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 Number:	103000 Supplement 5309 [redacted] (b) (4)
Drug Name:	BOTOX® (onabotulinumtoxinA)
Indications:	Pediatric Upper Limb Spasticity (Supplement 5309) (b) (4) [redacted] (b) (4)
Applicant:	Allergan, Inc.
Dates:	Receipt date: December 20, 2018 PDUFA Goal Date: June 20, 2019 for Supplement 5309 [redacted] (b) (4)
Review Priority:	Priority for Supplement 5309 [redacted] (b) (4)
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader Hsien Ming Hung, Ph.D., Director
Medical Division:	Division of Neurology Products
Clinical Team:	Susanne Goldstein, M.D., Clinical Reviewer Gerald Podskalny, D.O., Team Leader Eric Bastings, M.D., Deputy Director William Dunn, M.D., Director
Project Manager:	Taura Holmes, PharmD

Keywords: clinical studies, mixed models, BLA review

TABLE OF CONTENTS

LIST OF TABLES

1 EXECUTIVE SUMMARY

Allergan, Inc. submitted a supplemental biologic license application (sBLA) that included two clinical studies: Study 191622-101 is used to support the indication for the treatment of pediatric upper limb spasticity and Study 191622-111 (b) (4) Both clinical studies were randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies similar in analysis and design (e.g. number of follow-up visits, study duration, and primary statistical analysis methods). Both studies investigated the single treatment of two doses of Botox (onabotulinumtoxinA) and compared the Botox groups to the placebo group using the following co-primary endpoints:

- Average grade change from baseline in Modified Ashworth Scale – Bohannon (MAS-B) score of the principal muscle group (elbow or wrist) at Weeks 4 and 6
- Average Clinical Global Impression of Overall Change (CGI) by Physician at Weeks 4 and 6

The clinical study to support the pediatric upper limb spasticity indication failed to demonstrate statistical signicance for both 3 U/kg group and 6 U/kg group: although the nominal p-values were smaller than 0.05 for the MAS-B co-primary endpoint (nominal p-values < 0.001 for both dose groups), the nomial p-values for the CGI endpoint were larger than 0.05 for both dose groups (nominal p-values = 0.155 for the 6 U/kg group and 0.147 for the 3 U/kg group). (b) (4)

(b) (4)

2 INTRODUCTION

2.1 Overview

On December 20, 2018, Allergan, Inc. (the Applicant) submitted (b) (4) to the approved biologic license application (BLA) of Botox: Supplement 5309 is for additional indication for the treatment of pediatric upper limb spasticity (b) (4)

(b) (4)

clinical studies - Study 191622-101 and Study 191622-111- are summarized below and reviewed in Section 3. They are hereafter referred to as Study 101 and Study 111, respectively.

Table 1. Clinical studies in this review

Study	Indication	Phase and Design	Study Duration	Study Arm (Number of randomized subjects per arm)	Study Population
191622-101	Pediatric upper limb spasticity	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	16 Weeks (up to 4 weeks of screening and 12 weeks of post-treatment follow-up)	6 U/kg (77) 3 U/kg (78) Placebo (80)	Pediatraic patients with spasticity of the upper limb
191622-111	Pediatric lower limb spasticity	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	16 Weeks (up to 4 weeks of screening and 12 weeks of post-treatment follow-up)	8 U/kg (127) 4 U/kg (125) Placebo (129)	Pediatraic patients with spasticity of the lower limb

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of the BLA supplements is located at
\\CDSESUB1\evsprod\BLA103000\0363\

The study reports are located at
\\CDSESUB1\evsprod\BLA103000\0363\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-spasticity\5351-stud-rep-contr\191622-101\
\\CDSESUB1\evsprod\BLA103000\0363\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-spasticity\5351-stud-rep-contr\191622-111\

The datasets are located at
\\CDSESUB1\evsprod\BLA103000\0363\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality and analysis quality are adequate. The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Study 101

3.2.1.1 Design and Endpoints

Study 101 was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multi-center clinical study to evaluate the safety and efficacy of a single treatment of two doses (6 U/kg and 3 U/kg) of Botox with occupational therapy (OT) in pediatric patients with upper limb spasticity. Approximately 224 subjects 2 to 16 years and 11 months of age were planned to be enrolled and randomized in a 1:1:1 ratio to the Botox 6 U/kg group, Botox 3 U/kg group, or placebo group.

The study consisted of a screening period of up to four weeks. Subjects had post-injection follow-up visits at Weeks 2, 4, 6, 8, and 12 and weekly OT sessions from Week -2 to Week 11.

