Cross-Discipline Team Leader Review

Date	7/26/2016
From	Gerald D. Podskalny, DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 125274 (S105)
Applicant	Ipsen Biopharm Ltd
Date of Submission	09/30/2015
PDUFA Goal Date	07/30/2016
Proprietary Name / Established (USAN) names	Dysport (abobotulinumtoxinA)
Dosage forms / Strength	Sterile 300 Unit and 500 Unit vials for injection
Proposed Indication(s)	1. Pediatric Lower Limb Spasticity
Recommended:	***Approval***

1. Introduction

Dysport (abobotulinumtoxinA) was first approved on April 29, 2009, for the treatment of cervical dystonia, and for 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. The Agency approved efficacy supplement 102 that added the indication of treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in the elbow, wrist, and finger flexors on July 15, 2015.

Ipsen Biopharm Ltd Dysport submitted BLA supplement, (BLA/STN 125274, S-105) on September 30, 2015, that proposes to add an indication for the treatment of lower limb spasticity in pediatric (b) (4) patients 2 years of age and older. Dysport and other botulinum toxin type A products have been used "off-label" for the treatment of children with spasticity (upper or lower limb) with spasticity due to several causes since the late 1980's. There was evidence of substantial use in the pediatric population to treat spasticity with reports of serious adverse events, some with fatal outcomes that led the FDA to issue postmarketing requirements (PMR) and postmarketing commitments (PMC). The Agency issued PMRs and PMCs in 2009 for Ipsen to study the safe and effective use of Dysport for the treatment of spasticity in the children (under FDAAA). The other sponsors of botulinum toxins approved for use in the US received the same requirements to study the treatment of spasticity in children with their products.

2. Background

This submission is a pediatric efficacy supplement for the treatment of pediatric lower limb spasticity un children ages 2 to 17 years. The supplement is also intended to fulfill PMC 2564-6 (goal date July 9, 2016) and FDAAA Safety PMR 2564-5. The status of the PMC (submitted (September 4, 2015) to study the use of Dysport for the treatment of lower limb in children with spasticity is officially listed as (b) (4)

Postmarketing Commitment (Set 2564)

6. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with lower extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

    PMC Establishment Date, 04/29/2009
    Final Protocol Due Date 11/30/2009
    Final Report Due Date 09/30/2013

Postmarketing Requirement (Set 2564)

5. Submit safety data assessing distant spread of toxin effects after multiple administrations of Dysport (abobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years) (approximately half upper, and half lower extremity spasticity). In addition, submit data assessing the effects of Dysport (abobotulinumtoxinA) on blood glucose and alkaline phosphatase as a marker of bone metabolism. These safety data could come from open-label extensions of the clinical studies specified under #5-8 below, from separate long-term open-label safety studies, or from a long-term controlled safety and efficacy study. The doses evaluated must be at least as high as those shown effective in studies specified under #5-8 below, or those commonly used to treat spasticity.

    Final Protocol Due Date 07/31/2010
    Final Report Due Date 05/31/2015

The Agency granted Orphan Status for Dysport (and not on its formulation) on October 20, 1999, for “the treatment of dynamic muscle contractures in pediatric cerebral palsy patients”.

The definition of Cerebral Palsy (CP) has evolved since 1999. In July 2004, the International Workshop on Definition and Classification of Cerebral Palsy was held to update the definition of CP to include the cognitive, behavioral and sensory deficits that are part of the diseases that children classified as having CP experience. The Executive Committee published their report on the Definition and Classification of Cerebral Palsy in April 2006 (Rosenbaum, 2007). The committee stated “They underlined that CP is not an etiologic diagnosis, but a clinical descriptive term” ("A report: the definition and classification of cerebral palsy April 2006," 2007).

Proposed Updated definition of CP ("A report: the definition and classification of cerebral palsy April 2006," 2007)

Cerebral palsy (CP) describes a group[1] of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to no progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavioral; by epilepsy, and by secondary musculoskeletal problems.

In addition, Dysport is approved for the treatment of adults for upper limb spasticity (b) (4) . Botulinum toxins including Dysport are used (off label) for the treatment of overactive bladder in adults and children.

In the Filing Review Letter (December 11, 2015), the FDA notified the sponsor their application would be reviewed in a Standard Review cycle and requested the sponsor (b) (4) provide labeling (b) (4) the indication to include pediatric lower limb spasticity in all pediatric patients. On June 2, 2016, the sponsor opted to (b) (4)

(b) (4)

However, there are oral medications approved to treat spasticity caused by upper motor neuron disorders (such as cerebral palsy and spinal cord injury). Dosing information in the Diazepam label describes treatment in children older than 6 months. The Lioresal (intrathecal baclofen injection) label describes its use in patients as young as age 4 years provided the patient has sufficient body mass to accommodate the implantable pump used for chronic infusion. Lioresal tablets states the "Safety and effectiveness in pediatric patients below the age of 12 years have not been established." Dantrolene is approved for use in children down to age 5 years. Surgical treatments for spasticity such as dorsal rhizotomy usually performed in older children but provide long lasting relief from spasticity.

(b) (4)

Dysport has been used off label to treat spasticity in children for the treatment of spasticity in the US for years. Providers are generally reimbursed for the treatment of spasticity with a botulinum toxin products in the US (Neurology, 2010). It is approved for the treatment of pediatric lower limb spasticity in the UK and Australia; the dosing recommendations are similar to those in the proposed US label.

[1] 'a group' -There is general agreement that CP is a heterogeneous condition in terms of aetiology as well as in types and severity of impairments. Several groupings are possible and warranted to serve different purposes. These groupings may show overlap. Therefore, the singular form 'CP' is used (as opposed to 'cerebral palsies')

Dysport is approved in the US to treat upper limb spasticity in adults. Although the spasticity studies in adults were conducted in stroke patients, the labeled indication is for adults with upper limb spasticity. There is no restriction in the indication limiting treatment to adults with spasticity caused by stroke. Based on the mechanism of action at the presynaptic neuromuscular junction, the cause or location in the CNS of the upper motor neuron lesion causing spasticity, is not relevant to the effect of Dysport on the treatment of spasticity.

There is a narrow, if any, unmet medical need in pediatric patients ages 2-4 years who may benefit from botulinum toxin product. These patients are usually able to obtain treatment with an approved botulinum toxin product. Health insurers usually cover the cost related to the treatment of pediatric spasticity. (b) (4)

Reviewer	**Review Discipline/Division**
Susanne Goldstein, MD	Clinical Review/Division of Neurology Products
Xiangmin Zhang, Ph.D. (Statistical Reviewer:) Kun Jin, Ph.D., (Team Leader) Hsien Ming Hung, Ph.D., (Director)	Statistics Review/Division of Biometrics I
Justine Harris, RPh (Primary Reviewer) Danielle Harris, PharmD, BCPS (Team Leader)	Labeling Review/Division of Medication Error Prevention and Analysis (DMEPA)
Sharon W. Williams, MSN, BSN, RN (Reviewer) Shawna Hutchins, MPH, BSN, RN (Team Leader) LaShawn Griffiths, MSHS-PH, BSN, RN (Associate Director)	Patient Labeling Review/Division of Medical Policy Programs
Dhara Shah, PharmD, Regulatory (Review Officer) Mathilda Fienkeng, PharmD, (Team Leader)	Package Insert (PI) and Medication Guide Review/Office of Prescription Drug Promotion (OPDP)

3. CMC/Device

The clinical trials supporting this sBLA were conducted using the approved Dysport. The supplement did not included changes to the approved drug product.

4. Nonclinical Pharmacology/Toxicology

The supplement included changes to section 8.4 of the full prescribing information regarding the juvenile toxicology study results. The nonclinical review team has provided comment and edits to the sponsor's proposed labeling changes in section 8.4.

5. Clinical Pharmacology/Biopharmaceutics

The submission did not include new Clinical Pharmacology information.

6. Clinical Microbiology

The submission did not include new Microbiology information.

