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:	125,274
Supplement Number:	105
Drug Name:	Dysport® (abobotulinumtoxinA)
Indication:	Lower limb spasticity in pediatric patients 2 years of age and older
Applicant:	Ipsen Biopharmaceuticals, Inc.
Dates:	Receipt Date: September 30, 2015
	PDUFA Goal Date: July 30, 2016
Review Priority:	Priority
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Keywords: analysis of covariance, clinical studies, BLA review

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1 EXECUTIVE SUMMARY

This review describes the statistical findings of Dysport for injection (abobotulinumtoxinA) as a treatment of lower limb spasticity in pediatric patients 2 years of age and older. The review confirms that Study Y-52-52120-141 in the 351(a) supplemental biologic license application provided statistically significant evidence that Dysport for injection is superior to placebo as a treatment of lower limb spasticity in pediatric patients 2 years of age and older in terms of change from Baseline to Week 4 in Modified Ashworth Scale score and Physician's Global Assessment score at Week 4.

2 INTRODUCTION

2.1 Overview

Ipsen Pharmaceutcals, Inc. (the Sponsor) sumitted a supplemental biologic license applicantion (sBLA) for Dysport for injection for the treatment of lower limb spasticity in pediatric patients 2 years of age and older. Dysport for injection is currently licensed for (1) the treatment of adults with cervical dystonia, (2) the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age, and (3) the treatment of upper limb spasticity in adults.

Table 1. Summary of the efficacy study reviewed

Study Number	Phase and Study Design	Treatment Period	Study Arm (Number of randomized and treated patients per arm)
Y-55-52120-141	Phase 3, randomized, placebo-controlled	Single treatment cycle with 12 to 28 weeks of follow-up	Placebo (79) 10 Units/kg/leg (80) 15 Units/kg/leg (80)

Source: selected from Sponsor's tabular listing of all clinical studies

The pivotal efficacy study Study Y-52-52120-141 (Study 141) for the proposed indication is summarized in Table 1. The study is reviewed in more details in Section 3.2.

2.2 Data Sources

The electronic submission of this BLA supplement is located at
\\cdsesub1\evsprod\BLA125274\0218\
\\cdsesub1\evsprod\BLA125274\0226\

The study report is located at
\\cdsesub1\evsprod\BLA125274\0218\m5\53-clin-stud-rep\535-rep-effic-safety-stud\spasticity\5351-stud-rep-contr\y5552120141\y-55-52120-141\

The datasets are located at
\\cdsesub1\evsprod\BLA125274\0218\m5\datasets\y-55-52120-141

The SAS programs are located at
\\cdsesub1\evsprod\BLA125274\0218\m5\datasets\y-55-52120-141\analysis\adam\programs\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

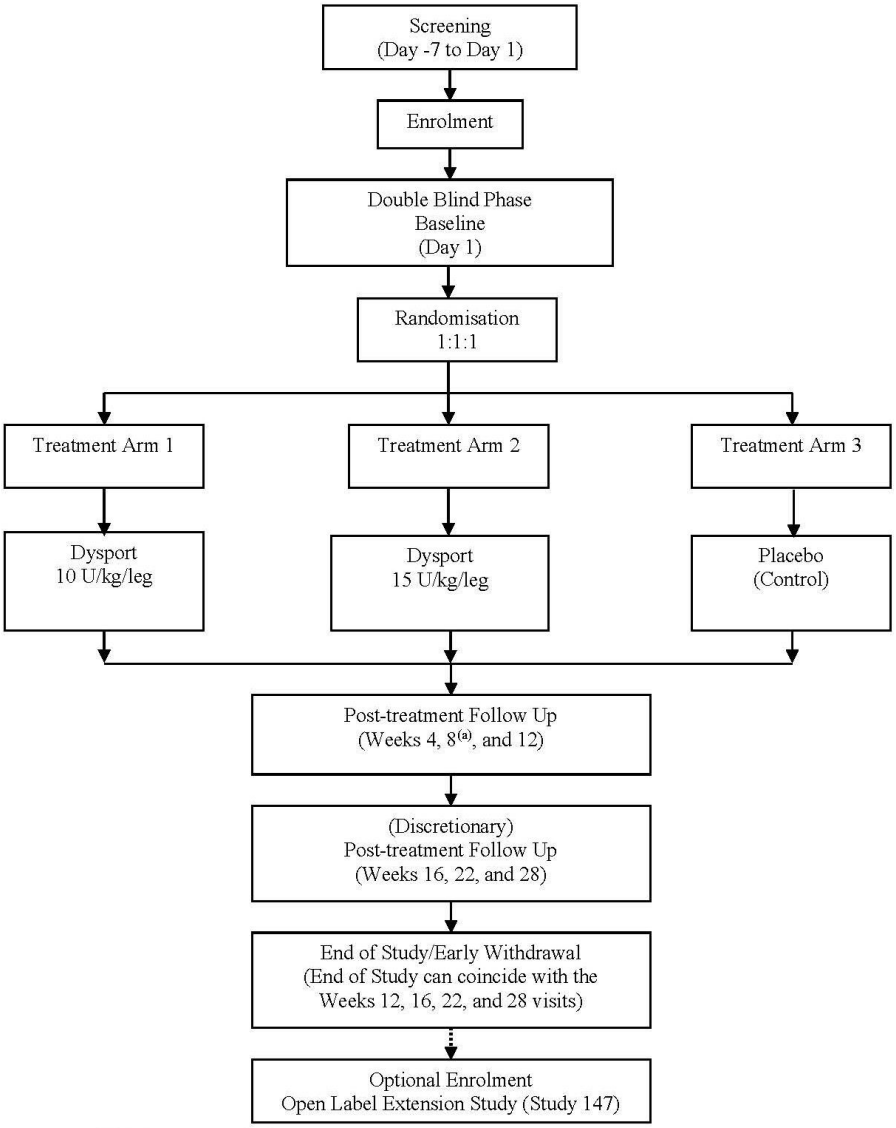
The data quality and analysis quality are adequate. The reviewer was able to perform independent review using Sponsor's submitted datasets and confirm Sponsor's efficacy analysis results.