The co-primary endpoints were

- Average grade change from baseline in Modified Ashworth Scale – Bohannon (MAS-B) score of the principal muscle group (elbow or wrist) at Weeks 4 and 6
- Average Clinical Global Impression of Overall Change (CGI) by Physician at Weeks 4 and 6

The raw MAS-B has 6 grades:

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved. There can be a catch, but movement should be stiff through most of range.
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

In the statistical analyses, the MAS-B raw scores of 0, 1, 1+, 2, 3, and 4 were coded as 0, 1, 2, 3, 4, and 5, respectively.

The principal muscle group must have a baseline MAS-B score of 2 or greater. The muscle group that had the higher baseline MAS-B score was planned to be designated as the principal muscle group. When both the wrist and elbow flexors had the same baseline MAS-B score, the elbow flexors was designated as the principal muscle group. In some cases of equal baseline MAS-B scores in wrist and elbow, the principal muscle group designation was changed to ensure that at least 40% of subjects enrolled have elbow flexors spasticity and 40% have wrist/finger flexors spasticity.

Subjects were stratified based on the following three factors:

- Age (≤ 6 years and > 6 years)
- Designated principal muscle group (elbow flexors and wrist flexors)
- Baseline MAS-B score of the principal muscle group (MAS-B = 2 and MAS-B > 2)

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized sujbects with a valid MAS-B baseline score of the principal muschle group and at least one at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B of the principal muscle group and CGI by Physician.

The co-primary endpoint of the change from baseline in MAS-B score was analyzed using mixed model repeated measures (MMRM) that included the baseline MAS-B score as the covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The co-primary endpoint of CGI by physician was analyzed using MMRM that included the baseline MAS-B score as the covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The Hochberg procedure was planned to control the family-wise type I error rate. The statistical analysis plan (SAP) defined the following values:

p11: p value for Botox 6 U/kg vs placebo comparing MAS-B
p12: p value for Botox 3 U/kg vs placebo comparing MAS-B
p21: p value for Botox 6 U/kg vs placebo comparing CGI
p22: p value for Botox 3 U/kg vs placebo comparing CGI
p1 = max(p11, p21)
p2 = max(p12, p22)

and planned to sort p1 and p2 in an increasing order to get p(1) ≤ p(2). The SAP also pre-specified the following decision rule:

Step 1: If p(2) ≤ 0.05, both doses are considered efficacious; otherwise go to step 2.
Step 2: If p(1) ≤ 0.025, its corresponding dose is considered efficacious; otherwise go to step 3.
Step 3: Neither dose is considered efficacious.

3.2.1.3 Subject Disposition, Demographic and Baseline Characteristics

Table 2. Study 101 subject disposition

Participant Status	*BOTOX 6 U/kg (N = 77) n (%)*	*BOTOX 3 U/kg (N = 78) n (%)*	*Placebo (N = 80) n (%)*	*Total (N = 235) n (%)*
Screened (screen population)	--	--	--	292
Not enrolled	--	--	--	57
Consent withdrawn	--	--	--	3
Other	--	--	--	6
Screen failed	--	--	--	48
Inclusion Criteria	--	--	--	33
Exclusion Criteria	--	--	--	16
Randomized	77 (100.0)	78 (100.0)	80 (100.0)	235 (100.0)
Treated (safety population)	77 (100.0)	78 (100.0)	79 (98.8)	234 (99.6)
mITT population[a]	77 (100.0)	78 (100.0)	79 (98.8)	234 (99.6)
Completed Study	75 (97.4)	78(100.0)	79 (98.8)	232 (98.7)
Prematurely discontinued	2 (2.6)	0 (0.0)	1 (1.3)	3 (1.3)
Adverse events	1 (1.3)	0 (0.0)	1 (1.3)[b]	2 (0.9)
Personal reasons	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)

CGI = Clinical Global Impression of Overall Change; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat

[a] The mITT population included all randomized participants with a valid MAS-B score of the principal muscle group and ≥ 1 postbaseline measurement at Weeks 2, 4, or 6 for the MAS-B of the principal muscle group and the CGI by Physician.

[b] Participant (b) (6) in the placebo group was withdrawn from the study due to an adverse event before receiving study treatment.

Source: Table 10-1 in the clinical study report body of Study 191622-101

Table 2 presents the subject disposition of Study 101. A total of 292 subjects were screened in 46 study centers in 9 countries; a total of 235 subjects were randomized in 40 study centers in 9 countries. Among the randomized subjects, 77 subjects (32.8%) were randomized to the 6 U/kg group, 78 (33.2%) to the 3 U/kg group, and 80 (34.0%) to the placebo group.

