МИНИСТЕРСТВО
ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ

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Clinical Review Report

Botulinum Toxin Type A (Maytox Therapeutic) (RM Pharma, ZAO. Moscow)
Indication: For the symptomatic treatment of focal spasticity affecting the upper limbs in adults.

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

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Drug Name:	Maytox (Botulinum Toxin Type A)
Indication(s):	Treatment of upper limb spasticity in pediatric patients 2 years of age or older
Applicant:	RM Pharma, ZAO. Moscow
Date(s):	Receipt Date: March 17, 2018 Due Date: September 17, 2018
Review Priority:	Priority
Biometrics Division:	DBI
Statistical Reviewer:	Viktor V. FOMIN
Concurring Reviewers:	James SPILSBURY Colin DRUMMOND
Medical Division:	DNP
Clinical Team:	Ashwini Sehgal
Project Manager:	Denis V. BUTNARU
Keywords:	Pediatrics, Spasticity, Maytox (Botulinum Toxin Type A), Cerebral Palsy

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1. EXECUTIVE SUMMARY

This is a BLA application that includes a study (Y-52-52120-153) to evaluate the efficacy of two doses of Maytox (8 U/kg and 16 U/kg) compared to the low dose Maytox 2 U/kg for the treatment of upper limb spasticity in children with Cerebral Palsy (CP) following a single treatment. According to the pre-specified criteria, to claim the efficacy of any of the two tested doses of Maytox, the tested dose of Maytox (8 U/kg or 16 U/kg) needs to be superior to Maytox 2 U/kg on both the primary efficacy endpoint of the mean change on Modified Ashworth Scale (MAS) score from baseline at Week 6 and the first secondary efficacy endpoint of Physician Global Assessment (PGA) score at Week 6. In addition, per the pre-specified hierarchical testing procedure, the dose of 16 U/kg will be tested first for both the primary and secondary efficacy endpoints, then the dose of 8 U/kg will be tested similarly. During the review period, the clinical review team recommended that an endpoint of MAS responder be used as a substitute for the first secondary efficacy endpoint, which has been used in other similar submissions.

The study results demonstrate that the dose of Maytox 16 U/kg is superior to the dose of Maytox 2 U/kg U/kg for the primary efficacy endpoint (MAS) ($p<0.0001$) but not for the original secondary endpoint (PGA) ($p=0.1880$). The dose of Maytox 16 U/kg appears to be superior to Maytox 2 U/kg for the substituted secondary efficacy endpoint (MAS responder) (OR=4.15, 95% CI (1.21, 14.29), nominal p-value=0.024).

In summary, the efficacy seems to be demonstrated only for the dose of Maytox 16 U/kg based on the primary endpoint and the substituted secondary endpoint. There was no sufficient evidence to support the efficacy of Maytox 8U/kg.

2. INTRODUCTION

2.1 Overview

Spasticity is a chronic manifestation of upper motor neuron syndrome due to lesions of the pyramidal tract (an aggregation of upper motor neurons). In the upper limbs specifically, the increased muscle tone impairs the reach, grasp, manipulation and release, leading to restriction in everyday life and educational activities.

Maytox has already been approved in the Europe for the treatment of upper limb and lower limb spasticity in adult patients and for lower limb spasticity in pediatric patients. The aim of this submission is to support the use of Maytox for the treatment of upper limb spasticity in pediatric patients.

2.2 Data Sources

The applicant's SAS datasets were stored in the directory of datasets the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Generally, datasets were clearly defined and easily accessed. Analyses were properly performed.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Primary Study Objective: The primary objective of this study was to assess the efficacy of two doses of Maytox (8 U/kg and 16 U/kg) compared to Maytox 2 U/kg for the treatment of upper limb spasticity in children with CP following a single treatment.