3.2 Evaluation of Efficacy

3.2.1 Design and Endpoints

Study 141 was a double-blind, placebo-controlled, randomized, 3-arm, parallel-group, phase 3, multi-national, multi-center study to evaluate the safety and efficacy of Dysport as a treatment of lower limb spasticity in pediatric patients 2 years of age and older. Approximately 228 patients between 2 and 17 years of age were planned to be randomized in a 1:1:1 ratio to placebo, Dysport 10 Units/kg/leg (U/kg/leg), and Dysport 15 U/kg/leg. Ranomization was stratified by age range (2 to 9 years and 10 to 17 years) and Botulinum Toxin (BTX) status (naïve or non-naïve) assessed at Baseline. After randomization, Dysport or placebo was administered by intramuscular injections into the gastrocnemius soleus complex (GSC) of each affected lower limb. The total dose of Dysport was 10 U/kg or 15 U/kg for unilateral injections and 20 U/kg or 30 U/kg for bilateral injections. Following a single treatment administration, patients attended follow up visits at Week 4 and Week 12 and had telephone follow up for safety at Week 8. Patients were screened in 27 study centers in Chile, France, Mexico, Poland, Turkey, and United States. After completing the study, the patients were offered entry into an open label extension study (Study Y-55-52120-147). The design flow is presented in Figure 1.

Figure 1. Study 141 design flow



Source: Figure 1 on page 18 of Sponsor's clinical report body

The co-primary efficacy endpoints were

- Change from Baseline to Week 4 in the Modified Ashworth Scale (MAS) score in the GSC at the ankle joint of the (most) affected lower limb. The MAS is a six point scale to measure the intensity of muscle tone. The definition of the MAS score is on page 82 of the protocol:

    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 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.
3: considerable increase in muscle tone, passive movement difficult.
4: affected part(s) rigid in flexion or extension.

- Physician's Global Assessment (PGA) score at Week 4. PGA is a nine point scale:

-4: markedly worse.
-3: much worse
-2: worse
-1: slightly worse
0: no change
1: slightly improved
2: improved
3: much improved
4: markedly improved

The secondary efficacy endpoint was the Goal Attainment Sclae (GAS) score at Week 4. GAS is a functional scale. Individual goals (one to three goals) were defined for each patient by the physician, and the patient's parents where applicable, prior to treatment. The goals were ranked according to their importance to the parent(s)/child. After goal identification, the physician and/or therapist rated the level of difficulty of each goal. The following table lised the goals, importance rating scale, difficult rating scale, and goal attainment scales, as defined on pages 84-85 of the protocol:

Goals	**Rating Scale Score**
Improved endurance	
Looks better	
Improved walking pattern	
Increased walking speed	
Improved balance	
Decreased frequency of tripping	
Decreased frequency of falling	
Decreased foot pain	
Longer shoe wear	
Improved tolerance of the AFO	
Improved ease in putting on the AFO	
Other (please specify)	

Please rate the goals chosen at the baseline visit using the following scale:

-**2** = Much less than expected outcome
-**1** = Somewhat less than expected outcome
0 = Expected outcome
+**1** = Somewhat more than expected outcome
+**2** = Much more than expected outcome

Importance Rating Scale:
0 = Not at all (important)
1 = A little (important)
2 = Moderately (important)
3 = Very (important)
Difficulty Rating Scale:
0 = Not at all
1 = A little
2 = Moderately
3 = Very

The overall GAS score is based on weighted average of ratings of the goals, with weights calculated from importance rating scores and difficulty rating scores (Turner-Stokes 2009)[1].

3.2.2 Statistical Methodologies

The Sponsor defined the intent-to-treat (ITT) population as all randomized patients who recived at least one injection of study medication and had a non-missing MAS score assessed both at Baseline and at Week 4.

The primary efficacy analysis for MAS was performed on the ITT population using an analysis of covariance (ANCOVA) model, with Baseline MAS score as the covariate and the two randomization stratification factors (age range and BTX status assessed at Baseline) and center as the factors.

Because the original MAS score is a categorical variable, in order to treat it as a continuous variable and apply the ANCOVA model, derivation from the original MAS score to the MAS score analysis value is needed. The derivation is presented in Table 2.