Table 3. Study 101 Subject demographics and baseline characterisitcs, mITT population

Characteristic	*BOTOX* *6 U/kg (N = 77)*	*BOTOX* *3 U/kg (N = 78)*	*Placebo (N = 79)*	*Total (N = 234)*
Age, years				
Mean ± SD	7.6 ± 3.66	8.3 ± 4.48	7.8 ± 4.06	7.9 ± 4.07
Min, Max	2, 16	2, 16	2, 16	2, 16
≤ 6, n (%)	35 (45.5)	33 (42.3)	34 (43.0)	102 (43.6)
> 6, n (%)	42 (54.5)	45 (57.7)	45 (57.0)	132 (56.4)
Sex, n (%)				
Male	50 (64.9)	42 (53.8)	47 (59.5)	139 (59.4)
Female	27 (35.1)	36 (46.2)	32 (40.5)	95 (40.6)
Race, n (%)				
White	51 (66.2)	42 (53.8)	51 (64.6)	144 (61.5)
Non-white	26 (33.8)	36 (46.2)	28 (35.4)	90 (38.5)
Black	3 (3.9)	3 (3.8)	3 (3.8)	9 (3.8)
Asian	19 (24.7)	27 (34.6)	19 (24.1)	65 (27.8)
Hispanic	2 (2.6)	4 (5.1)	5 (6.3)	11 (4.7)
Other	2 (2.6)	2 (2.6)	1 (1.3)	5 (2.1)
Principal Muscle Group				
Elbow Flexors	48 (62.3)	48 (61.5)	48 (60.8)	144 (61.5)
Wrist Flexors	29 (37.7)	30 (38.5)	31 (39.2)	90 (38.5)
MAS-B of Principal Muscle Group				
2	55 (71.4)	57 (73.1)	58 (73.4)	170 (72.6)
>2	22 (28.6)	21 (26.9)	21 (26.6)	64 (27.4)

SD = standard deviation; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat

Source: Table 10-4 in the clinical study report body of Study 191622-101

Table 3 summarizes the demographic and baseline characteristics of subjects in the mITT population. The treatment groups appeared similar in terms of age, sex, race, and baseline MAS-B scores of the principal muscle group. The average age of the subjects was approximately 7.9 years (standard deviation (SD) = 4.1). There were more males than females in the study. The majority of the subjects were white.

3.2.1.4 Results and Conclusions

Table 4. Study 101 primary analysis of MAS-B, mITT population

		BOTOX		
Visit	*Statistic*	*6 U/kg (N = 77)*	*3 U/kg (N = 78)*	*Placebo (N = 79)*
Baseline	n	77	78	79
	Mean ± SD	3.3 ± 0.45	3.3 ± 0.45	3.3 ± 0.44
Weeks 4 & 6	n	74	76	75
	Mean ± SD	1.4 ± 1.01	1.4 ± 0.98	2.1 ± 0.90
	Mean Change from Baseline ± SD	-1.9 ± 0.98	-1.9 ± 0.97	-1.2 ± 0.85
	LS Mean Change from Baseline (SE)	-1.87 (0.102)	-1.92 (0.101)	-1.21 (0.102)
	Difference (SE)	-0.66 (0.142)	-0.71 (0.143)	
	95% CI	(-0.938, -0.379)	(-0.992, -0.426)	
	P-value [a]	< 0.001	< 0.001	

CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

Source: Table 11-1 in the clinical study report body of Study 191622-101

Table 4 presents the primary analysis of the change from baseline in MAS-B score. Desicptive statistics in the table were calculated for subjects who had MAS-B scores at both Week 4 and Week 6. The percentages of missing average MAS-B scores at Week 4 and Week 6 were low for all treatment groups: the missing percentages were 3.9%, 2.6%, and 5.1% for the the Botox 6 U/kg group, Botox 3 U/kg group,. and placebo group, respectively. The treatment difference between the Botox 6 U/kg group and placebo group was in the direction favoring Botox; the treatment difference between the Botox 3 U/kg group and placebo group also favored Botox.