7. Clinical/Statistical- Efficacy

The primary evidence of effectiveness is provided by the results of study Y-55-52120-141. The remaining supportive studies listed in Table 1, did not include assessments of spasticity (e.g., Modified Ashworth Scale (MAS) or Tardieu scale) among the endpoints for these studies. However, some supportive information can be obtained from the global measures assessed in these studies. The global measure used in the supportive studies was a 4 point scale which is different from the 7 to 9 point Likert scale typically used to assess global response that support the clinical meaningfulness of changes in the MAS. Study 141 used a 9 point Likert scale, the Physician's Global Assessment (PGA).

Table 1 Summary of the Double Blind Placebo Controlled Studies of Dysport for the Treatment of Pediatric Lower Limb Spasticity

Study ID	Subjects (N)	Design	Population	Dose Groups	Muscles Injected[a]	Study Duration	Primary endpoint(s)
Y-55-52120-141 Module 5.3.5.1 (Pivotal)	241	Multicenter, randomized, DB, PC	Dynamic equinus foot deformity due to CP	10 U/kg/leg i.e. 10 U/kg for unilateral treatment; 20 U/kg for bilateral treatment 15 U/kg/leg i.e. 15 U/kg for unilateral treatment;30 U/kg for bilateral treatment Placebo	Distal muscles: gastrocnemius, soleus (unilateral or bilateral injections)	12 to 28 weeks	Co-primary change in MAS from baseline to week 4 after injection and the Physician's Global assessment.
Y-97-52120-040 Module 5.3.5.1 (Supportive)	126	Multicenter, randomized, DB, PC	Dynamic equinus foot deformity due to CP	10 U/kg 20 U/kg 30 U/kg Placebo	Distal muscles: gastrocnemius (bilateral injections)	16 to 36 weeks	Electrogoniometry (dynamic component, active gastrocnemius length) at week 4, and the duration of improvement in dynamic component The Ashworth scale was not administered.
Y-97-52120-701 Module 5.3.5.1 (Supportive)	52	Multicenter, randomized, DB, PC	Dynamic equinus foot deformity due to CP	30 U/kg Placebo	Distal muscles: gastrocnemius (bilateral injections)	16 to 36 weeks	Gross Motor Function Measure (GMFM) overall score at week 4. The Ashworth scale was not administered

Y-97-52120-033 Module 5.3.5.4 [b]	40	Single center, randomized, DB, PC	Dynamic equinus foot deformity due to CP	11 to 32 U/kg Placebo	Distal/proximal muscles: gastrocnemius, ± soleus, ± hamstrings (unilateral or bilateral injections)	2 to 24 weeks	The study was stopped prematurely after 40 of the planned 100 patients had been treated. Primary endpoint was the Leeds Functional Mobility Questionnaire The Ashworth scale was not administered. The sponsor's completed
A-94-52120-094 Module 5.3.5.1	61	Multicenter, randomized, DB, PC	Adductor muscle spasticity due to CP	30 U/kg Placebo	Proximal muscles: adductor, medial hamstring (bilateral injections)	12 weeks	Studied proximal lower limb not plantar flexors and the primary endpoint was The target criterion is the result of the assessment of the joint status according to the "Neutral-Null" method. Abduction/adduction in the hip joint defines the range of motion of the joint for abduction/ adduction The Ashworth scale was administered to assess the effect n spasticity for the medial Hamstrings and the Adductor muscles only. .

CDTL Comments

Study 094
Of the studies listed as supportive, only one study, 094 included an assessment of spasticity using the Ashworth Scale but the Ashworth Scale was used to assess proximal (medial hamstring and thigh adductor muscles) leg muscles instead of the plantar flexors which is the focus of this application. The change in MAS score was not the primary endpoint. The primary endpoint was the change in range of passive motion (ROM) for hip abduction. After database lock and a blinded review of the study data, the sponsor changed the primary endpoint. In addition, the data from this study was reanalyzed after unblinding and a second completed study report was written and submitted by the sponsor. The study results from the reanalyzed study report is unreliable because there is no way to determine how many analyses were performed after unblinding of the data to arrive at the final result presented in reanalyzed study report.

Study 033 was terminated prematurely due to poor subject recruitment (40 subjects were recruited from a planned target of 100 subjects. The sponsor did not select a primary endpoint for this study.

Table 2 Summary of the Open Label Studies of Dysport for the Treatment of Paediatric Lower Limb Spasticity

Study ID (Type)	Subjects (N)	Design	Population	Dose Groups	Muscles Injected[a]	Number of Treatment	Study Duration
Y-55-52120-147 Module 5.3.5.2 (Extension to pivotal Study 141)	216	Multicenter OL	Dynamic equinus foot deformity due to CP	Treatment 1 10 U/kg for unilateral treatment; 20 U/kg for bilateral treatment Treatments 2 to 4 Up to 15 U/kg for unilateral treatment; Up to 30 U/kg for bilateral treatment	Treatment 1 Distal/proximal muscles: gastrocnemius, soleus ± hamstrings Treatments 2 to 4 Distal/proximal muscles: gastrocnemius, soleus ± hamstrings and other lower limb muscles (unilateral or bilateral injections)	Up to 4	52 to 56 weeks (from entry in Study 141)
Y-97-52120-702 Module 5.3.5.2 (Supportive)[c]	214	Multicenter, OL (assessor blinded)	CP lower limb spasticity	30 U/kg at 12 month intervals 30 U/kg at 4 month intervals	Distal muscles: gastrocnemius (bilateral injections)	3 to 7	28 months (112 weeks)

A-38-52120-052 Module 5.3.5.2	15	Multicenter, OL	CP equinus foot deformity	10 U/kg if unilateral treatment and 20 U/kg if bilateral treatment	Distal muscles: gastrocnemius (unilateral or bilateral injections)	Up to 2	32 weeks
A-38-52120-711 Module 5.3.5.2	25	Multicenter, OL	CP equinus foot deformity	10 U/kg if unilateral treatment and 20 U/kg if bilateral treatment	Distal muscles: gastrocnemius (unilateral or bilateral injections)	1	16 weeks
A-94-52120-062 Module 5.3.5.2 [d]	15	Multicenter	Dynamic equinus foot deformity due to CP	Low dose: 15 U/kg if unilateral treatment; 20 U/kg if bilateral treatment Standard dose: 25 U/kg if unilateral treatment; 30 U/kg if bilateral treatment	Distal muscles: gastrocnemius + soleus if unilateral injections; only gastrocnemius if bilateral injections	1	36 weeks

Study 147 permitted the concomitant treatment of pediatric upper limb spasticity but only the pediatric lower limb dose was used in analysis in this analysis. This was the follow-up study to the pivotal efficacy study in this application, study 141.

Study 062 was terminated prematurely due to poor subject recruitment (15 subjects were recruited from a planned target of 280 subjects). While this study was blinded only with respect to treatment with low or high dose Dysport. All subjects received active treatment, therefore; it is included in the open label study category.

Efficacy Resets

Study Y-55-52120-141
Xiangmin Zhang, Ph.D. was the primary statistical reviewer for this BLA supplement.

Study Y-55-52120-141 (referred to as study 141 in this review) was a Phase 3, multicenter, double blind, prospective, randomized, placebo controlled study assessing the efficacy and safety of Dysport used in the treatment of lower limb spasticity in children with dynamic equinus foot deformity due to cerebral palsy (CP).

Enrollment was planned for approximately 228 patients to take part in this study. Two hundred fifty three patients were screened and 241 subjects were randomized (1:1:1) into the three treatment groups (81 in the placebo group, 80 in the Dysport 10 U/kg treatment group and 80 in the Dysport 15 U/kg treatment group). Two subjects, who were screening failures, were randomized to the placebo group in error.

Study Populations

The Randomized Population-was defined as all randomized subjects, (i.e. all subjects allocated to a treatment group at random).

The Safety Population-was defined as all randomized subjects who received at least one injection of study treatment.

The Intent To Treat (ITT) population-included all randomized subjects who received at least one injection of study treatment and who had a MAS score in the Gastrocnemius-Soleus Complex (GSC) assessed both at baseline and at Week 4.

The Per Protocol (PP) population-was defined as all subjects in the ITT population who did not have major protocol violations between baseline and Week 4, inclusive.

The primary population for the efficacy analyses was the ITT population.

Table 3: Study 141 Analysis Populations:

Populations	N
Randomized	241
ITT	235
Per Protocol	224
Safety	239

The first patient enrolled on July 5, 2011, and the last patient completed the last study visit on June 25, 2014.