Table 2. Derivation from the original MAS score to the MAS score analysis value

Original MAS score	Derived MAS score
0	0
1	1
1+	2
2	3
3	4
4	5

Source: table on page 12 of Sponsor's reporting analysis plan

[1] Turner-Stokes, L, 2009, Goal attainment scaling (GAS) in rehabilitation: a practical guide, Clin Rehabil, 23: 362-370.

The efficacy endpoints of PGA and GAS were analyzed on the ITT population using analysis of variance (ANOVA) models with the two randomization stratification factors (age range and BTX status assessed at Baseline) and center as the factors.

Pooling of center was planned and performed according to the following rules:

- if there is a small center in a single recruiting centre country then it is pooled with the center of another country on the basis of the geographical proximity,
- if there is only one small centre in a multiple-centre country then it is pooled with the center(s) within the same country having the closest to six actual number of randomized subjects,
- if there are two small centers in a multiple-centre country then the two small centers within the country will be pooled,
- if there are more than two small centers in a multiple-center country then apply the following two-step procedure:
    Step 1: the smallest centers are pooled until the pooled centers reach the threshold of six randomized subjects. If there are no more small centers the procedure stops. Otherwise, Step 2 applies.
    Step 2: if there is at least one remaining small center, the following approach is applied:
        - if there is one remaining small center then it is pooled with the center within the same country having the closest to six actual number of randomized subjects and the procedure stops,
        - if there are two remaining small center then the two small centers within the country are pooled and the procedure stops,
- if there are more than two remaining small centers then Step 1 is reiterated.

In order to handle the multiplicity of doses and endpoints, Dysport was planned to be tested versus placebo in the following order:

(1) Dysport 15 U/kg/leg versus placebo on the endpoint of MAS
(2) Dysport 10 U/kg/leg versus placebo on the endpoint of MAS
(3) Dysport 15 U/kg/leg versus placebo on the endpoint of PGA
(4) Dysport 10 U/kg/leg versus placebo on the endpoint of PGA

Each test was conducted at the two-sided significance level $\alpha = 0.05$.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 253 patients were screened, of which 241 (95.3%) randomized. Among the 241 randomized patients, 81 (33.6%) were randomized to the placebo group, 80 (33.2%) to the 10 U/kg/leg group, and 80 (33.2%) to the 15 U/kg/leg group.

Table 3. Study 141 patient disposition, randomized population

	Placebo N (%)	Dysport 10 U/kg/leg N (%)	Dysport 15 U/kg/leg N (%)
Randomized	81 (100.0)	80 (100.0)	80 (100.0)
Received Treatment	79 (97.5)	80 (100.0)	80 (100.0)
ITT	77 (95.1)	79 (98.8)	79 (98.8)
Completed study (follow-up ≥ Week 12 visit)	75 (92.6)	78 (97.5)	77 (96.3)
Completed study (retreated or not eligible for retreatment at Week 28 visit)	73 (90.1)	78 (97.5)	75 (93.8)
Withdrawn from study	8 (9.9)	2 (2.5)	5 (6.3)

%: percentage based on the number of patients in each treatment group randomized population; ITT: intent-to-treat; N: number of patients

Source: selected from Tables 14.1.1.2 and 14.1.2.2 on pages 3 and 89 of Sponsor's clinical study report demographic tables, figures and graphs

The patient disposition is summarized in Table 3. The ITT population sizes are 77, 79, and 79 for the placebo group, Dysport 10 U/kg/leg group, and Dysport 15 U/kg/leg group, respectively. The Sponsor reported that two patients, who were screen failures, were randomized to the placebo group by mistake and did not receive any study medication. The withdrawal percentages of the randomized population are 9.9%, 2.5%, and 6.3% for the placebo group, Dysport 10 U/kg/leg group, and Dysport 15 U/kg/leg group, respectively.

Table 4. Study 141 patient withdrawal reasons, randomized population

REASON FOR WITHDRAWALS	STATISTIC	Placebo (N=81)	Dysport 10 U/kg per leg (N=80)	Dysport 15 U/kg per leg (N=80)	Total Dysport (N=160)	All Subjects (N=241)
OVERALL @	n (%)	8 (9.9)	2 (2.5)	5 (6.3)	7 (4.4)	15 (6.2)
Does Not Meet Entry Criteria	n (%)	1 (12.5)	0	0	0	1 (6.7)
Adverse Event	n (%)	1 (12.5)	0	0	0	1 (6.7)
Protocol Violation	n (%)	0	0	0	0	0
Consent Withdrawn	n (%)	3 (37.5)	1 (50.0)	3 (60.0)	4 (57.1)	7 (46.7)
Lost To Follow-Up	n (%)	1 (12.5)	0	1 (20.0)	1 (14.3)	2 (13.3)
Other	n (%)	2 (25.0)	1 (50.0)	1 (20.0)	2 (28.6)	4 (26.7)

%: percentage based on the number of patients in each treatment group randomized population; n: number of patients

Source: selected from Table 14.1.2.4 on page 91 of Sponsor's clinical study report demographic tables, figures and graphs

The withdrawal reasons of the randomized population are summarized in Table 4. The placebo group had more withdrawals, compared to the Dysport 10 U/kg/leg and Dysport 15 U/kg/leg groups. Withdrawal of consert was the main reason for patient withdrawal.

