17 years	High/Low	39/ 23	2.8 (0.6)/ 2.6 (0.6)	-1.05 (0.12)/ -0.83 (0.16)	-0.23 (-0.63, 0.18)
		Mid/Low	17/ 23	2.7 (0.5)/ 2.6 (0.6)	-1.06 (0.18)/ -0.83 (0.15)	-0.23 (-0.71, 0.24)
Gender	Female	High/Low	61/ 38	2.7 (0.5)/ 2.6 (0.5)	-1.07 (0.09)/ -0.95 (0.11)	-0.12 (-0.41, 0.17)
		Mid/Low	30/ 38	2.7 (0.5)/ 2.7 (0.6)	-1.23 (0.14)/ -0.95 (0.12)	-0.29 (-0.65, 0.08)
	Male	High/Low	112/ 47	2.7 (0.6)/ 2.6 (0.5)	-1.22 (0.07)/ -0.85 (0.10)	-0.36 (-0.61, -0.12)
		Mid/Low	57/ 47	2.6 (0.5)/ 2.6 (0.5)	-1.0 (0.10)/ -0.85 (0.11)	-0.15 (-0.44, 0.14)
Race	Black or African	High/Low	2/ 3	2.5 (0.7)/ 2.7 (0.6)	-0.5 (0.7)/ -1.0 (0.0)	--*

Subgroup		Treatment Arm	Sample Size	Baseline Mean (SD)	LS Mean Difference from Baseline (SE)	LS Mean Difference from NT 201 Low (95% CI)
	American	Mid/Low	2/ 3	3.0 (0.0)/ 2.7 (0.6)	-1.0 (0.0)/ -1.0 (0.0)	--*
	White	High/Low	157/ 79	2.7 (0.6)/ 2.6 (0.5)	-1.18 (0.06)/ -0.89 (0.08)	-0.30 (-0.49, -0.11)
		Mid/Low	74/ 79	2.7 (0.5)/ 2.6 (0.5)	-1.11 (0.09)/ -0.89 (0.09)	-0.22 (-0.47, 0.02)
	Others	High/Low	14/ 3	2.6 (0.6)/ 2.7 (0.6)	-0.93 (0.21)/ -1.0 (0.45)	0.07 (-0.97, 1.12)
		Mid/Low	11/ 3	2.5 (0.5)/ 2.7 (0.6)	-0.91 (0.15)/ -1.0 (0.28)	0.09 (-0.61, 0.79)

** Not estimable due to small cells. It is replaced by the simple mean change (standard deviation) in AS score of plantar flexors of the primary body side from baseline of the first injection cycle to Week 4.*
Source: Reviewer.

Table 32. Study 3072: Subgroup Analysis – Investigator's GICS of the UL at Week 4 (V3) (FAS, ANCOVA)