As a pre-specified additional analysis, observed percentages of responders with at least a 1-grade reduction from baseline in MAS-B score were calculated and reported. The percentages of reponders with at least 1-grade reduction from baseline to average of Week 4 and Week 6 were 86.5% (64 out of 74), 86.8% (66 out of 76), and 70.7% (53 out of 75) for the Botox 6 U/kg group, Botox 3 U/kg group, and placebo group, respectively. The Botox 6 U/kg and placebo difference was 15.8%, showing that more subjects in the Botox group had improvements, compared to subjects in the placebo group; the Botox 3 U/kg and placebo difference was 16.2%.

Table 5. Study 101 primary analysis of CGI by physician, mITT population

		BOTOX		
Visit	*Statistic*	*6 U/kg (N = 77)*	*3 U/kg (N = 78)*	*Placebo (N = 79)*
Weeks 4 & 6	n	74	76	75
	Mean ± SD	2.0 ± 1.01	1.9 ± 1.07	1.7 ± 1.12
	LS Mean (SE)	1.87 (0.108)	1.88 (0.108)	1.66 (0.108)
	Difference (SE)	0.21 (0.150)	0.22 (0.153)	
	95% CI	(-0.082, 0.511)	(-0.079, 0.523)	
	P-value [a]	0.155	0.147	

CGI = Clinical Global Impression of Overall Change; CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

Source: selected from Table 11-7 in the clinical study report body of Study 191622-101

Table 5 presents the primary analysis of CGI by physician. Desicptive statistics in the table were calculated for subjects who had MAS-B scores at both Week 4 and Week 6. The treatment differences between Botox and placebo favored Botox. However, the p-values of Botox-placebo comparisons for both doses were greater than 0.05.

Based on the statistical testing results in **Table 4** and **Table 5** and pre-specified Hochberg procedure that was planned to handle multiplicity due to multiple endpoints and doses, neither Botox 6 U/kg nor Botox 3 U/kg was statistically significantly different from placebo.

3.2.2 Study 111

3.2.2.1 Design and Endpoints

Study 111 was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multi-center clinical study to evaluate the safety and efficacy of a single treatment of two doses (4 U/kg and 8U/kg) of Botox with standardized physical therapy (PT) in pediatric patients with lower limb spasticity. Approximately 412 subjects 2 to 16 years and 11 months of age were planned to be enrolled and randomized in a 1:1:1 ratio to the Botox 8 U/kg group, Botox 4 U/kg group, or placebo group.

The study consisted of a screening period of up to four weeks. Subjects had post-injection follow-up visits at Weeks 2, 4, 6, 8, and 12 and weekly PT sessions from Week -2.

The co-primary endpoints were

- Average grade change from baseline in MAS-B ankle score with knee extended at Weeks 4 and 6

- Average CGI by Physician at Weeks 4 and 6

In the statistical analyses, the 6-grade MAS-B raw scores of 0, 1, 1+, 2, 3, and 4 were coded as 0, 1, 2, 3, 4, and 5, respectively.

Subjects were stratified based on the following two factors:

- Age (≤ 6 years and > 6 years)
- Baseline MAS-B ankle score with knee extended (MAS-B = 2 and MAS-B > 2)

3.2.2.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized sujbects with a valid baseline MAS-B ankle score with knee extended and at least one at least one post-baseline measurement at Weeks 2, 4, or 6 for the MAS-B ankle score with knee extended and the CGI by Physician.

The co-primary endpoint of change from baseline in MAS-B ankle score was analyzed using MMRM that included the baseline MAS-B ankle score as the covariate and factors of age group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The co-primary endpoint of CGI by physician was analyzed using MMRM that included the baseline MAS-B ankle score as the covariate and factors of age group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure.

The same Hochberg procedure as proposed in Study 101 (see Section 3.2.1.2) was planned to control the family-wise type I error rate for Study 111.

3.2.2.3 Subject Disposition, Demographic and Baseline Characteristics

Table 6. Study 111 subject disposition

	BOTOX			
Participant Status	*8 U/kg (N = 128) n (%)*	*4 U/kg (N = 126) n (%)*	*Placebo (N = 130) n (%)*	*Total (N = 384) n (%)*
Screened (Screen Population)	--	--	--	466
Not enrolled	--	--	--	82
Consent withdrawn				10
Other				8
Screen failed	--	--	--	64
Inclusion Criteria	--	--	--	46
Exclusion Criteria	--	--	--	20
Randomized	128 (100.0)	126 (100.0)	130 (100.0)	384 (100.0)
Treated (safety population)	128 (100.0)	126 (100.0)	128 (98.5)	382 (99.5)
mITT population[a]	127 (99.2)	125 (99.2)	129 (99.2)	381 (99.2)
Completed Study	125 (97.7)	123 (97.6)	128 (98.5)	376 (97.9)
Prematurely discontinued	3 (2.3)	3 (2.4)	2 (1.5)	8 (2.1)
Personal reasons	1 (0.8)	1 (0.8)	2 (1.5)	4 (1.0)
Protocol violation	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)
Lost to follow-up	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Other	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)