Table 5. Study 141 patient demographic characteristics, ITT population

Parameter Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)	Total Dysport (N=158)	All Subjects (N=235)
Age, years					
n	77	79	79	158	235
Mean (SD)	5.9 (3.5)	6.0 (3.3)	5.7 (3.2)	5.9 (3.3)	5.9 (3.3)
Median (range)	5.0 (2, 17)	5.0 (2, 16)	5.0 (2, 16)	5.0 (2, 16)	5.0 (2, 17)
Age Categories, n (%)					
2 - 9 years	65 (84.4)	67 (84.8)	67 (84.8)	134 (84.8)	199 (84.7)
10 - 17 years	12 (15.6)	12 (15.2)	12 (15.2)	24 (15.2)	36 (15.3)
Sex, n (%)					
Male	48 (62.3)	45 (57.0)	48 (60.8)	93 (58.9)	141 (60.0)
Female	29 (37.7)	34 (43.0)	31 (39.2)	65 (41.1)	94 (40.0)
Race, n (%)					
Black/African American	5 (6.5)	2 (2.5)	0	2 (1.3)	7 (3.0)
Caucasian/White	55 (71.4)	57 (72.2)	60 (75.9)	117 (74.1)	172 (73.2)
American Indian/Alaskan Native	0	1 (1.3)	0	1 (0.6)	1 (0.4)
Multiple	17 (22.1)	19 (24.1)	19 (24.1)	38 (24.1)	55 (23.4)
Ethnicity, n (%)					
Hispanic/Latino	20 (26.0)	21 (26.6)	21 (26.6)	42 (26.6)	62 (26.4)
Not Hispanic/Latino	57 (74.0)	58 (73.4)	58 (73.4)	116 (73.4)	173 (73.6)
Height, cm					
n	77	78	78	156	233
Mean (SD)	114.6 (19.7)	117.1 (20.7)	111.6 (18.5)	114.4 (19.7)	114.4 (19.7)
Median (range)	109.0 (85, 167)	112.5 (88, 182)	106.0 (83, 165)	109.0 (83, 182)	109.0 (83, 182)
Weight, kg					
n	77	79	78	157	234
Mean (SD)	22.6 (11.9)	23.1 (13.4)	21.1 (10.7)	22.1 (12.1)	22.3 (12.0)
Median (range)	18.8 (11.0, 62.0)	19.0 (11.0, 77.6)	17.0 (11.0, 67.1)	18.0 (11.0, 77.6)	18.1 (11.0, 77.6)
BMI, kg/m^2					
n	77	78	78	156	233
Mean (SD)	16.2 (2.7)	15.8 (2.9)	16.1 (2.7)	15.9 (2.8)	16.0 (2.8)
Median (range)	15.5 (11.8, 27.6)	15.1 (11.5, 25.9)	15.6 (12.7, 26.5)	15.2 (11.5, 26.5)	15.5 (11.5, 27.6)
BMI Categories, n (%)					
<5th percentile (underweight)	10 (13.0)	18 (22.8)	14 (17.7)	32 (20.3)	42 (17.9)
5th percentile to <95th percentile (healthy to overweight)	61 (79.2)	58 (73.4)	57 (72.2)	115 (72.8)	176 (74.9)
≥95th percentile (obese)	6 (7.8)	2 (2.5)	7 (8.9)	9 (5.7)	15 (6.4)

Abbreviations: BMI=body mass index; ITT=intent to treat; N=number of subjects in group; n=number of subjects with data; SD=standard deviation; U=Units.
Data Source: Table 14.1.5.1, Listing 16.2.4.1 and Listing 16.2.9.2.
Note: The denominator is the number of subjects in the given column (N).

Source: Table 8 on page 49 of Sponsor's clinical study report

The patient demographic characteristics of the ITT population are summarized in Table 5. The treatment groups appeared similar in terms of age, gender and race. The ITT population was mainly White patients and it had an average age of approximately 6 years. There were more males than females in the ITT population.