There were 27 sites that enrolled at least one patient. The number of site per country and the number of patients enrolled in each country are shown in table 4

Table 4: Study 141 Number of Sites and Enrolled Patients in The ITT Population By Country

	CHL	FRA	MEX	POL	TUR	USA	TOTAL
# of Sites	3	1	3	4	8	8	27
# of Patients (ITT)	15	2	39	71	61	47	235

Source CDTL Table

Patient Disposition

Table 5: Study 141 Patient Disposition

	Actual Treatment for Period 01										
	Dysport 10 U/kg		Dysport 15 U/kg		Dysport 20 U/kg		Dysport 30 U/kg		Placebo		All
	N	PctN	N	PctN	N	PctN	N	PctN	N	PctN	N
Standardized Disposition Term											
ADVERSE EVENT									1	0.03	1

	Actual Treatment for Period 01										
	Dysport 10 U/kg		Dysport 15 U/kg		Dysport 20 U/kg		Dysport 30 U/kg		Placebo		All
	N	PctN	N	PctN	N	PctN	N	PctN	N	PctN	N
LOST TO FOLLOW-UP							1	0.03	1	0.03	2
OTHER	1	0.03					1	0.03	1	0.03	3
WITHDRAWAL BY SUBJECT			1	0.03	1	0.03	2	0.06	3	0.09	7
PROTOCOL VIOLATION											0
RANDOMIZED	43	1.23	50	1.43	37	1.06	30	0.86	79	2.26	239
COMPLETED	43	1.23	49	1.40	36	1.03	27	0.77	74	2.12	229

Source CDTL Table

Relatively few patients withdrew early from study 141. Patient disposition is discussed in greater detail in the Safety section of this review.

Design of Study 141

Patients were randomized into one of three treatment groups in a ratio of 1:1:1:

- Dysport 10 U/kg,
- Dysport15 U/kg,
- Placebo

Enrollment was stratified according to:

- Age range (2 to9 years and 10 to 17 years) and
- Botulinum toxin (BTX) naïve or non-naïve status as assessed at baseline.

Dysport or placebo was administered by intramuscular injections into the GSC of each affected lower limb.

Eligible patients received treatment on Day 1 and they were followed for a minimum of 12 weeks to a maximum of 28 weeks. All patients who had had at least 12 weeks of follow up were considered to have completed the study.

In-person follow up visits occurred at Week 4 and Week 12 after treatment. A telephone visit for safety follow up was made to the parents/guardians of the patient at Week 8. Additional visits were permitted at:

- Week 16 (for subjects who did not require retreatment at Week 12),
- Week 22 (for subjects who did not require retreatment at Week 16) and
- Week 28 (for subjects who did not require retreatment at Week 22).

Patients requiring retreatment at Week 12, 16, 22or 28 completed the study and were offered continued treatment in an open label extension study (study 147). Patients who did not require retreatment at the Week 28 visit were offered entry into the Observational Phase of the open

label extension study which continued until they required retreatment or until they had been followed up for at least 1-year.

Eligibility Criteria

Key Inclusion Criteria

- Were from 2 to 17 years of age, inclusive
- Had a diagnosis of CP as defined by Rosenbaum et al
- Ambulatory with spastic hemiparesis, paraparesis, dipalrgia or tetraparesis characterized by an equinus foot positioning during the stance phase of the gait.
- Had a MAS score ≥2 at the ankle joint of the (most) affected lower limb to be injected.
- Botulinum toxin naïve subjects or subjects having received their last Botulinum Toxin (BTX) treatment of any type more than 6 months prior to study entry for any condition.
- Pre-study physiotherapy must have begun at least 4 weeks prior to study start and was to continue during the study at the same pre-study frequency and intensity (as well as maintaining the usual level of physical activity until the end of the study) up to at least the Week 12 visit. casting/orthoses in the same way as before entry into the study until the end of the Week 12 visit

Key Exclusion Criteria

- Resistant to BTX treatment of any type
- Non-ambulatory
- Major limitation in the passive range of motion at the ankle
- Severe athetoid or dystonic movements in the targeted lower limb(s).
- Current need for surgery or previous surgery for spasticity of the GSC and/or hamstring muscles (and tendons) in the most affected leg to be injected.
- Previous injection of alcohol and/or phenol into the GSC and/or hamstrings in the most affected leg to be injected.
- Ongoing treatment with intrathecal baclofen or previous/planned rhizotomy

Prohibited Treatments

Concomitant treatment with anticholinergic drugs dantrolene, tizanidine, gabaergic, opioid or other anti-spasticity agents, including baclofen and benzodiazepines was permitted, if the dosage had been stable for the 4 weeks prior to study treatment and was expected to remain at this stable dose throughout the study.

Treatment with any type of botulinum toxin into any site of the body other than the lower limb (during the study) was not permitted

No new casts and/or orthoses were to be initiated until Week 12, pretreatment use of casts and/or orthoses initiated prior to the start of the double blind study, were continued at the same frequency and intensity until at least Week 12. No physiotherapy was to be initiated less than 4 weeks prior to study entry or during the course of study up to the Week 12 visit

Treatment Blind
Each treatment pack of study medication contained two identical vials of Dysport and/or placebo and an instruction leaflet specific to the corresponding pack. The materials (syringes, needles tubing etc.) required for each injection were supplied. Before administration, each vial was reconstituted with preservative free saline (sodium chloride for injection (0.9%)).

The study treatment was prepared by an" Independent Reconstitutor" (not involved in other study related activities) according to instructions in the protocol taking into account the subject's body weight and number of limbs being treated (one leg or two legs). The maximum dose injected in subjects was not to exceed 1000 U or 30 U/kg, whichever was lower.

Dosing
The dose was either 10 U/kg or 15 U/kg for unilateral lower limb injections, or 20 U/kg or 30 U/kg for bilateral injections. The 2.0 mL volume of injection per lower limb was split between gastrocnemius and soleus muscles according to a ratio of 3:2. The two sites in upper quadrants of the calf allowed injection into the gastrocnemius only but the sites in lower quadrants allowed dose injection into both gastrocnemius and soleus by deeper penetration of the muscle bulk (figure 1).

Table 6: Injection Volume in Gastrocnemius-Soleus Complex per Leg without Hamstring Injections

Muscle	Upper Quadrant (# of sites)	Lower Quadrant (# of sites)	Total
Gastrocnemius	0.4 ml (x2)	0.2 ml (x2)	1.2 ml
Soleus	N/A	0.4 ml (x2)	0.8 ml
Total Per leg			2.0 ml

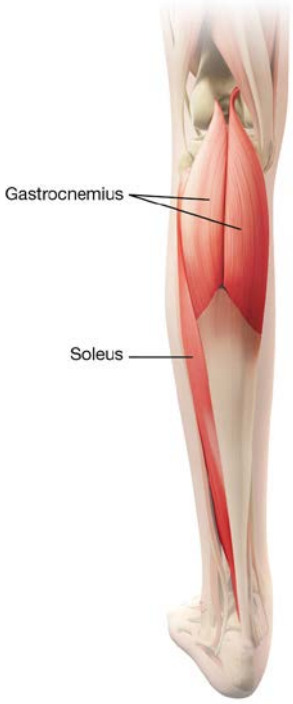
Abbreviations: N/A=not applicable
Source: Modified Ipsen Table

A bracketing strategy of weight and rounding up or down the dose to the closest 50 U of Dysport was used to maintain consistency among all study sites and avoid gross overdosing or under dosing of subjects.

Electrical stimulation (ES) or ultrasound was used to localize the targeted injection sites. Complimentary techniques such as electromyography in addition to ES, or ultrasound were permitted under the protocol.

Each participating center maintained their usual practice for injecting subjects and pain management strategies (e.g. use of topical anesthesia, or oral, intranasal or rectal medication).

Figure 1: Study 141 Location of Injections



Ipsen: Figure

Efficacy Endpoints

Modified Ashworth Scale (MAS)
The investigator graded muscle tone on a six point scale from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension). An independent investigator (different the one who assessed the PGA) performed the assessment of the MAS.

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.