CGI = Clinical Global Impression of Overall Change; MAS-B = Modified Ashworth Scale – Bohannon; mITT = modified intent-to-treat

[a] The mITT population included all randomized participants with a valid MAS-B baseline ankle score with knee extended and ≥ 1 postbaseline measurement at Weeks 2, 4, or 6 for the MAS-B ankle score with knee extended and the CGI by Physician.

Source: Table 10-1 in the clinical study report body of Study 191622-111

Table 6 presents the subject disposition of Study 111. A total of 466 subjects were screened in 51 study centers in 9 countries; a total of 384 subjects were randomized in 49 study centers in 9 countries. Among the randomized subjects, 128 subjects (33.3%) were randomized to the 8 U/kg group, 126 (32.8%) to the 4 U/kg group, and 130 (33.9%) to the placebo group.

Table 7. Study 111 Subject demographics and baseline characterisitcs, mITT population

Characteristic	*BOTOX 8 U/kg (N = 127)*	*BOTOX 4 U/kg (N = 125)*	*Placebo (N = 129)*	*Total (N = 381)*
Age, years				
Mean ± SD	6.7 ± 3.90	6.4 ± 3.58	6.7 ± 3.89	6.6 ± 3.79
Min, Max	2, 16	2, 16	2, 15	2, 16
≤ 6, n (%)	74 (58.3)	73 (58.4)	74 (57.4)	221 (58.0)
> 6, n (%)	53 (41.7)	52 (41.6)	55 (42.6)	160 (42.0)
Sex, n (%)				
Male	70 (55.1)	67 (53.6)	69 (53.5)	206 (54.1)
Female	57 (44.9)	58 (46.4)	60 (46.5)	175 (45.9)
Race, n (%)				
White	76 (59.8)	76 (60.8)	79 (61.2)	231 (60.6)
Non-white	51 (40.2)	49 (39.2)	50 (38.8)	150 (39.4)
Black	2 (1.6)	3 (2.4)	4 (3.1)	9 (2.4)
Asian	42 (33.1)	35 (28.0)	37 (28.7)	114 (29.9)
Hispanic	7 (5.5) 10	(8.0)	6 (4.7)	23 (6.0)
Other	0 (0.0)	1 (0.8)	3 (2.3)	4 (1.0)
MAS-B Ankle Score with Knee Extended				
2	66 (52.0)	66 (52.8)	68 (52.7)	200 (52.5)
>2	61 (48.0)	59 (47.2)	61 (47.3)	181 (47.5)