Table 6. Study 141 patient baseline characteristics, ITT population

Parameter Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)	Total Dysport (N=158)	All Subjects (N=235)
BTX status, n (%)					
Naïve	41 (53.2)	40 (50.6)	41 (51.9)	81 (51.3)	122 (51.9)
Non-naïve	36 (46.8)	39 (49.4)	38 (48.1)	77 (48.7)	113 (48.1)
Tanner grading scale, n (%)	n=29	n=34	n=31	n=65	n=94
I	21 (72.4)	28 (82.4)	23 (74.2)	51 (78.5)	72 (76.6)
II	1 (3.4)	2 (5.9)	3 (9.7)	5 (7.7)	6 (6.4)
III	3 (10.3)	1 (2.9)	0	1 (1.5)	4 (4.3)
IV	1 (3.4)	1 (2.9)	0	1 (1.5)	2 (2.1)
V	1 (3.4)	0	2 (6.5)	2 (3.1)	3 (3.2)
Missing	2 (6.9)	2 (5.9)	3 (9.7)	5 (7.7)	7 (7.4)
Number of legs being treated, n (%)					
One leg injected	47 (61.0)	42 (53.2)	50 (63.3)	92 (58.2)	139 (59. 1)
Two legs injected	30 (39.0)	37 (46.8)	29 (36.7)	66 (41.8)	96 (40.9)
Neutralising BTX-A-Abs present at baseline, n (%)					
Yes	1 (1.3)	0	1 (1.3)	1 (0.6)	2 (0.9)
No	74 (96.1)	76 (96.2)	71 (89.9)	147 (93.0)	221 (94.0)
Missing[(a)]	2 (2.6)	3 (3.8)	7 (8.9)	10 (6.3)	12 (5.1)
Geographical location, n (%)					
USA	16 (20.8)	17 (21.5)	14 (17.7)	31 (19.6)	47 (20.0)
Non USA	61 (79.2)	62 (78.5)	65 (82.3)	127 (80.4)	188 (80.0)
GMFCS level, n (%)					
I	40 (51.9)	46 (58.2)	45 (57.0)	91 (57.6)	131 (55.7)
II	30 (39.0)	24 (30.4)	24 (30.4)	48 (30.4)	78 (33.2)
III	7 (9.1)	9 (11.4)	10 (12.7)	19 (12.0)	26 (11.1)
MAS score, n (%)					
2	66 (85.7)	68 (86.1)	68 (86.1)	136 (86.1)	202 (86.0)
3	10 (13.0)	11 (13.9)	11 (13.9)	22 (13.9)	32 (13.6)
4	1 (1.3)	0	0	0	1 (0.4)
Derived baseline MAS score					
Mean (SD)	3.2 (0.4)	3.1 (0.3)	3.1 (0.3)	3.1 (0.3)	3.1 (0.4)
Baseline OGS question 2 score, n (%)					
0	11 (14.3)	10 (12.7)	8 (10.1)	18 (11.4)	29 (12.3)
1	40 (51.9)	32 (40.5)	38 (48.1)	70 (44.3)	110 (46.8)
2	20 (26.0)	26 (32.9)	20 (25.3)	46 (29.1)	66 (28.1)
3	3 (3.9)	5 (6.3)	2 (2.5)	7 (4.4)	10 (4.3)
Missing	3 (3.9)	6 (7.6)	11 (13.9)	17 (10.8)	20 (8.5)

Abbreviations: BTX=botulinum toxin; BTX-A-Abs=antibodies against BTX-A; GMFCS= Gross Motor Function Classification System; ITT=intent to treat; MAS=Modified Ashworth Scale; N=number of subjects in group; n=number of subjects with data; OGS=Observational Gait Scale; SD=standard deviation; U=Units; USA=United States.

[(a)] Ten out of the 12 missing values had no assessment for binding antibody at baseline and two had positive binding at baseline but neutralising antibodies were not assessed.

Data Source: Table 14.1.5.1, Table 14.2.4.3, Listing 16.2.4.4, Listing 16.2.4.5, Listing 16.2.5.1, Listing 16.2.6.1, Listing 16.2.6.5 and Listing 16.2.9.4.

Note: The denominator is the number of subjects in the given column (N). Tanner grading scale was only collected for female subjects so the denominator is the number of female subjects in the given column (n).

Source: Table 9 on page 50 of Sponsor's clinical study report

The patient baseline characteristics of the ITT population are summarized in Table 6. The three treatment groups appeared similar in terms of BTX status, which was a randomization stratification factor. The three treatment groups also appeard to have similar MAS scores (original or derived) at Baseline.

3.2.4 Results and Conclusions

Table 7. Study 141 analysis of MAS, ANCOVA, ITT population

Endpoint Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)	Total Dysport (N=158)
MAS score at baseline				
Mean (SD)	3.2 (0.4)	3.1 (0.3)	3.1 (0.3)	3.1 (0.3)
MAS score at Week 4				
Mean (SD)	2.6 (0.9)	2.3 (0.9)	2.2 (0.8)	2.2 (0.9)
Change in MAS score from baseline to Week 4				
Mean (SD)	-0.6 (0.8)	-0.9 (0.9)	-1.0 (0.9)	-0.9 (0.9)
LS mean (95% CI)	-0.48 (-0.69, -0.27)	-0.86 (-1.07, -0.65)	-0.97 (-1.18, -0.76)	ND
Comparison to placebo				
Difference in LS mean (95% CI)	N/A	-0.38 (-0.64, -0.13)	-0.49 (-0.75, -0.23)	ND
p-value	N/A	0.0029	0.0002	ND