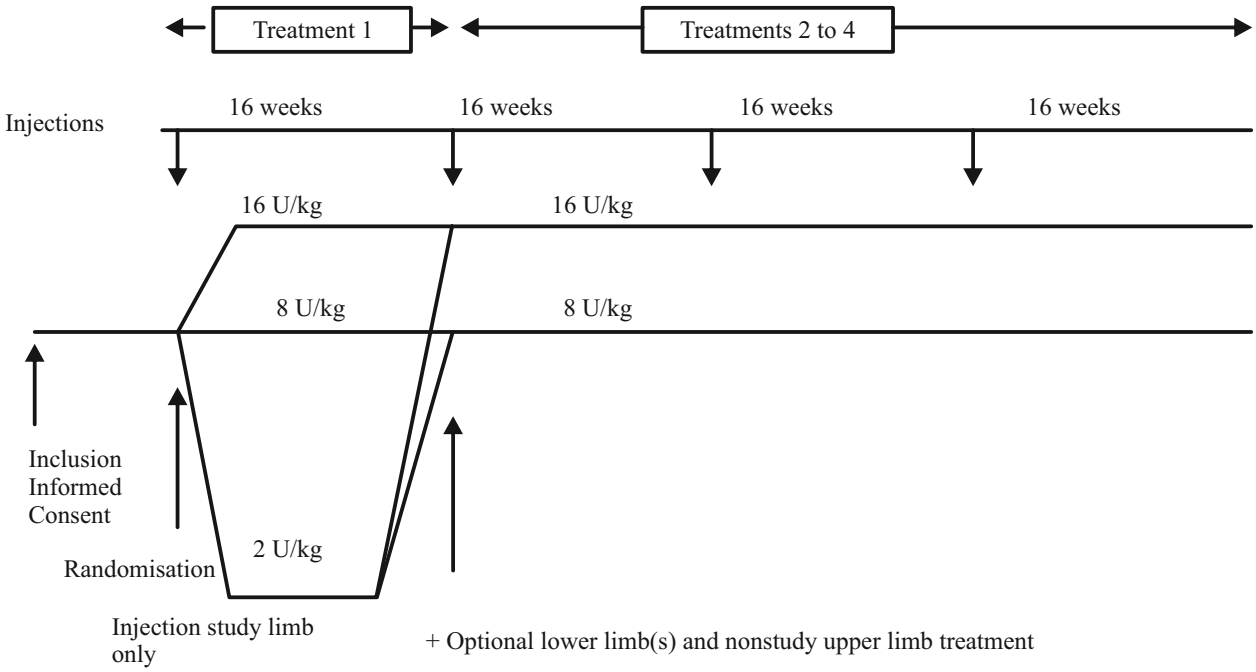
Study Design: The study was a phase III, multicenter, double blind, prospective, randomized, controlled, multiple treatment study conducted in subjects of age of 2 years and older with a diagnosis of CP and who had increased muscle tone/spasticity in at least one upper limb.

At entry of study, subjects were randomized in a 1:1:1 ratio into one of the following three treatment groups for Treatment Cycle 1 (TC 1):

- Maytox 16 U/kg in one upper extremity (the study limb)
- Maytox 8 U/kg in the study limb
- Maytox 2 U/kg in the study limb

Subjects could receive a maximum of four TCs over the course of a minimum of one year, with at least 16 weeks in between each TC, and a maximum of one year and 9 months study participation. Subjects were assessed for their eligibility to receive the next treatment at Week 16 (Figure 1)

Figure 1 Study Design



Primary efficacy endpoint: The primary efficacy endpoint was the mean change from baseline to TC 1, Week 6 in MAS score in the PTMG (elbow flexors or wrist flexors). MAS is a six-point scale from 0 (no increase in tone) to 5 (affected part(s) rigid in flexion or extension).

Secondary efficacy endpoints:

• 1° secondary efficacy endpoint: The mean Physician Global Assessment (PGA) score at TC1, Week6. PGA score is a nine-point rating scale (-4: markedly worse, -3: much worse, 2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved, and +4: markedly improved).

• 2° secondary efficacy endpoint: The mean Goal Attainment Scale (GAS) score at TC 1, Week 6. GAS score at baseline is rated on a scale from 0 (Not at all important/difficult) to 3 (very important/difficult); and a scale from -2 (Much less than expected outcome) to 2 (Much more than expected outcome) at post-baseline.

3.2.2 Statistical Methodologies

Determination of sample size: The primary (MAS), first secondary (PGA) efficacy endpoints, and long-term safety were considered in the sample size calculation:

• **Primary efficacy endpoint of MAS:** A total of 57 randomized subjects (i.e. 19 randomized subjects per treatment group) will provide 80% power to detect a difference of 0.6 in the mean changes from baseline to TC1, Week 6; assuming a common standard deviation of 0.5 and a 3% drop out rate, two- sided, α=0.05.