Modified Ashworth Scale Scoring

Original MAS score	Modified MAS score
0	0
1	1

1+	2
2	3
3	4
4	5

Physician's Global Assessment (PGA) of the Treatment Response

Global assessment of treatment response was assessed by asking the Investigator the following question: 'how would you rate the response to treatment in the subject's lower limb(s) since the last injection?' Answers were made on a 9 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, +4: markedly improved). A different investigator from the one who assessed the MAS performed the PGA.

Goal Attainment Scale (GAS)

The GAS was used to measure progress towards individual therapy goals. Between one and three individual goals (from a list of pre-selected goals relevant for this study population) were defined for each subject by the physician, and the child's parents (caregiver) where applicable, prior to treatment (Table 7). The goals were ranked according to their importance to the parent(s)/child. The goals were set under the principle of SMART – **S**pecific, **M**easurable, **A**ttainable, **M**easurable and **T**imely.

Table 7: Goal Attainment Scale (GAS)

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

After goal identification, the physician and/or therapist rated the level of difficulty of each chosen goal. The overall GAS score was based on weighted average of ratings of the goals,

with weights calculated from importance rating scores and difficulty rating scores (Turner-Stokes 2009). The three most commonly chosen goals in the study were 'improved walking pattern', 'improved balance' and 'decreased frequency of falling'.

The change in mean GAS score at Week 4 was analyzed using an ANOVA model controlling for the randomization stratification factors (age range and BTX status as being naïve or non-naïve status as assessed at baseline) and the center, all as fixed effects. There was no imputation for missing Week 4 GAS scores.

CDTL Comment
The Goals the GAS are not anchored in function or parameters that help ensure consistent rating. What may "Look Better" to one rater my not to another rater. The rating categories of "Somewhat less or more than expected" are vague and had similar problems with interpretability.

The Tertiary Endpoints:

Tardieu Scale (TS)
The TS scale is a more complex assessment tool for spasticity that evaluates the velocity of passive stretch and the angle at which spasticity is encounter within the available passive (slow stretch) range of motion.

Velocity of stretch

- SLOW = V1: As slow as possible (slower than the rate of natural drop of the limb segment under gravity).
- FAST = Either V2 or V3.
    - V2: Speed of the limb segment falling under gravity.
    - V3: As fast as possible (faster than the rate of natural drop of the limb segment under gravity).

Grading

X = Spasticity Angle (threshold)
Angle of arrest at slow speed (XV1) minus angle of catch at fast speed (XV3).

Y = Spasticity grade (gain)

Grade 0:	No resistance throughout passive movement.
Grade 1:	Slight resistance throughout passive movement.
Grade 2:	Clear catch at precise angle, interrupting passive movement, followed by release.
Grade 3:	Fatigable clonus (less than 10 sec when maintaining pressure) occurring at a precise angle, followed by release.
Grade 4:	Unfatigable clonus (more than 10 seconds when maintaining pressure) occurring at a precise angle.

Catch without release: is graded 0 if XV1=XV3; 'unratable' spasticity otherwise, catch with 'minimal' release: is graded 2 if XV3 is consistent and consistently less than XV1.

Angle 0 = position of minimal stretch of the tested muscle. For Grades 0 and 1, spasticity angle X = 0 by definition.

The Observational Gait Scale (OGS)
It is a modified version of the Physicians Rating Scale. The OGS was analyzed centrally using the 2D motion analysis video recorded at site and reviewed by a committee of independent clinical experts, who were completely blinded for the timing (baseline versus post-treatment with) of the video recording and identity for each subject.

Analysis Plan
The efficacy analyses was conducted on the ITT population. The sponsor used a gatekeeping procedure of the FDA submission described in the Reporting and Analysis Plan (RAP), protocol version and date: version 8.0 – 25 July 2013 (incorporating amendment 4). The US RAP treated the MAS and PGA to function as co-primary endpoints. However, the sponsor did not include the secondary or tertiary endpoints in a single hierarchy with the co-primary endpoints, therefore; there was no method in place to control the type I error for multiple comparisons of the secondary and tertiary endpoints.

Primary Efficacy Endpoints

- Mean change from baseline to Week 4 in the MAS score in the GSC at the ankle joint of the most affected lower limb. The analysis plan for the U.S. combined the change in MAS and the PGA at Week 4 to function as co-primary endpoints.
- 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.
- The analysis of the PGA used analysis of variance (ANOVA) models with the two randomization stratification factors (age range and BTX status assessed at Baseline) and center as the factors.

Secondary efficacy endpoints

- Mean Physician's Global Assessment (PGA) score at Week 4. (Non-U.S. Analysis Plan)
- Mean GAS score at Week 4. The analysis of the GAS used analysis of variance (ANOVA) models with the two randomization stratification factors (age range and BTX status assessed at Baseline) and center as the factors.

Tertiary efficacy endpoints

- Mean change from baseline to Week 12 in the MAS score at the ankle joint of the most affected lower limb.
- Proportion of subjects with at least one grade reduction in MAS score from baseline to Week 4 (and to Week 12) at the ankle joint of the(most affected lower limb.
- Mean PGA score at Week 12.

- Mean GAS score at Week 12.
- Mean change from baseline to Week 4 (and to Week 12) in the angle of catch (X_{V3}) at fast speed, spasticity angle (X) and spasticity grade (Y) derived from the Tardieu Scale (TS) at the ankle joint of the most affected lower limb.
- Mean change from baseline to Week 4 (and Week 12) in the Observational Gait Scale (OGS) total score.
- Proportion of subjects with at least one grade improvement from baseline to Week 4 (and to Week 12) in the "initial foot contact" subsection of the OGS as assessed by video 2-dimensional (2D) motion analysis (OGS responders).
- Mean change from baseline to Week 4 (and Week 12) in lower limb pain (FPS).
- Mean change from baseline to Week 12 in the PedsQL score.

If relevant, the tertiary endpoints above were also assessed at Week 16, Week 22, and Week 28.

Pooling Strategy

Small centers were pooled within the same country according to the size of the other centers within the same country.

Gatekeeping Procedure

In order to control the family-wise type I error rate, a 4-step hierarchical testing procedure was applied whereby a p-value lower than 0.05 had to be attained at each step in order to proceed to the following step. Otherwise the procedure was stopped. The sequence for testing Dysport versus placebo was as follows:

- Step 1: Dysport 15 U/kg versus placebo on the primary efficacy endpoint.
- Step 2: Dysport 15 U/kg versus placebo on the first secondary efficacy endpoint.
- Step 3: Dysport 10 U/kg versus placebo on the primary efficacy endpoint.
- Step 4: Dysport 10 U/kg versus placebo on the first secondary efficacy endpoint.

The superiority of Dysport 15 U/kg to placebo was demonstrated if the two p-values associated with the tests performed at Steps 1 and 2 were lower than 0.05. Similarly, the superiority of Dysport 10 U/kg to placebo was demonstrated if the two p-values associated with the tests performed at Steps 3 and 4 were lower than 0.05. Steps 1 and 3 only were used to demonstrate the superiority of Dysport in the non-USA regions.

In the event the hierarchical testing procedure was stopped at any step before Step 4, the testing(s) planned in the next step(s) were performed, in order to characterize the full clinical effect, but no formal statistical conclusion would be drawn.

In addition, the second secondary efficacy endpoint was analyzed to compare each Dysport dose to placebo.

Demographic and Baseline Disease Characteristics

Table 8: Demographic Characteristics, by Treatment Group (Dose per Leg) – 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.
Source: Ipsen

Table 9: Baseline Characteristics, by Treatment Group (Dose per Leg) – 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.

Source: Ipsen

The baseline patient characteristics (Table 8) show that there were substantially fewer patients in the upper older age group (10 to 17 years old). This is not unexpected considering that patients in the younger age group would be learning to walk and efforts to obtain functional ambulation would be focused on younger patients. The ability to ambulate would have been decided earlier for patients in the 10 to 17 year age group. Patients unable to ambulate independently by age 10 would have adapted to function at a wheelchair level. There were more male patients enrolled in the study compared to females, 60% versus 40%, respectively. The study population was predominately (73%) Caucasian.

Patients with similar baseline MAS scores (Table 9) were evenly distributed across the treatment arms. Patients naïve versus non-naive to treatment with a botulinum toxin were balanced across treatment arms in the study.