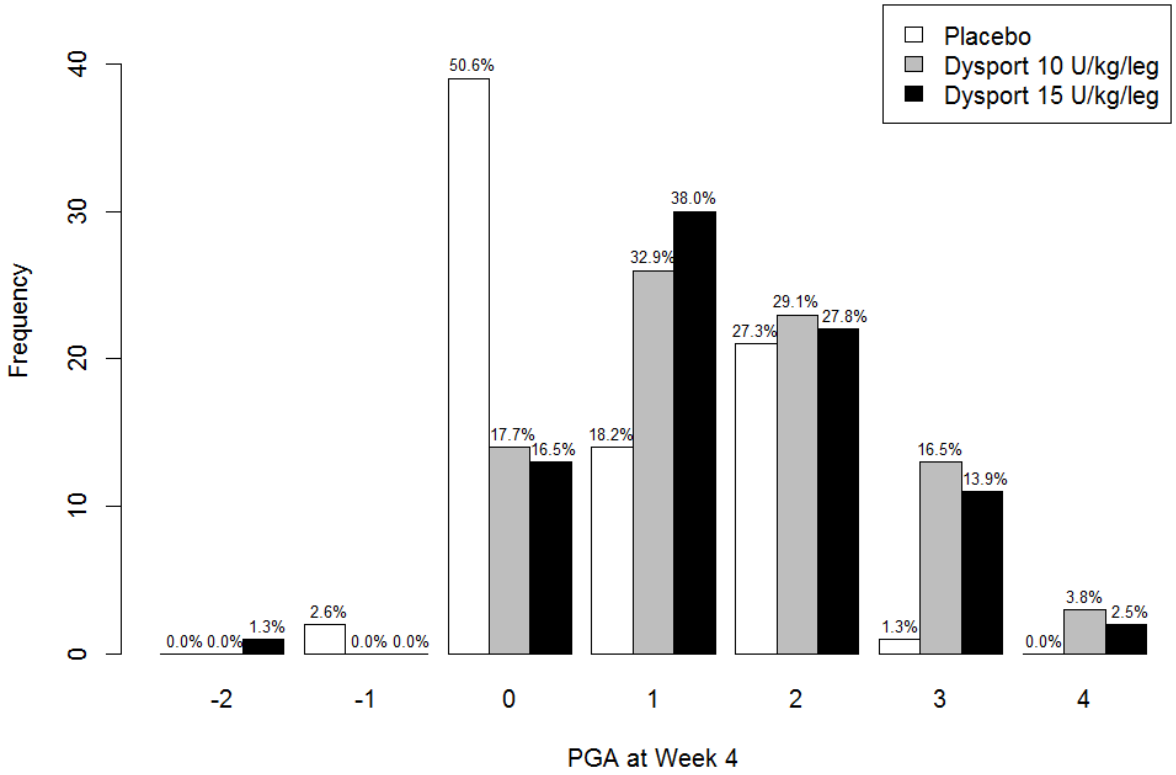
Abbreviations: CI=confidence interval; ITT=intent to treat; LS mean=least squares mean; MAS=Modified Ashworth Scale; N=number of subjects in group; N/A=not applicable; ND=not determined; SD=standard deviation; U=Units.
Data Source: Table 14.2.1.1, Table 14.2.1.2 and Listing 16.2.6.1.
Note: MAS is displayed on derived scale. LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANCOVA on the change from baseline with treatment, baseline MAS score, age range at baseline, BTX status at baseline and centre as covariates.

Source: Table 19 on page 60 of Sponsor's clinical study report

The analysis results of the endpoint of MAS are presented in Table 7. All ITT patients had MAS scores at Week 4. The MAS analysis values were derived following Sponsor's pre-specified derivation method (derivation details in Table 2). In terms of the change from Baseline to Week 4 in the MAS score, Dysport 10 U/kg/leg and Dysport 15 U/kg/lg were statistical significantly better than placebo (p-values = 0.0029 and 0.0002, respectively), with least squares Dysport-placebo differences of -0.38 point (95% CI = (-0.64, -0.13)) and -0.49 point (95% CI = (-0.75, -0.23)), respectively.

The reviewer checked normality of the residuals from the ANCOVA model and did not found violation of the normality assumption.

Figure 2. Distribution of PGA scores at Week 4



-2: worse; -1: slightly worse; 0: no change; 1: slightly improved;
2: improved; 3: much improved; 4: markedly improved.

Source: reviewer

Figure 2 illustrates the distributions of PGA scores by treatment at Week 4. The figure does not include the ratings of -4 (markedly worse) or -3 (much worse) on the PGA scale because none of the patients fell into these categories at Week 4. The firgure shows that, compared to patients in the placebo group, more patients in the Dysport groups were in the categories of "slightly improved", "improved", "much imporved", and "markedly improved" at Week 4.

Table 8. Study 141 analysis of PGA, ANOVA, ITT population

Endpoint Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)	Total Dysport (N=158)
PGA Score at Week 4				
Mean (SD)	0.7 (0.9)	1.6 (1.1)	1.4 (1.1)	1.5 (1.1)
LS mean (95% CI)	0.73 (0.46, 0.99)	1.54 (1.28, 1.81)	1.50 (1.23, 1.77)	ND
Comparison to placebo				
Difference in LS mean (95% CI)	N/A	0.82 (0.50, 1.14)	0.77 (0.45, 1.10)	ND
p-value	N/A	<0.0001	<0.0001	ND

Abbreviations: CI=confidence interval; ITT=intent to treat; LS mean=least squares mean; N=number of subjects in group; N/A=not applicable; ND=not determined; PGA=Physician's Global Assessment; SD=standard deviation; U=Units.
Data source: Table 14.2.2.1, Table 14.2.2.2 and Listing 16.2.6.2.
Note: LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BTX status at baseline and centre as covariates.