Subgroup		Treatment Arm	Sample Size	LS Mean (SE)	LS Mean Difference from NT 201 Low (95% CI)
Country	Argentina	High/Low	9/ 4	1.44 (0.25)/ 1.0 (0.38)	0.44 (-0.55, 1.44)
		Mid/Low	7/ 4	1.29 (0.29)/ 1.0 (0.39)	0.29 (-0.82, 1.39)
	Mexico	High/Low	32/ 18	1.78 (0.14)/ 1.58 (0.22)	0.20 (-0.32, 0.72)
		Mid/Low	12/ 18	1.78 (0.21)/ 1.58 (0.26)	0.19 (-0.48, 0.87)
	Poland	High/Low	39/ 26	1.59 (0.10)/ 1.50 (0.13)	0.09 (-0.23, 0.41)
		Mid/Low	18/ 26	1.33 (0.16)/ 1.50 (0.13)	-0.17 (-0.58, 0.24)
	Russia	High/Low	18/ 10	1.56 (0.21)/ 1.70 (0.28)	-0.14 (-0.87, 0.58)
		Mid/Low	8/ 10	1.13 (0.29)/ 1.70 (0.26)	-0.57 (-1.41, 0.26)
	Ukraine	High/Low	62/ 28	1.65 (0.08)/ 1.68 (0.13)	-0.03 (-0.33, 0.27)
		Mid/Low	32/ 28	1.66 (0.11)/ 1.68 (0.12)	-0.02 (-0.35, 0.31)
	USA	High/Low	16/ 7	2.06 (0.24)/ 1.57 (0.36)	0.49 (-0.40, 1.38)
		Mid/Low	4/ 7	2.0 (1.4)/ 1.6 (0.8)	--*
Age group	2-5 years	High/Low	73/ 41	1.73 (0.09)/ 1.46(0.11)	0.26 (-0.02, 0.54)
		Mid/Low	39/ 41	1.38 (0.12)/ 1.46 (0.12)	-0.08 (-0.43, 0.27)
	6-11 years	High/Low	63/ 23	1.63 (0.10)/ 1.70 (0.16)	-0.06 (-0.43, 0.31)
		Mid/Low	31/ 23	1.65 (0.14)/ 1.70 (0.16)	-0.05 (-0.48, 0.38)
	12-17 years	High/Low	40/ 23	1.65 (0.11)/ 1.65 (0.15)	-0.002 (-0.37, 0.37)
		Mid/Low	17/ 23	1.76 (0.15)/ 1.65 (0.13)	0.11 (-0.28, 0.51)
Gender	Female	High/Low	62/ 38	1.69 (0.09)/ 1.61 (0.12)	0.09 (-0.21, 0.39)
		Mid/Low	30/ 38	1.70 (0.14)/ 1.61 (0.13)	0.09 (-0.28, 0.47)
	Male	High/Low	114/ 49	1.67 (0.07)/ 1.55 (0.11)	0.12 (-0.13, 0.36)
		Mid/Low	57/ 49	1.47 (0.10)/ 1.55 (0.11)	-0.08 (-0.36, 0.21)
Race	Black or African American	High/Low	2/ 3	1.5 (2.1)/ 1.7 (0.6)	--*
		Mid/Low	2/ 3	3.0 (0.0)/ 1.7 (0.6)	--*
	White	High/Low	157/ 79	1.50 (0.15)/ 1.45 (0.25)	0.05 (-0.54, 0.63)
		Mid/Low	74/ 79	1.46 (0.24)/ 1.45 (0.26)	0.01 (-0.72, 0.73)
	Others	High/Low	14/ 3	1.71 (0.12)/ 2.0 (0.25)	-0.29 (-0.88, 0.31)
		Mid/Low	11/ 3	1.82 (0.11)/ 2.0 (0.21)	-0.18 (-0.71, 0.34)

** Not estimable due to small cells. It is replaced by the simple mean change (standard deviation) in Investigator's GICS-PF of the primary body side at Week 4 of the first injection cycle.*
Source: Reviewer.

4.2 Gender, Race, Age, and Geographic Region in Study 3072

AS score/ Investigator's GICS of the UL: All subgroup analyses presented in Table 31 and Table 32 show the similar trend as the entire population except for the investigator's GICS of the UL in Russia which shows the most treatment effect in NT 201 low dose.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues affected the primary, co-primary and key secondary endpoints.

5.2 Collective Evidence

(b) (4)

Study 3072 showed a significantly greater treatment effect of NT 201 high dose compared to the NT 201 low dose in AS score in the primary clinical target pattern, however, the investigator's GICS of the UL did not reach a statistical significance.

5.3 Conclusions and Recommendations

(b) (4)

(b) (4)

However, there may be an adequate evidence to support a significant treatment effect of 200 U of NT 201 compared to 50 U of NT 201 in subjects aged 2-17 years with UL spasticity

(b) (4)

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MINJEONG PARK
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KUN JIN
07/21/2020 12:40:00 PM
I concur with the review.

HSIEN MING J HUNG
07/21/2020 12:58:58 PM