• **First secondary efficacy endpoint of PGA:** A total of 99 randomized subjects (i.e. 33 subjects per treatment group) will provide 85% power to detect a difference of 0.7 in the mean PGA score at Week 6; assuming a common standard deviation of 1.1 and a 3% drop out rate, two-sided, α=0.05.

• **Long-term safety:** The number of 210 randomized subjects (i.e.70 subjects in each treatment group) was considered sufficient to meet the long-term safety requirements recommended by ICH guideline:

• At least 150 subjects exposed to Maytox doses intended for clinical use per study limb over 12 months.

• At least 150 subjects exposed to the highest recommended Maytox dose per study limb over the first 6 months.

• At least 100 subjects exposed to the highest recommended Maytox dose per study limb over 12 months.

Primary efficacy analysis: Analysis of Covariance (ANCOVA) on the rank of the mean changes was performed with treatment group, the baseline value, the two stratification factors (age range and BTX treatment naïve status at baseline) and the pooled center as fixed effects.

Sensitivity Analyses of the Primary Analysis:

• Center effect: The ANCOVA model on the rank of the mean changes of MAS score was re-run, adding the treatment by center interaction term as a fixed effect. If the p-value from the interaction term in the model was lower than 0.1, then the influence of center on the treatment effect was further investigated by estimating and plotting the treatment groups differences separately for each center.

• Robustness: The proportional odds model was applied to the ordered mean changes of MAS score with treatment group, the baseline value, the two stratification factors (age range and BTX treatment naive status at baseline) and the pooled center as fixed effects.
• Missing data: The primary analysis was performed using all randomized subjects. Any missing assessment on the MAS at TC 1, Week 6 visit were imputed with the assessment on the MAS at the baseline visit.

Secondary efficacy analyses:
• 1° secondary efficacy endpoint: An Analysis of Variance (ANOVA) was performed on the rank of the mean PGA score with treatment group, the two stratification factors and the pooled center as fixed effects.
• 2° secondary efficacy endpoint: A similar analysis used for the first secondary efficacy endpoint was performed on the rank of the mean GAS score.

Multiplicity: For the Europe registration, the following strategies were pre-specified and applied:

The superiority of any of the two tested doses of Maytox (8 U/kg or 16 U/kg) was demonstrated if the tested dose of Maytox (8 U/kg or 16 U/kg) was superior to Maytox 2 U/kg for **both the primary efficacy endpoint (MAS) and the first secondary efficacy endpoint (PGA).**

Four steps of hierarchical testing procedure were applied for the testing of the superiority of each of the two tested doses of Maytox (8 U/kg or 16 U/kg) to Maytox 2 U/kg as the following:
• **Step 1:** The superiority of Maytox 16 U/kg to Maytox 2 U/kg on the primary efficacy endpoint will be tested at a significance level of 0.05. If the p-value is lower than 0.05 then it will be considered significant and Step 2 will be applied. Otherwise, the procedure will be stopped.
• **Step 2:** The superiority of Maytox 16 U/kg to Maytox 2 U/kg on the first secondary efficacy endpoint will be tested at a significance level of 0.05. If the p-value is lower than 0.05 then it will be considered significant and Step 3 will be applied. Otherwise, the procedure will be stopped.
• **Step 3:** The superiority of Maytox 8 U/kg to Maytox 2 U/kg on the primary efficacy endpoint will be tested at a significance level of 0.05. If the p-value is lower than 0.05 then it will be considered significant and Step 4 will be applied. Otherwise, the procedure will be stopped.
• **Step 4:** The superiority of Maytox 8 U/kg to Maytox 2 U/kg on the first secondary efficacy endpoint will be tested at a significance level of 0.05. If the p-value is lower than 0.05 then it will be considered significant.

The superiority of Maytox 16 U/kg to Maytox 2 U/kg will be demonstrated if the two p-values associated with the tests performed at Steps 1 and 2 are lower than 0.05. Similarly, the superiority of Maytox 8 U/kg to Maytox 2 U/kg will be demonstrated if the two p-values associated with the tests performed at Steps 3 and 4 are lower than 0.05.