Source: Table 20 on page 61 of Sponsor's clinical study report

The analysis results of the endpoint of PGA are presented in Table 8. All ITT patients had PGA scores at Week 4. In terms of the PGA score at Week 4, Dysport 10 U/kg/leg and Dysport 15 U/kg/lg were statistical significantly better than placebo (p-values < 0.0001 for both doses), with least squares Dysport-placebo differences of 0.82 point (95% CI = (0.50, 1.14)) and 0.77 point (95% CI = (0.45, 1.10)), respectively.

Table 9. Study 141 analysis of GAS, ANOVA, ITT population

Endpoint Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)	Total Dysport (N=158)
GAS Score at Week 4	n=76	n=78	n=79	n=157
Mean (SD)	45.5 (10.4)	50.4 (10.1)	49.8 (11.1)	50.1 (10.6)
LS mean (95% CI)	46.21 (43.70, 48.72)	51.53 (49.05, 54.01)	50.86 (48.36, 53.36)	ND
Comparison to placebo				
Difference in LS mean (95% CI)	N/A	5.32 (2.31, 8.32)	4.65 (1.59, 7.71)	ND
p-value	N/A	0.0006	0.0031	ND

Abbreviations: CI=confidence interval; GAS=Goal Attainment Scale; ITT=intent to treat; LS mean=least squares mean; N=number of subjects in group; n=number of subjects with data; N/A=not applicable; ND=not determined; SD=standard deviation; U=Units.
Data source: Table 14.2.3.1, Table 14.2.3.2 and Listing 16.2.6.3.
Note: LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BTX status at baseline and centre as covariates.

Source: Table 21 on page 61 of Sponsor's clinical study report

The analysis results of the endpoint of GAS are presented in Table 9. Not all ITT patients had GAS scores at Week 4. No imputation was performed for the patients that missed the GAS scores at Week 4. In terms of the GAS score at Week 4 , Dysport 10 U/kg/leg and Dysport 15 U/kg/lg appeared statistical significantly better than placebo (nominal p-values = 0.0006 and 0.0031, respectively), with least squares Dysport-placebo differences of 5.32 points (95% CI = (2.31, 8.32)) and 4.65 points (95% CI = (1.59, 7.71)), respectively.

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Overall, there is no compelling evidence from the subgroup analyses in Section 4.1 that a specific gender, race, age, or geographic region subgroup may benefit differently from the Dysport treatment.

4.1 Gender, Race, Age, and Geographic Region

Gender

Table 10. Study 141 analysis of MAS by gender, ITT population

Gender	Change from Baseline to Week 4 in MAS score	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
Female	N	29	34	31
	Mean (SD)[a]	-0.5 (0.8)	-1.0 (1.0)	-1.1 (0.9)
Male	N	48	45	48
	Mean (SD)[a]	-0.6 (0.8)	-0.8 (0.8)	-0.9 (0.8)

ITT: intent-to-treat; MAS: Modified Ashworth Scale; N: number of patients in the ITT population; SD: standard deviation.
[a] Obtained from all changes from Baseline to Week 4 in MAS score in the gender specific ITT population.

Source: selected from Tables 14.2.13.17 on pages 2-3 of Sponsor's clinical study report body subgroup analysis submitted on December 22, 2015

Table 11. Study 141 analysis of PGA by gender, ITT population

Gender	PGA score at Week 4	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
Female	N	29	34	31
	Mean (SD)[a]	0.7 (1.0)	1.7 (1.1)	1.4 (1.0)
Male	N	48	45	48
	Mean (SD)[a]	0.8 (0.9)	1.4 (1.0)	1.4 (1.1)

ITT: intent-to-treat; N: number of patients in the ITT population; PGA: Physician's Global Assessment; SD: standard deviation.
[a] Obtained from all PGA scores at Week 4 in the gender specific ITT population.

Source: selected from Tables 14.2.14.17 on pages 10-11 of Sponsor's clinical study report body subgroup analysis submitted on December 22, 2015

For both gender groups, Dysport appeared superior to placebo in terms of mean change from Baseline to Week 4 in MAS score and mean PGA score at Week 4.

Race

Table 12. Study 141 analysis of MAS by race, ITT population

Race	Change from Baseline to Week 4 in MAS score	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
American Indian/ Alaskan Native	N	0	1	0
	Mean[a]	--	-1.0	--
Black/African American	N	5	2	0
	Mean (SD)[a]	-1.2 (1.30)	0.0 (0.00)	-- (--)
Caucasian/ White	N	55	57	60
	Mean (SD)[a]	-0.5 (0.77)	-1.0 (0.93)	-1.0 (0.86)
Multiple	N	17	19	19
	Mean (SD)[a]	-0.7 (0.79)	-0.7 (0.67)	-0.8 (0.83)

ITT: intent-to-treat; MAS: Modified Ashworth Scale; N: number of patients in the ITT population; SD: standard deviation.

[a] Obtained from all changes from Baseline to Week 4 in MAS scores in the race specific ITT population.