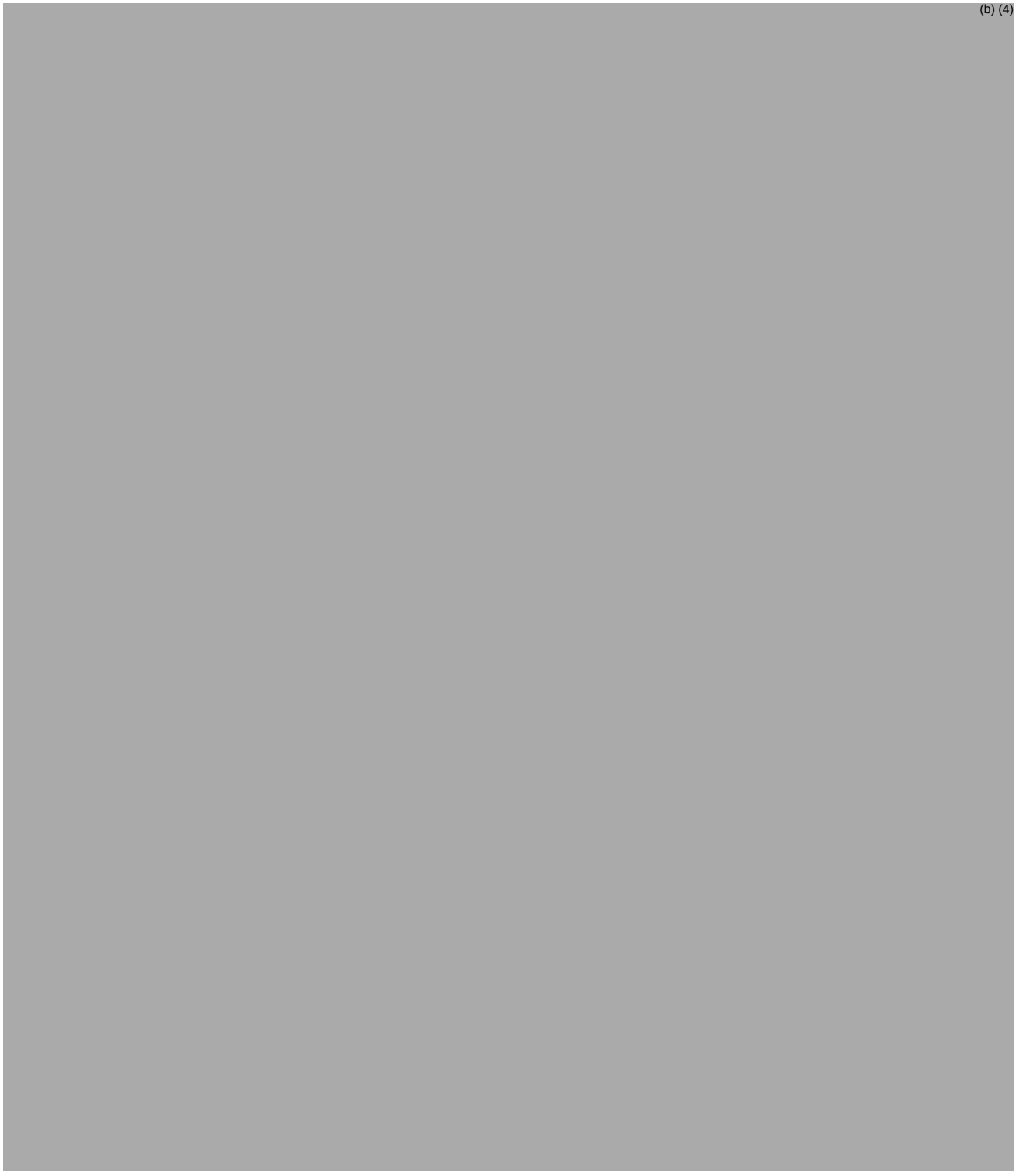
MAS-B = Modified Ashworth Scale – Bohannon; mITT = modified intent-to-treat; SD = standard deviation

Source: Table 10-4 in the clinical study report body of Study 191622-111

Table 7 summarizes the demographic and baseline characteristics of subjects in the mITT population. The treatment groups appeared similar in terms of age, sex, race, and baseline MAS-B ankle scores. The average age of the subjects was approximately 6.6 years (SD = 3.8). There were more males than females in the study. The majority of the subjects were white.

3.2.2.4 Results and Conclusions

(b) (4)



(b) (4)

3.3 Evaluation of Safety

Please refer to Dr. Susanne Goldstein's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 101

4.1.1 Gender, Race, Age, and Geographic Region

Table 10. Study 101 analyses by gender, mITT population

		MAS-B			CGI		
Female							
Visit	Statistic	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)
Baseline	n	27	36	32	--	--	--
	Mean±SD	3.3±0.45	3.2±0.42	3.2±0.42	--	--	--
Weeks 4&6	n	26	35	32	26	35	32
	Mean±SD	1.4±0.84	1.2±0.80	2.1±0.73	1.9±1.05	2.1±1.17	1.6±1.04
	Mean change from Baseline ±SD	-1.8±0.94	-2.0±0.85	-1.1±0.72	--	--	--
Male							
Baseline	n	50	42	47	--	--	--
	Mean±SD	3.3±0.46	3.3±0.47	3.3±0.46	--	--	--
Weeks 4&6	n	48	41	43	48	41	43
	Mean±SD	1.4±1.10	1.5±1.11	2.1±1.01	2.0±1.00	1.7±0.95	1.8±1.19
	Mean change from Baseline ±SD	-1.9±1.01	-1.8±1.07	-1.2±0.93	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-2.1, and Table 1-2.2 in the integrated summary of efficacy tables