Efficacy Results

Dr. Zhang independently assessed the primary analysis for the primary endpoints which was the same as the sponsor's analysis, therefore; the sponsor's tables are presented in the primary statistical review and in this review. The results showed that patients treated with Dysport had a statistically significant improvement on the (change from baseline to Week 4) on the MAS (Table 10) in the most affected leg, and the PGA (table 11) showed that patients treated with Dysport compared to the group that received placebo.

Primary Endpoints

Table 10: Modified Ashworth Scale Score in the (Most) Affected Leg, Change from Baseline at Week 4, by Treatment Group (Dose per Leg) - 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.
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, Botulinum Toxin status at baseline and center as covariates.

Table 11: Physician's Global Assessment of Treatment Response at Week 4, by Treatment Group (Dose per Leg) - 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.
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 center as covariates.

Secondary Endpoint

Table 12: Goal Attainment Scale Total Score at Week 4, by Treatment Group (Dose per Leg) - 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.
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 center as covariates.

The analysis of the GAS involved a complex system of goal selection, ranking and weighting of the goals. The list of goals that were used to select individual goals for each patient were poorly defined and the meaning of what constitutes "Improved Walking Pattern", Improved Balance and "Decreased Frequency of Falling is unclear. For example, Decreased Frequency of Falling is difficult to interpret because parents/caregivers were not asked to keep a diary or count of falls before and after treatment with study medication.

Generally, the analysis of the GAS has been the proportion of responders in each treatment group compared to the placebo group. The sponsor's analysis of the proportion of responders achieving their selected goal(s) revealed a trend (Table 13) for the high dose group (15 U/kg) that but it was not significant at a nominal alpha of less than 0.05 (p=0.0602).

Table 13: The Proportion of Patients Who Reached Their Primary Goal.

DYSPORT (Y-55-52120-141) Page

Table 14.2.6.5: Goal Attainment Scale (Responders, by Dose per Leg – Overall and by Pooled Centre)
ITT Population

STATISTIC	Placebo (N=77)	Dysport 10 U/kg per leg (N=79)	Dysport 15 U/kg per leg (N=79)
Proportion whose primary goal reached expected outcome or higher at any time during the study (%)	47 / 76 (61.8)	62 / 79 (78.5)	60 / 79 (75.9)
Comparison with Placebo:			
Odds ratio		2.2	1.9
95% CI		(1.1, 4.6)	(1.0, 3.9)
p-value		0.0255	0.0602

Tertiary Endpoints

Table 14: Modified Ashworth Scale Score in the (Most) Affected Leg, Change from Baseline at All Timepoints (except Week 4), by Treatment Group (Dose per Leg) ITT Population

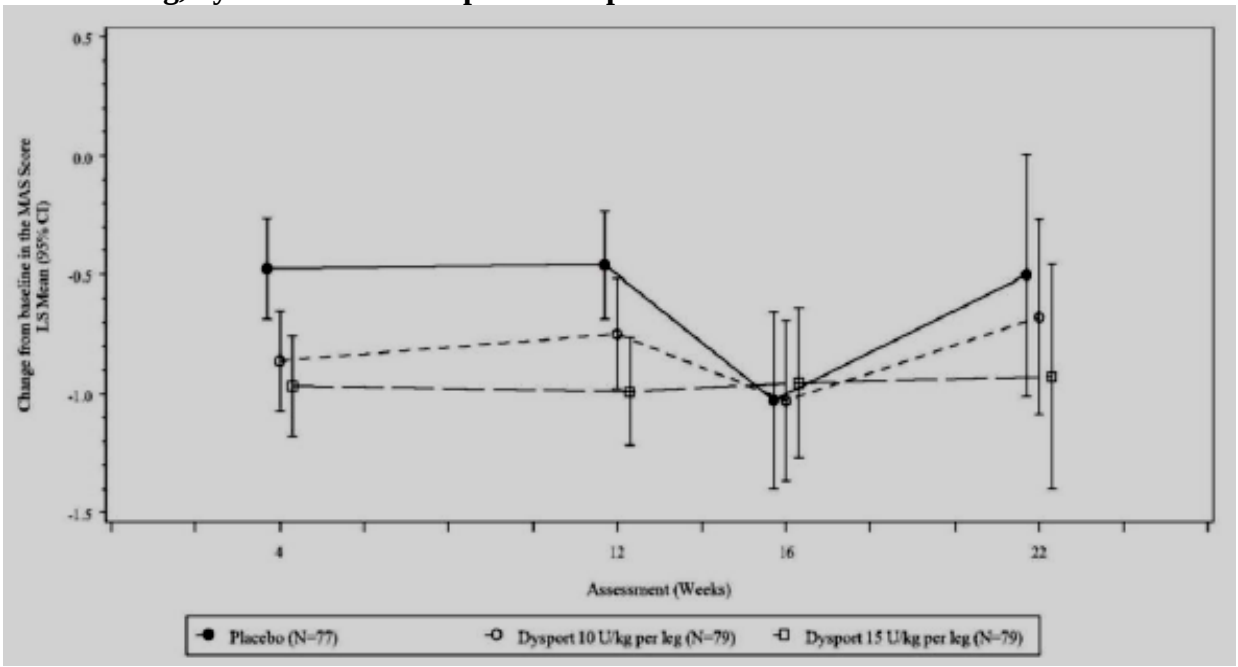
Visit Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)
Week 12	n=70	n=69	n=74
Mean change (SD)	-0.5 (0.8)	-0.7 (0.8)	-1.1 (0.9)
LS mean change (95% CI)	-0.5 (-0.7, -0.2)	-0.8 (-1.0, -0.5)	-1.0 (-1.2, -0.8)
LS mean change vs placebo (95% CI)	N/A	-0.3 (-0.6, -0.0)	-0.5 (-0.8, -0.3)
p-value	N/A	0.0401	0.0002
Week 16	n=30	n=42	n=47
Mean change (SD)	-0.8 (0.7)	-1.0 (0.8)	-0.8 (0.9)
LS mean change (95% CI)	-1.0 (-1.4, -0.7)	-1.0 (-1.4, -0.7)	-1.0 (-1.3, -0.6)
LS mean change vs placebo (95% CI)	N/A	0.0 (-0.4, 0.4)	0.1 (-0.3, 0.5)
Week 22	n=18	n=31	n=30
Mean change (SD)	-0.7 (0.9)	-0.5 (0.5)	-0.9 (1.0)
LS mean change (95% CI)	-0.5 (-1.0, 0.0)	-0.7 (-1.1, -0.3)	-0.9 (-1.4, -0.5)
LS mean change vs placebo (95% CI)	N/A	-0.2 (-0.7, 0.4)	-0.4 (-1.0, 0.1)
Week 28[(a)]	n=3	n=19	n=14
Mean change (SD)	-0.7 (0.6)	-0.7 (0.7)	-0.8 (0.8)

Abbreviations: CI=confidence interval; 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; SD=standard deviation; U=Units; vs=versus.

[(a)] ANOVA not performed due to the low number of subjects. Data

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 center as covariates.

Figure 2: Change from Baseline in the Modified Ashworth Scale Score in the (Most) Affected Leg, by Treatment Group - ITT Population



The change in the MAS for the most affected leg remained nominally significant at Week 12 (Table 14 and Figure 2) for both Dysport doses compared to placebo.