Handling of dropouts/missing data:

• **Efficacy:**

• MAS score: Any missing assessment on the MAS at TC 1, Week 6 visit will be imputed with the assessment at the baseline visit. In case any baseline assessment on the MAS is missing, the baseline assessment is imputed with the average baseline assessments on all randomized subjects.

• PGS score: Any missing assessment on the PGA at TC 1, Week 6 visit for a subject in a higher dose Maytox group will be imputed with the assessment 'markedly worse' and the assessment 'markedly improved' for a subject in the low dose Maytox group.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition: A total of 226 subjects were enrolled, 212 were randomized and 210 received at least one Maytox injecton, 70 per dose group. 2 subjects were randomized and did not receive any Maytox treatment during the study. 4.8% (10/210) subjects discontinued at TC 1—the time point to assess primary efficacy (4, 3 and 3 subjects in Maytox 2 U/kg, Maytox 8 U/kg and Maytox 16 U/kg groups, respectively) (Table 1).

Table 1 Subject Disposition

Number of Subjects, n (%)		Maytox All Doses		
	TC 1 N=210	TC 2 N=178	TC 3 N=107	TC 4 N=55
Entered Treatment Cycle	210 (100.0)	178 (100.0)	107 (100.0)	55 (100.0)
Completed Treatment Cycle	200 (95.2)	170 (95.5)	98 (91.6)	52 (94.5)
Withdrawn from Study During Treatment Cycle	10 (4.8)	8 (4.5)	9 (8.4)	3 (5.5)
Adverse Event	2 (1.0)	2 (1.1)	1 (0.9)	0
Lack of Efficacy	0	0	0	0
Protocol Violation	0	0	0	0
Consent Withdrawn	3 (1.4)	2 (1.1)	2 (1.9)	2 (3.6)
Lost to Follow-Up	1 (0.5)	0	1 (0.9)	0
Other	4 (1.9)	4 (2.2)	5 (4.7)	1 (1.8)
Completed Study (a)	22	63	43	52

n=number of subjects with events, N=total number of subjects, TC=treatment cycle.
Data Source: Table 14.1.1.4.
Notes: The percentages are calculated using the total number of subjects entering the TC as denominator. Subjects not discontinuing the study during the cycle are considered as completers.
a These subjects completed the study at the stated TC and did not receive any subsequent treatment with Maytox.

Patient demographic and baseline characteristics: Demographic and baseline characteristics ware similar across treatment groups. Most of the subjects were males (60.1%), white (74.5%), and not Hispanic or Latino (78.8%). 86% subjects received physiotherapy, 57% females were at tanner grading scale I and 70% subjects were recruited from outside of the Russia. Mean age was 9 years old, mean height at screening was 131 cm and mean weight at baseline was 32 kg (Table 2).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition: A total of 226 subjects were enrolled, 212 were randomized and 210 received at least one Maytox injecton, 70 per dose group. 2 subjects were randomized and did not receive any Maytox treatment during the study. 4.8% (10/210) subjects discontinued at TC 1—the time point to assess primary efficacy (4, 3 and 3 subjects in Maytox 2 U/kg, Maytox 8 U/kg and Maytox 16 U/kg groups, respectively) (Table 1).