Table 11. Study 101 analyses by race, mITT population

		MAS-B			CGI		
Non-White							
Visit	Statistic	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)
Baseline	n	26	36	28	--	--	--
	Mean±SD	3.2±0.40	3.1±0.35	3.1±0.26	--	--	--
Weeks 4&6	n	25	34	28	25	34	28
	Mean±SD	1.3±0.99	1.4±0.97	2.1±0.86	2.1±1.07	1.7±1.30	1.7±1.16
	Mean change from Baseline ±SD	-1.9±1.04	-1.8±1.05	-0.9±0.80	--	--	--
White							
Baseline	n	51	42	51	--	--	--
	Mean±SD	3.3±0.48	3.4±0.49	3.4±0.49	--	--	--
Weeks 4&6	n	49	42	47	49	42	47
	Mean±SD	1.5±1.02	1.4±1.00	2.0±0.93	1.9±0.98	2.0±0.83	1.7±1.11
	Mean change from Baseline ±SD	-1.9±0.96	-2.0±0.91	-1.4±0.84	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-3.1, and Table 1-3.2 in the March 7, 2019 response to information request

Table 12. Study 101 analyses by region, mITT population

		MAS-B			CGI		
Non-US							
Visit	Statistic	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)
Baseline	n	60	58	53	--	--	--
	Mean±SD	3.3±0.47	3.3±0.46	3.3±0.48	--	--	--
Weeks 4&6	n	60	57	53	60	57	53
	Mean±SD	1.4±1.05	1.5±1.01	2.1±0.93	2.0±1.07	1.9±1.15	1.7±1.15
	Mean change from Baseline ±SD	-1.9±1.04	-1.8±0.98	-1.2±0.89	--	--	--
US							
Baseline	n	17	20	26	--	--	--
	Mean±SD	3.2±0.39	3.2±0.41	3.1±0.33	--	--	--
Weeks 4&6	n	14	19	22	14	19	22
	Mean±SD	1.3±0.85	0.9±0.78	1.9±0.83	1.8±0.70	1.7±0.77	1.7±1.08
	Mean change from Baseline ±SD	-1.8±0.67	-2.3±0.87	-1.2±0.75	--	--	--

Source: selected from Table 1-1.1, Table 1-1.2, Table 1-2.1, and Table 1-2.2 in the May 1, 2019 response to information request

Table 10, **Table 11**, and **Table 12** present the analyses of the co-primary endpoints by gender, race, and geographic region, respectively. There is no compelling evidence from these subgroup analyses that a specific gender, race, or geographic region benefits differently from Botox. However, US subjects appeared to have little or none Botox-placebo differences in mean CGI by physician.

4.1.2 Other Subgroup Populations

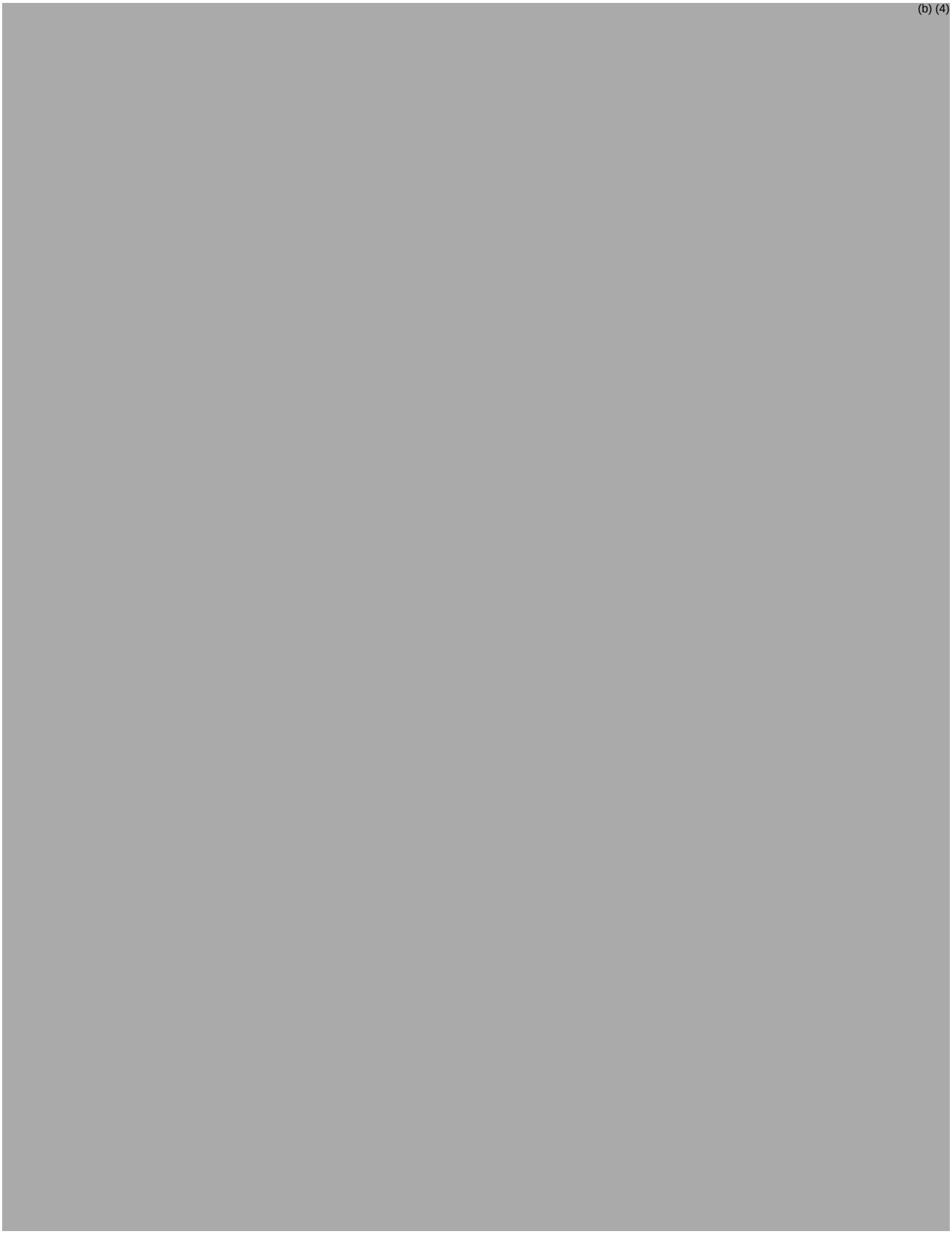
Table 13. Study 101 analyses by principal muscle group, mITT population