Table 15: Modified Ashworth Scale Score Responders in the (Most) Affected Leg (One Grade Improvement), by Treatment Group (Dose per Leg) ITT Population

Visit Statistic	**Placebo (N=77)**	**Dysport 10 U/kg/leg (N=79)**	**Dysport 15 U/kg/leg (N79)**
Week 4	n=77	n=79	n=79
Responders (%)	35 (45.5)	48 (60.8)	54 (68.4)
Odds ratio vs placebo (95% CI)	N/A	1.9 (1.0, 3.6)	2.7 (1.4, 5.2)
p-value	N/A	0.0562	0.0038
Week 12	n=70	n=69	n=74
Responders (%)	29 (41.4)	38 (55.1)	51 (68.9)
Odds ratio vs placebo (95% CI)	N/A	1.7 (0.9, 3.3)	3.1 (1.6, 6.2)
p-value	N/A	0.1334	0.0012
Week 16	n=30	n=42	n=47
Responders (%)	20 (66.7)	32 (76.2)	27 (57.4)
Odds ratio vs placebo (95% CI)	N/A	1.6 (0.5, 4.5)	0.6 (0.2, 1.6)
Week 22	n=18	n=31	n=30
Responders (%)	11 (61.1)	17 (54.8)	17 (56.7)
Odds ratio vs placebo (95% CI)	N/A	0.8 (0.2, 2.9)	0.8 (0.2, 2.9)
Week 28	n=3	n=19	n=14
Responders (%)	2 (66.7)	12 (63.2)	8 (57.1)

Abbreviations: CI=confidence interval; ITT=intent to treat; N=number of subjects in group; n=number of subjects with data; N/A=not applicable; U=Units; vs=versus. Data

Note: For a given post baseline visit and treatment group, the denominator is the number of subjects in the given treatment group assessed both at baseline and at the given post baseline visit. The proportion is the number of subjects with ≥1 grade reduction at the visit / number of subjects with a MAS score at the visit. The odds ratio, it's 95% CI and p-value were calculated from a logistic regression with treatment, baseline MAS score, age range and BTX status at baseline as covariates.

Source: Ipsen

The proportion of patients who improved by 1 full MAS point from baseline to Week 4 (Table 15) was nominally significant for the Dysport high dose group compared to the proportion of responders in the placebo group. There was a trend favoring a higher portion of responders in the Dysport low dose group compared to placebo.

Table 16: 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: FDA Statistical Review

Table 17: 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: FDA Statistical Review

For the age group of 2-9 years, Dysport appeared superior to placebo in terms of mean change from baseline to Week 4 on the MAS score, and the mean PGA score at Week 4. There were too few patients in 10-17 year old age group to show statistically superiority for the effect of Dysport compared to placebo, however; both of the Dysport treated groups showed improvement on the MAS compared to placebo.

Dr. Zhang noted there were no significant differences in the change in MAS scores or PGA scores in men compared to women. The comparison of the effects of race on the study outcomes was unrevealing because study population was mostly (73%) Caucasian.

Table 18: 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: Ipsen

Table 19: 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: Ipsen

The sponsor evaluated the effect of region (U.S. sites versus non-U.S. sites) on the change in MAS at Week 4, and the PGA at Week 4 Tables 18 and 19). Dr. Zhang concurred that region had no significant effect on the primary endpoints.

Sensitivity Analyses to Explore the Effects of Missing Data

For registration in the US:

- The effect of missing values on the change in MAS at Week 4 used a Baseline Observation Carried Forward (BOCF) approach for imputation of the missing (Table 20).

Table 20: Study 141 Sensitivity Analysis for Change in MAS Using BOCF for Missing Values For The Week 4 Visit-ITT Population

DYSPORT (Y-55-52120-141) Page 1 of 1

Table 14.2.1.5: Modified Ashworth Scale in (Most) Affected Leg (Analysis of Covariance of Change from Baseline at Week 4, by Dose per Leg) – Sensitivity Analysis

All Randomised Subjects Who Received Study Treatment

STATISTIC	Placebo (N=79)	Dysport 10 U/kg per leg (N=80)	Dysport 15 U/kg per leg (N=80)
n	79	80	80
LS Mean (SE)	-0.49 (0.11)	-0.86 (0.11)	-0.95 (0.11)
95% CI of LS Mean	(-0.70, -0.28)	(-1.07, -0.65)	(-1.16, -0.74)
Dysport dose compared to Placebo			
Difference (Dysport dose - Placebo) in LS Means (95% CI)		-0.37 (-0.62, -0.12)	-0.46 (-0.72, -0.21)
p-value		0.0035	0.0004
Baseline MAS score effect p-value		0.2298	
Age range at baseline effect p-value		0.4068	
BTX status at baseline effect p-value		0.7401	
Centre effect p-value		<0.0001	
Treatment by centre interaction p-value [1]		0.2211	

Source: Data listing 16.2.6.1 Analysis dataset: ADEFF

Note: Any subject with a missing assessment for the MAS at Week 4 has had their result imputed with the assessment for the MAS at baseline.
n= number of subjects taken into account for the analysis.
LS Mean = least squares mean, SE = standard error of LS Mean, CI = confidence interval.
LS Means for each treatment group and treatment comparisons, as well as the p-values are obtained from an analysis of covariance on the change from baseline with treatment, baseline MAS score, age range at baseline, BTX status at baseline and centre as covariates.
MAS is displayed on derived scale.
[1]: The treatment by centre interaction p-value is obtained from a repeat of the model above, with the treatment by centre interaction term added (sensitivity analysis). The treatment by centre interaction will be considered to be statistically significant if the associated p-value for the interaction term is <0.1

Program: Ipsen_Ltd Y_55_52120_141\Final Run\TLF\t14-2-1-5.sas (13OCT2014 13:26); Analysis dataset run: 13OCT2014 9:15

Source: Ipsen

The first sensitivity analysis (#1) for any missing assessment on the PGA at Week 4 visit imputed the "markedly worse" (Table 21). The second approach (sensitivity analysis #2) imputed any missing assessment on the PGA at Week 4 visit for a subject in a Dysport group using "markedly worse" and any missing assessment on the PGA at Week 4 visit with "markedly improved" (most conservative approach) (Table 22). The results for the sponsor's sensitivity analyses did not change the statistical conclusion for the high dose Dysport group

but the results for the low dose group was no longer significant for the change in MAS, and on the PGA for either method of imputation.

Table 21: Study 141 Sensitivity Analysis PGA at Week 4 Visit with "Markedly Worse" Imputed for Missing Week 4 Values – ITT Population

DYSPORT (Y-55-52120-141) Page 1 of 1

Table 14.2.2.4: Physician's Global Assessment of Treatment Response (Analysis of Variance of Visit Results at Week 4, by Dose per Leg) – Sensitivity Analysis 1
All Randomised Subjects Who Received Study Treatment

STATISTIC	Placebo (N=79)	Dysport 10 U/kg per leg (N=80)	Dysport 15 U/kg per leg (N=80)
n	79	80	80
LS Mean (SE)	0.68 (0.15)	1.56 (0.15)	1.41 (0.15)
95% CI of LS Mean	(0.38, 0.99)	(1.26, 1.86)	(1.10, 1.71)
Dysport dose compared to Placebo			
Difference (Dysport dose - Placebo) in LS Means (95% CI)		0.87 (0.51, 1.24)	0.72 (0.36, 1.09)
p-value		<0.0001	0.0001
Age range at baseline effect p-value		0.8577	
BTX status at baseline effect p-value		0.7168	
Centre effect p-value		0.0061	
Treatment by centre interaction p-value [1]		0.3338	

Source: Data listing 16.2.6.2 Analysis dataset: ADEFF
Note: Any subject with a missing assessment for the PGA at Week 4 has had their result imputed with the assessment 'Markedly worse' (-4).
n= number of subjects taken into account for the analysis.
LS Mean = least squares mean, SE = standard error of LS Mean, CI = confidence interval.
LS Means for each treatment group and treatment comparisons, as well as the p-values are obtained from an analysis of variance on the visit value with treatment, age range at baseline, BTX status at baseline and centre as covariates.
[1]: The treatment by centre interaction p-value is obtained from a repeat of the model above, with the treatment by centre interaction term added (sensitivity analysis). The treatment by centre interaction will be considered to be statistically significant if the associated p-value for the interaction term is <0.1
Program: Ipsen_Ltd Y_55_52120_141\Final Run\TLF\t14-2-2-4.sas (13OCT2014 13:34); Analysis dataset run: 13OCT2014 9:15

Table 22: Study 141 Sensitivity Analysis PGA at Week 4 Visit with Markedly Worse Imputed for Missing Week 4 Values in the Dysport Groups and Markedly Improved for Missing Values in The Placebo Group

DYSPORT (Y-55-52120-141) Page 1 of 1

Table 14.2.2.6: Physician's Global Assessment of Treatment Response (Analysis of Variance of Visit Results at Week 4, by Dose per Leg) – Sensitivity Analysis 2
All Randomised Subjects Who Received Study Treatment