Source: reviewer

Table 13. Study 141 analysis of PGA by race, ITT population

Race	PGA score at Week 4	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
American Indian/ Alaskan Native	N	0	1	0
	Mean[a]	--	1.0	--
Black/African American	N	5	2	0
	Mean (SD)[a]	0.8 (0.84)	0.5 (0.71)	-- (--)
Caucasian/ White	N	55	57	60
	Mean (SD)[a]	0.8 (0.98)	1.5 (1.15)	1.6 (1.13)
Multiple	N	17	19	19
	Mean (SD)[a]	0.4 (0.80)	1.1 (0.85)	1.7 (0.87)

ITT: intent-to-treat; N: number of patients in the ITT population; PGA: Physician's Global Assessment; SD: standard deviation.

[a] Obtained from all PGA scores at Week 4 in the race specific ITT population.

Source: reviewer

For the Caucasian/White and multiple race patients, Dysport appeared superior to placebo in terms of mean change from Baseline to Week 4 in MAS score and mean PGA score at Week 4. The numbers of the American Indian/Alaskan Native and Black/African American patients are too small to draw any conclusion.

Age

Because the study population of Study 141 is pediatric patients 2 years of age and older, there is no subgroup analysis on senior patients.

Table 14. Study 141 analysis of MAS by age group, ITT population

Age Group	Change from Baseline to Week 4 in MAS score	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
2-9 years	N	65	67	67
	Mean (SD)[a]	-0.5 (0.85)	-0.8 (0.85)	-1.0 (0.85)
10-17 years	N	12	12	12
	Mean (SD)[a]	-0.8 (0.62)	-1.1 (1.00)	-0.6 (0.79)

ITT: intent-to-treat; MAS: Modified Ashworth Scale; N: number of patients in the ITT population; SD: standard deviation.

[a] Obtained from all changes from Baseline to Week 4 in MAS score in the age group specific ITT population.

Source: reviewer

Table 15. Study 141 analysis of PGA by age group, ITT population

Age group	PGA score at Week 4	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
2-9 years	N	65	67	67
	Mean (SD)[a]	0.7 (0.94)	1.6 (1.08)	1.5 (1.10)
10-17 years	N	12	12	12
	Mean (SD)[a]	0.8 (0.94)	1.4 (1.16)	1.3 (0.98)

ITT: intent-to-treat; N: number of patients in the ITT population; PGA: Physician's Global Assessment; SD: standard deviation.

[a] Obtained from all PGA scores at Week 4 in the age group specific ITT population.

Source: reviewer

For the age group of 2-9 years (about 84% of the study sample size), Dysport appeared superior to placebo in terms of mean change from Baseline to Week 4 in MAS score and mean PGA score at Week 4. For the age group of 10-17 years, Dysport 15 U/kg/leg appeared superior to placebo in terms of mean PGA score at Week 4; Dysport 15 U/kg/leg appeared worse than placebo in terms of mean change from Baseline to Week 4 in MAS score, which may be due to the small sample size of this age group.

Geographic Region

Table 16. Study 141 analysis of MAS by geographic region, ITT population

Region	Change from Baseline to Week 4 in MAS score	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
Non-US	N	61	62	65
	Mean (SD)[a]	-0.5 (0.7)	-0.9 (0.8)	-1.0 (0.9)
US	N	16	17	14
	Mean (SD)[a]	-0.7 (1.1)	-0.9 (1.2)	-0.8 (0.8)

ITT: intent-to-treat; MAS: Modified Ashworth Scale; N: number of patients in the ITT population; SD: standard deviation.

[a] Obtained from all changes from Baseline to Week 4 in MAS score in the gerographic region specific ITT population.

Source: selected from Table 14.2.13.7 on pages 446-447 of Sponsor's clinical study report body efficacy tables, figures and graphs

Table 17. Study 141 analysis of PGA by geographic region, ITT population

Region	PGA score at Week 4	Placebo	Dysport 10 U/kg/leg	Dysport 15 U/kg/leg
Non-US	N	61	62	65
	Mean (SD)[a]	0.8 (0.9)	1.5 (0.9)	1.3 (1.0)
US	N	16	17	14
	Mean (SD)[a]	0.7 (1.0)	1.9 (1.5)	2.0 (1.2)

ITT: intent-to-treat; N: number of patients in the ITT population; PGA: Physician's Global Assessment; SD: standard deviation.

[a] Obtained from all PGA scores at Week 4 in the gerographic region specific ITT population.

Source: selected from Table 14.2.14.7 on pages 482-483 of Sponsor's clinical study report body efficacy tables, figures and graphs

For patients from both geographic regions, Dysport appeared superior to placebo in terms of mean change from Baseline to Week 4 in MAS score and mean PGA score at Week 4.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues were identified.

5.2 Collective Evidence

Study 141 provided statistically significant evidence that Dysport is efficacious as a treatment of lower limb spasticity in pediatric patients 2 years of age and older: Dysport for injection is statistically significantly better than placebo in terms of change from Baseline to Week 4 in Modified Ashworth Scale score and Physician's Global Assessment score at Week 4.

5.3 Conclusions and Recommendations

Based on the statistical evidences from Study 141, the reviewer concludes that Dysport is superior to placebo as a treatment of lower limb spasticity in pediatric patients 2 years of age and older.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIANGMIN ZHANG
07/05/2016

KUN JIN
07/05/2016
I concur with the review.

HSIEN MING J HUNG
07/05/2016