	Control Group	**Treatment Groups**		
Parameter Statistic	Maytox 2 U/kg (N=69)	Maytox 8 U/kg (N=69)	Maytox 16 U/kg (N=70)	**All Subjects (N=208)**
Age, years				
n	69	69	70	208
Mean (SD)	8.94 (4.58)	9.03 (4.28)	9.17 (4.30)	9.05 (4.37)
Median (Range)	9.00 (2.0; 17.0)	9.00 (2.0; 17.0)	8.00 (2.0; 17.0)	9.00 (2.0; 17.0)
Age Categories, n (%)				
2 - 9 Years	39 (56.5)	39 (56.5)	40 (57.1)	118 (56.7)
10 - 17 Years	30 (43.5)	30 (43.5)	30 (42.9)	90 (43.3)
Sex, n (%)				
Male	38 (55.1)	45 (65.2)	42 (60.0)	125 (60.1)
Female	31 (44.9)	24 (34.8)	28 (40.0)	83 (39.9)
Race, n (%)				
Asian	2 (2.9)	1 (1.4)	0	3 (1.4)
Black or African	7 (10.1)	6 (8.7)	3 (4.3)	16 (7.7)
White	48 (69.6)	53 (76.8)	54 (77.1)	155 (74.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0
American Indian or Alaska Native	0	1 (1.4)	0	1 (0.5)
Multiple	12 (17.4)	8 (11.6)	13 (18.6)	33 (15.9)
Ethnicity, n (%)				
Hispanic or Latino	16 (23.2)	13 (18.8)	15 (21.4)	44 (21.2)
Not Hispanic or Latino	53 (76.8)	56 (81.2)	55 (78.6)	164 (78.8)
Geographical Location, n (%)				
US	21 (30.4)	24 (34.8)	17 (24.3)	62 (29.8)
Non-US	48 (69.6)	45 (65.2)	53 (75.7)	146 (70.2)
Height, cm				
n	69	67	68	204
Mean (SD)	130.4 (26.1)	130.4 (25.0)	132.1 (22.4)	131.0 (24.5)
Median (Range)	129.0 (81: 191)	132.0 (90: 178)	129.9 (85: 178)	129.9 (81: 191)
Weight, kg				
n	69	69	70	208
Mean (SD)	31.48 (16.50)	32.91 (18.10)	32.68 (16.35)	32.36 (16.93)
Median (Range)	27.00 (10.0: 73.9)	28.00 (11.0: 81.1)	27.35 (10.8: 73.0)	27.60 (10.0: 81.1)
BMI, kg				
n	69	67	68	204
Mean (SD)	17.14 (3.23)	17.78 (4.10)	17.83 (4.00)	17.58 (3.79)
Median (Range)	16.22 (11.4: 24.5)	16.93 (9.6: 34.6)	17.20 (12.1: 28.2)	16.95 (9.6: 34.6)
BMI Categories, n (%)				
Underweight	14 (20.3)	6 (8.7)	14 (20.0)	34 (16.3)
Healthy weight/ Overweight	49 (71.0)	55 (79.7)	48 (68.6)	152 (73.1)
Obese	6 (8.7)	6 (8.7)	6 (8.6)	18 (8.7)
Missing	0	2 (2.9)	2 (2.9)	4 (1.9)
Tanner Grading Scale, n (%)				
I	19 (61.3)	13 (54.2)	15 (53.6)	47 (56.6)
II	3 (9.7)	1 (4.2)	2 (7.1)	6 (7.2)
III	2 (6.5)	2 (8.3)	2 (7.1)	6 (7.2)
IV	3 (9.7)	3 (12.5)	6 (21.4)	12 (14.5)
V	3 (9.7)	4 (16.7)	2 (7.1)	9 (10.8)
Missing	1 (3.2)	1 (4.2)	1 (3.6)	3 (3.6)
Physiotherapy/occupational therapy status (a)				
Yes	58 (84.1)	59 (85.5)	61 (87.1)	178 (85.6)
No	11 (15.9)	10 (14.5)	9 (12.9)	30 (14.4)

BMI=body mass index; mITT=modified intent-to-treat; N=total number of subjects; n=number of subjects with data; SD=standard deviation TC=treatment cycle; U=units; US= United States
Data Source: Table 14.1.5.1.

3.2.4 Results and Conclusion

Applicant's Primary Efficacy Result: The primary analysis result shows that the mean changes of MAS scores were statistically significantly lower (i.e., better) in both doses of Maytox(8 U/kg and 16 U/kg) compared to the dose of Maytox 2 U/kg (difference in back transformed LS means: -0.4 (p=0.0118) for Maytox 8 U/kg vs. Maytox 2 U/kg; -0.7 (p<0.0001) for Maytox 16 U/kg vs. Maytox 2 U/kg) (Table 3).