STATISTIC	Placebo (N=79)	Dysport 10 U/kg per leg (N=80)	Dysport 15 U/kg per leg (N=80)
n	79	80	80
LS Mean (SE)	0.80 (0.15)	1.57 (0.15)	1.45 (0.15)
95% CI of LS Mean	(0.51, 1.10)	(1.27, 1.86)	(1.15, 1.75)
Dysport dose compared to Placebo			
Difference (Dysport dose - Placebo) in LS Means (95% CI)		0.76 (0.41, 1.12)	0.65 (0.29, 1.01)
p-value		<0.0001	0.0005
Age range at baseline effect p-value		0.6869	
BTX status at baseline effect p-value		0.2802	
Centre effect p-value		0.0153	
Treatment by centre interaction p-value [1]		0.2016	

Source: Data listing 16.2.6.2 Analysis dataset: ADEFF
Note: Any subject in a Dysport treatment group with a missing assessment for the PGA at Week 4 has had their result imputed with the assessment 'Markedly worse' (-4).
Any subject in the Placebo treatment group with a missing assessment for the PGA at Week 4 has had their result imputed with the assessment 'Markedly improved' (4).
n= number of subjects taken into account for the analysis.
LS Mean = least squares mean, SE = standard error of LS Mean, CI = confidence interval.
LS Means for each treatment group and treatment comparisons, as well as the p-values are obtained from an analysis of variance on the visit value with treatment, age range at baseline, BTX status at baseline and centre as covariates.
[1]: The treatment by centre interaction p-value is obtained from a repeat of the model above, with the treatment by centre interaction term added (sensitivity analysis). The treatment by centre interaction will be considered to be statistically significant if the associated p-value for the interaction term is <0.1
Program: Ipsen_Ltd Y_55_52120_141\Final Run\TLF\t14-2-2-6.sas (13OCT2014 13:34); Analysis dataset run: 13OCT2014 9:15

CDTL Comment

The results of study 141 show that Dysport is effective for the treatment of lower limb spasticity (Gastrocnemius and Soleus muscles) based on the change in MAS from baseline to Week 4 with the clinical meaningfulness of the MAS change supported by the PGA at Week 4. The version of the GAS used in study 141 is ambiguous and the clinical meaning of the scale is unknown. For this reason, (b) (4) In addition Dr, Zhang notes that the sponsor's gatekeeping procedure did not include the results for the GAS.

(b) (4)

Study Y-97-52120-040

Study Y-97-52120-040 was a double blind, randomized, placebo controlled, dose ranging study to compare the efficacy and safety of Dysport (10 units/kg, 20 units/kg, and 30 units/kg) with placebo in patients with bilateral pediatric dynamic equinus spasticity associated with cerebral palsy.

Patients were randomized (1:1:1:1) to one four treatment arms, Dysport 10 units/kg, 20 units/kg, and 30 units/kg or placebo. Patients received 1 mL of study drug into the

gastrocnemius muscle of each leg that was divided equally at two sites (0.5 mL/site). The total study medication volume was 2 mL; and the maximum total body dose was 750 U (375 U per leg) for subjects with a body weight of 25 kg, and 900 U (450 U per leg) for subjects with a body weight of 30 kg.

The study was conducted in six centers in the UK, 1 in Ireland (aka Eire), and 5 centers in Poland. The first patient enrolled on August 6, 1997, and the last patient completed the last study visit on February 23, 2000.

The study recruited 126 patients. Enrolled patients were:

- Between 2-9 years old,
- Weighed between 10-25 kg,
- Ambulatory,
- Had a diagnosis of diplegic cerebral palsy,
- Had a dynamic component of spasticity of >1.5% in at least one leg, and the potential to benefit from administration of DYSPORT to the gastrocnemius muscles of both legs.

All patients were assessed prior to treatment, and at weeks 4, 8 and 16 post-treatment.

Primary Endpoint

The primary efficacy variables were:

- The decrease in dynamic component of spasticity compared with baseline (Magnitude of Response),
- The duration of time over which this decrease was observed (Duration of response)
- The change in active gastrocnemius muscle length compared to baseline using Electrogoniometry.

Dynamic Component Of Spasticity

The sponsor defined the dynamic component of spasticity as, the muscle lengths expressed as a percentage of the normal muscle length with the leg in the anatomical position, with the dynamic component is calculated by subtracting active muscle length from passive muscle length. The primary analysis time-point was week 4 post-treatment.

Electrogoniometry was performed using the technique described by Eames et al (Eames, Baker, & Cosgrove, 1997) originally performed using manual goniometry. The maximum gastrocnemius length was measured at rest with the knee in maximum possible extension (passive length) for each patient. Patients were asked to walk up and down a 10 m walkway (or a shorter distance if the patient was unable to walk 10m) during which, the maximum active length was recorded using electrogoniometry. The measurements of gastrocnemius muscle length were normalized and expressed the length as a percentage of length of the muscle in anatomical position (0˚ knee extension and ankle dorsiflexion). The assessment for this study used flexible electrogoniometers supplied by Penny and Giles Biometrics Limited in the UK. Custom software developed for this study controlled the data acquisition system, calculated muscle length and stored both the raw data and the calculated maximum muscle lengths in a database. The validation status of this device and software are unknown. Based

on the results of a PubMed search, the technique described by Eames et al, does not appear to be a widely accepted or widely used method for assessing spasticity.

Duration of Response
The duration of response was defined as the proportion of treated legs at all five post-treatment assessments that demonstrated a better dynamic component than at baseline. Missing values were treated as being no better than at baseline.

Secondary Endpoints

- Electrogoniometry (dynamic component, active gastrocnemius length) at weeks 8 and 16
- Electrogoniometry (passive gastrocnemius length and passive dorsiflexion)
- Gross Motor Function Measure (GMFM)
- Subjective functional assessment of gait
- Overall (Global) efficacy assessment

Analysis Plan

Electrogoniometry and GMFM data were analyzed using analysis of covariance "with center, strata, and baseline scores included in the model as appropriate".

The duration of response was defined as the proportion of treated legs at all five post-treatment assessments that demonstrated a better dynamic component than at baseline. Missing values were treated as being no better than at baseline. The duration of improvement in dynamic component and subjective functional assessments were analyzed using logistic regression with center, strata, and baseline scores included in the model as appropriate.

Global efficacy assessments were analyzed using the Cochran Mantel Haenszel test. Missing data was imputed using the last observation carried forward (LOCF).

There was no prespecified method to control for the experiment-wise Type I error including testing of the two components of the primary endpoint.

Analysis Plan Amendments
Two changes were made to the prospective Analysis Plan after code breaking had occurred. First, the intention to summarize and analyses percentage changes in electrogoniometric data did not anticipate the effect of very small baseline values, for which even modest changes appeared large. Consequently, the wide range of percentage changes was difficult to interpret, and it was considered more appropriate to summarize and analyze the absolute changes from baseline.

Second, for analysis demonstrating a significant difference between placebo and at least one active treatment group, the sponsor added a quadratic trend analysis in addition to the linear trend analysis.