		MAS-B			CGI		
Principal Muscle Group = Elbow							
Visit	Statistic	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)	Botox 6 U/kg (N = 77)	Botox 3 U/kg (N = 78)	Placebo (N = 79)
Baseline	n	48	48	48	--	--	--
	Mean±SD	3.3±0.48	3.3±0.47	3.3±0.47	--	--	--
Weeks 4&6	n	46	46	46	46	46	46
	Mean±SD	1.4±1.00	1.5±0.93	2.1±0.91	2.1±0.82	2.0±0.97	1.7±1.13
	Mean change from Baseline ±SD	-1.9±0.91	-1.9±0.92	-1.3±0.81	--	--	--
Principal Muscle Group = Wrist							
Baseline	n	29	30	31	--	--	--
	Mean±SD	3.2±0.41	3.2±0.41	3.2±0.4	--	--	--
Weeks 4&6	n	28	30	29	28	30	29
	Mean±SD	1.4±1.04	1.2±1.05	2.1±0.90	1.7±1.24	1.8±1.21	1.7±1.13
	Mean change from Baseline ±SD	-1.8±1.08	-2.0±1.05	-1.1±0.91	--	--	--

Source: selected from Table 14.5-1.2 and Table 14.5-2.2 in the clinical study report body of Study 191622-101

Table 13 presents the analyses of the co-primary endpoints by principal muscle group. While the analysis results of the MAS-B endpoint appeared similar regardless of principal muscle group, subjects whose principal muscle groups were wrist appeared to have little or none Botox-placebo differences in mean CGI by physician.

4.2 Study 111


(b) (4)

(b) (4)

4.2.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues that changed the overall conclusions.

5.2 Collective Evidence

Placebo response was observed for both co-primary endpoints (b) (4) Study 191622-101 (b) (4) and might contribute to the non-significant statistical results in these studies. Nonetheless, the MAS-B endpoint had nominal p-values smaller than 0.05 (b) (4); Botox-placebo differences were around -0.7 in Study 101 (b) (4) large mean reductions compared to placebo considering that MAS-B is only a 6 grade scale. In exploratory subgroup analyses, there were little or none observed Botox-placebo differnces in mean CGI by physician in several subgroups, such as the US subgroup in Study 101, (b) (4) It remains inconclusion as to which subgroup had smaller Botox response in terms of the Botox-placebo difference in mean CGI by physician.

5.3 Conclusions and Recommendations

(b) (4) . Data from from Study 19162-101 were not sufficient to estabilish statistically significant Botox-placebo difference, further clinical input and benefit-risk evaluation might be needed for the clinical efficacy evaluation of Botox in treating pediatric upper limb spasticity.

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.

/s/

XIANGMIN ZHANG
05/21/2019 01:52:42 AM

KUN JIN
05/21/2019 03:53:19 PM
I concur with the review.

HSIEN MING J HUNG
05/21/2019 03:59:08 PM