Table 3 Primary Efficacy Analysis of MAS: mITT

	Control Group	Treatment Groups	
Visit Statistic	Maytox 2 U/kg (N=69)	Maytox 8 U/kg (N=69)	Maytox 16 U/kg (N=70)
Baseline	**n=69**	**n=69**	**n=70**
Mean (SD)	3.1 (0.3)	3.1 (0.3)	3.1 (0.5)
Week 6 (primary timepoint)	**n=69**	**n=69**	**n=70**
Mean (SD)	1.6 (1.0)	1.2 (1.0)	0.9 (0.9)
Mean change (SD)	-1.5 (1.1)	-1.9 (1.0)	-2.2 (0.9)
LS mean of ranked change from baseline values (SE) (95% CI)	125.8 (6.6) (112.7, 138.9)	102.5 (6.6) (89.5, 115.6)	85.4 (6.6) (72.3, 98.5)
LS mean of back transformed change from baseline values	-1.6	-2.0	-2.3
Difference in LS means back transformed		-0.4	-0.7
p-value(a)		0.0118	<0.0001

a: p-value based on ANCOVA on the ranked changes from baseline including treatment group, the baseline value, the two stratification factors (age range and BTX treatment naïve status at baseline) and the pooled center as fixed effects.

Sensitivity Analyses of primary efficacy analysis: To assess the robustness of the primary efficacy analysis--rank ANCOVA, sensitivity analyses were performed using:

1) The proportional odds model: The results supported the primary efficacy analysis (OR=2.6 (95% CI: 1.3, 5.1) and 4.5 (95% CI: 2.3, 9.0) for the Maytox 8 U/kg and Maytox 16 U/kg groups, respectively).

2) ANCOVA with imputation for missing data by BOCF--Baseline Observation Carried Forward on all randomized subjects: The results were similar to the primary efficacy results based on mITT population (difference in back transformed LS means: -0.4 (p=0.0111) for Maytox 8 U/kg vs. Maytox 2 U/kg; -0.7 (p<0.0001) for Maytox 16 U/kg vs. Maytox 2 U/kg).

Reviewer's Note: Sensitivity analyses confirm that the primary efficacy result is robust.

Applicant's Secondary Efficacy Results:

1) 1° secondary efficacy endpoint of PGA: The mean PGA scores in both doses of Maytox 8 U/kg and 16 U/kg were numerically (but not statistically significantly) lower compared to the dose of Maytox 2 U/kg (difference in back transformed LS means: 0.2 (p=0.2043) for Maytox 8 U/kg vs. Maytox 2 U/kg; 0.2 (p=0.1880) for Maytox 16 U/kg vs. Maytox 2 U/kg)) (Table 4).

Table 4 Secondary Efficacy Analysis of PGA: mITT

	Control Group	Treatment Groups	
Statistic	Maytox 2 U/kg (N=69)	Maytox 8 U/kg (N=69)	Maytox 16 U/kg (N=70)
Week 6 (primary timepoint)	n=68	n=69	n=70
Mean score (SD)	1.7 (0.9)	2.0 (0.9)	2.0 (0.9)
LS mean of ranked score (SE)	97.1 (7.1)	109.5 (7.0)	109.7 (7.1)
LS mean of back transformed score	1.8	2.0	2.0
Difference in LS means scores back transformed		0.2	0.2
p-value*		0.2043	0.1880

*LDV with treatment, age range at baseline, BTX status at baseline, and center as explanatory variables

Reviewer's Results:
This reviewer verified the applicant's primary and secondary analyses and concurred with the results.

Reviewer's Note:

*1. Per **the pre-specified criteria for efficacy determination and the hierarchical testing procedures for the primary (MAS) and secondary endpoints (PGA) analyses (see 3.2.2)**, the efficacy of Maytox was not established for neither dose of 8 U/kg nor dose of 16 U/kg. The hierarchical test only passed Step 1 and stopped at Step 2, winning only on the primary efficacy endpoint but not the first secondary endpoint for the 16 U/kg dose. The dose of 8 U/kg did not get a change to be tested as the dose of 16 U/kg was failed and the hierarchical test was stopped.*

*2. The **clinical review team** recommended using an endpoint of **MAS responder (defined as ≥1 grade reduction on MAS) as a substitute for secondary efficacy endpoint**, which has been used in other similar submissions. A logistic regression analysis using the PENALIZED LIKELIHOOD METHOD OR FIRTH METHOD (to correct convergence failure issue) was applied for the responder analysis. The results showed that the responder rate was statistically significantly higher in the Maytox 16 U/kg group (94.3%) compared to the Maytox 2 U/kg group (81.2%) (OR=4.15, 95% CI (1.21, 14.29), nominal p-value=0.024). The responder rate in the Maytox 8 U/kg group (88.4%) was only numerically higher compared to the Maytox 2 U/kg group (OR=1.60, 95% CI (0.62, 4.10), nominal p-value=0.3276).*

Based on the substituted secondary endpoint of MAS responder analysis result, the efficacy of Maytox can be asserted only for the dose 16 U/kg: that is, the hierarchical test passed Steps 1 & 2, winning on both the primary (MAS) and first secondary endpoint (MAS responder) for the dose 16 U/kg. The efficacy of the 8 U/kg dose is not established as the hierarchical test only passed Step 3 but not Step 4, winning only on the primary endpoint but not the first secondary endpoint.

3. The decision on whether the change for the criteria of efficacy determination is acceptable is deferred to the clinical team.

3.3 Evaluation of Safety

Please refer to clinical review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses of primary endpoint were performed by age, gender, race and geographic region. The numerical results seemed trending in favor of Maytox 8 U/kg and Maytox 16 U/kg for all subgroups (Table 5).

Table 5 Subgroup analysis of Primary Efficacy Endpoint (1)

Subgroup n (%)	**Ranked LS Mean (SE)**			**Difference in Ranked LS Means (95% CI)**	
	Maytox 2 U/kg (N=69)	Maytox 8 U/kg (N=69)	Maytox 16 U/kg (N=70)	Maytox 8 U/kg vs. Maytox 2 U/kg	Maytox 16 U/kg vs. Maytox 2 U/kg
Age					
2-9 years 118 (56.7)	124.7 (8.6)	94.0 (8.6)	76.4 (8.6)	-30.7 (-54.4, -7.1)	-48.3 (-71.7, -24.9)
10-17 years 90 (43.3)	125.0 (10. 1)	112.0 (9.9)	95.4 (10.0)	-12.8 (-38.3, 12.8)	-29.3 (-55.2, -3.4)
BTS Status at Baseline					
Naïve 70 (33.7)	116.6 (11.2)	106.2 (11.3)	70.6 (11.0)	-27.9 (-55.5, -0.3)	-63.5 (-90.5, -36.5)
Non-naïve 138 (66.4)	134.1(8.2)	104.2 (7.7)	96.0 (8.0)	-30.0 (-52.5, -7.5)	-38.1 (-60.4, -15.8)
Sex					
Male 125 (60.1)	135.9 (8.6)	109.9 (8.1)	89.8 (8.4)	-25.9 (-48.7, -3.2)	-46.0 (-69.1, -23.0)
Female 83 (40.0)	113.4 (9.8)	88.8 (10.8)	80.4 (10.1)	-24.7 (-4.0, 53.3)	-33.1 (-60.7, -5.4)
Race					
White 155(74.5)	126.5 (8.4)	105.6 (7.8)	87.0 (8.10)	-20.9 (-0.2, 42.0)	-37.2 (-70.4, -3.9)
Non-white 53 (25.5)	124.2 (13.6)	93.0 (14.5)	81.5 (15.5)	-33.5 (-0.8, 67.8)	-42.7 (-77.9, -7.5)
Geographic Region*					
US 62 (29.8)	117.0 (15.1)	109.9 (12.7)	78.4 (17.2)	-7.1 (-46.1, 31.9)	-38.6 (-85.1, 7.9)
Non-US 146 (70.2)	129.5 (7.4)	99.0 (8.0)	86.9 (7.2)	-30.5 (-51.5, -9.5)	-42.6 (-61.9, -23.3)

Russia, Belgium, Spain, Israel, Turkey, Poland, Czech Republic, Mexico

4.2 Other Special/Subgroup Populations

Exploratory subgroup analysis of primary endpoint was also performed by BTX status at baseline and physiotherapy/occupational therapy status. The results are similar to other subgroups- trending in favor of Maytox 8 U/kg and Maytox 16 U/kg (Table 6).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses of primary endpoint were performed by age, gender, race and geographic region. The numerical results seemed trending in favor of Maytox 8 U/kg and Maytox 16 U/kg for all subgroups (Table 5).

Table 6 Subgroup analysis of Primary Efficacy Endpoint (2)

Subgroup n (%)	**Ranked LS Mean (SE)**			**Difference in Ranked LS Means (95% CI)**	
	Maytox 2 U/kg (N=69)	Maytox 8 U/kg (N=69)	Maytox 16 U/kg (N=70)	Maytox 8 U/kg vs. Maytox 2 U/kg	Maytox 16 U/kg vs. Maytox 2 U/kg
BTS Status at Baseline					
Naïve 70 (33.7)	116.6 (11.2)	106.2 (11.3)	70.6 (11.0)	-27.9 (-55.5, -0.3)	-63.5 (-90.5, -36.5)
Non-naïve 138 (66.4)	134.1 (8.2)	104.2 (7.7)	96.0 (8.0)	-30.0 (-52.5, -7.5)	-38.1 (-60.4, -15.8)
Physiotherapy/Occupational Therapy					
Yes 178 (85.6)	126.2 (7.3)	89.4 (18.2)	88.6 (7.4)	-21.6 (-40.9, -2.3)	-37.6 (-56.9, -18.3)
No 30 (14.4)	131.6 (16.9)	104.6 (7.3)	70.2 (19.2)	-42.2 (-7.6, 92.0)	-61.4 (-112.4, -10.1)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Based on the pre-specified statistical analysis plan (SAP), the efficacy of Maytox treatment for upper limb spasticity in pediatric patients is not conclusive. To demonstrate the superiority of any of the two tested doses of Maytox (8 U/kg or 16 U/kg), the tested dose of Maytox needs to be superior to Maytox 2 U/kg for both the primary efficacy endpoint (MAS) and the first secondary efficacy endpoint (PGA). The dose of Maytox 16 U/kg is superior to Maytox 2 U/kg for the primary efficacy endpoint (MAS) ($p<0.0001$) only but not for the first secondary efficacy endpoint (PGA) ($p=0.1880$). The dose of 8 U/kg is not tested as the dose of 16 U/kg is failed to show efficacy and the hierarchical test for the dose of 8 U/kg is stopped.

The clinical review team recommend using a substituted secondary endpoint of MAS responder to assess efficacy. The analysis results show that the responder rate is statistically significantly higher only in the Maytox 16 U/kg group (94.3%) compared to the Maytox 2 U/kg group (81.2%) (OR=4.15, 95% CI (1.21, 14.29)), but only numerically higher in the Maytox 8 U/kg group compared to the Maytox 2 U/kg group (OR=1.60, 95% CI (0.62, 4.10)).

Based on the substituted secondary endpoint of MAS responder analysis results, it appears that the efficacy of Maytox is demonstrated only for the dose of Maytox 16 U/kg if the substituted secondary endpoint of MAS responder is accepted and the pre-specified hierarchical testing procedures are still valid to be applied.

5.2 Collective Evidence

The dose of Maytox 16 U/kg are superior to Maytox 2 U/kg for the primary efficacy endpoint (MAS) and the substituted secondary endpoint (MAS responder), but not for the original secondary endpoint (PGA).
The efficacy is not demonstrated for both doses of Maytox (8 U/kg and 16 U/kg) based on the original SAP. However, it appears that the efficacy can be asserted based on the substituted secondary efficacy endpoint analysis result for the dose of 16 U/kg

There are two outcomes for the dose of 8 U/kg: 1) The dose of 8 U/kg is not hierarchically tested as the dose of 16 U/kg is failed, thus the efficacy of Maytox 8 U/kg is not conclusive. 2) The dose of 8 U/kg is possibly tested if the substituted secondary endpoint is accepted and used in the hierarchical testing procedure.
The dose of 8 U/kg is superior to the dose of 2 U/kg for the primary efficacy endpoint but not for the substituted secondary endpoint, thus the efficacy of Maytox 8 U/kg is not demonstrated.

5.3 Conclusions and Recommendations

From statistical point of view, there is no sufficient evidence to support the efficacy of Maytox, based on the original statistical analysis plan and endpoints. If the original first secondary endpoint is replaced by the MAS responder endpoint recommended by the clinical review team, then the dose of 16 U/kg appears to be superior to the dose of 2 U/kg. There is no sufficient evidence to support efficacy of the 8 U/kg dose.

5.4 Labeling Recommendations

No additional recommendation.

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