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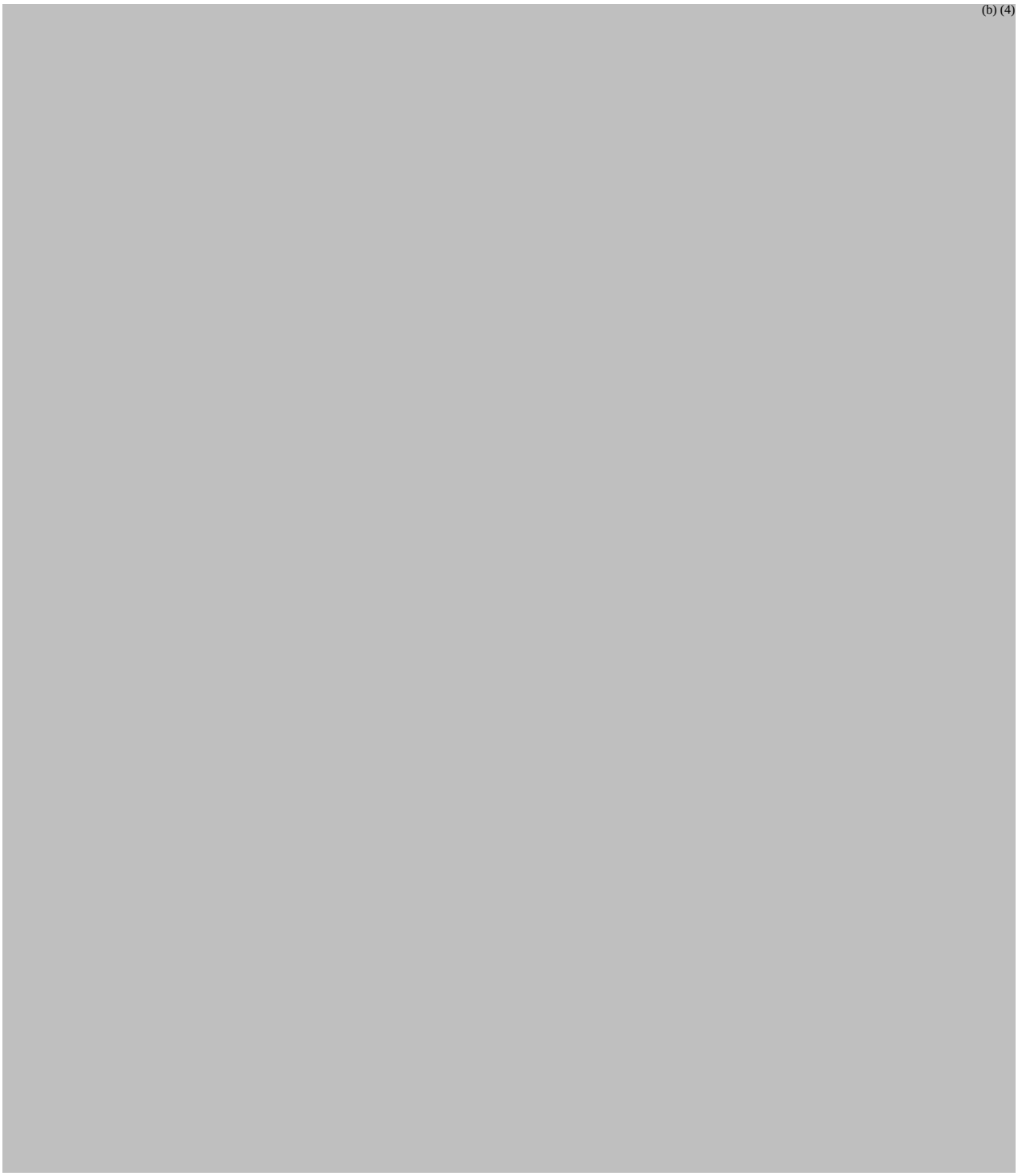

Study Y-97-52120-701
Study Y-97-52120-701 was a double-blind, prospective, randomized, placebo-controlled study to assess the efficacy and safety of Dysport(30 units/kg) in the treatment of pediatric dynamic equinus spasticity associated with cerebral palsy.

In this prospective, double-blind study, eligible patients were randomized after the completion of baseline assessments to receive Dysport (30 units/kg) or placebo. Patients returned for assessment 4, 8 and 16 weeks post-treatment. Patients considered to have ongoing benefit at the final scheduled visit (week 16) could continue in the study up to 36 weeks post-treatment.

Study Populations

The study enrolled 52 patients in total

- All patients population (APP); N=52 all randomized patients
- All patients treated (APT) population; N=26 Dysport and 26 placebo)
- Per-protocol (PP) population; N 33 patients total, 15 Dysport and 18 placebo

Enrolled patients patients were:

- Between 2-7 years old
- Ambulatory
- Had a diagnosis of diplegic cerebral palsy with no evidence of fixed contracture (able to achieve 10˚ passive ankle dorsiflexion in both legs)
- The potential to benefit from the injection of Dysport to the gastrocnemius muscle

Patients were excluded if:

- They had previously had surgery to the affected limbs or if there was a need for surgery within the next 6 months
- If multi-level injections were required
- If the patient had significant foot deformity
- If they had botulinum toxin treatment within the previous 9 months
- Had previous phenol treatment for lower limb spasticity, or known hypersensitivity to botulinum toxin.
- Had received an investigational new drug in the 30 days prior to entry
- Were receiving aminoglycoside antibiotics or spectinomycin
- Had a generalized disorder of muscle activity (e.g. myasthenia gravis)

Dosing

Dysport 30 units/kg was administered by intramuscular injection to two sites (0.5 ml/site) in the gastrocnemius of each leg.

A single administration of study medication was given, followed by assessment for up to 36 weeks post-treatment.

Primary Endpoint

Gross Motor Function Measure (GMFM) overall score at week 4 with or without walking aids or orthoses.

Secondary Endpoints

- GMFM overall score at weeks 8 and 16
- GMFM goal total score at weeks 4, 8, and 16
- Leeds Videographic Gait Assessment at weeks 4 and 16

- Leeds Functional Mobility Questionnaire (FMQ) at weeks 4 and 16
- Subjective functional assessments of gait at weeks 4, 8, and 16

Analysis Populations

The analysis plan identified three patient populations that would be considered:

All Patients Population: Comprised all patients recruited to the study.

All Patients Treated (APT) Population: Comprised all patients randomized to the study who received some study medication. This population has been used for all efficacy and safety summaries and analyses.

Per-protocol (PP) Population: Comprised all patients, in the APT population, who were not major protocol violators. All efficacy summaries and analyses were performed for this population.

Analysis Plan

Analyses were performed at week 4, 8 and 16 after treatment. GMFM scores were analyzed using an analysis of covariance (ANCOVA). For all other efficacy variables the analysis was performed using logistic regression. Center, strata, and baseline scores were included in the model as appropriate. Adverse event incidence was compared using a Chi-Square or Fisher's Exact test. All missing data was imputed using LOCF.

(b) (4)

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Study Y-97-52120-033
Study Y-97-52120-033 was a prospective, placebo-controlled, randomized, double blind, parallel group study to determine the efficacy and safety of Dysport for the treatment of lower limb muscle spasticity in patients with cerebral palsy.

Eligible patients were randomly allocated to receive a single flexible dose treatment with Dysport or placebo by intramuscular injection to the gastrocnemius, soleus and/or hamstring muscles of one or both legs. Follow-up assessments were performed at 2, 6, 12 and 24 weeks after treatment to assess efficacy and safety.

The original recruitment target was 100, but recruitment was stopped after 40 patients received treatment. All patients were included in the analysis. The study recruited patients (2-16 years) with dynamic equinus spasticity associated with cerebral palsy, without evidence of fixed contractures, and with no previous botulinum toxin treatment.

Doses were patient dependent and were higher for diplegics (range 18-32 Units/kg) than for hemiplegics (11- 25 Units/kg).

The study report stated," No primary efficacy variable was prospectively defined for this study." All of the endpoints were listed as "Secondary endpoints" with no identified gate-keeping procedure or other prespecified method of to control Type I error for multiple assessment (at 6 and 12 weeks after injection) or for multiple endpoints. All of the enrolled patients completed the trial.

Safety data from study 033 was not included in the ISS datasets.

CDTL Comment:

(b) (4)

Study A-94-52120-094

Design
Study A-94-52120-094 was a multicenter, double-blind, prospective, randomized, placebo controlled Phase 2 study to assess the efficacy and safety of Dysport for the treatment of lower limb adductor muscle spasticity in children with cerebral palsy.

There were15 sites in German and Austrian centers specialized in muscle disease and/or pediatrics. Ten centers recruited patients into the study. Studied opened on January, 18, 1999 (first patient visit) and the final visit for the last patient occurred on March 26, 2001.

The study protocol specified up to 4 visits, at weeks -2, 0, 4 and 12. A single follow up visit occurred 4 weeks after treatment and the end of study visit was at week 12 after injection.

Review of the Data

The data were reviewed prior to unblinding during a blind review meeting held on June 23, 2003. The data were unblinded on October 20, 2003 after confirmation by (b) (4) (from a CRO- (b) (4) statistician) that the database had been closed on September 30, 2003. After unblinding, a statistical analysis was carried out by Dr. (b) (4), based on a blind review report dated September 30, 2003, which included a statistical analysis plan. Following the internal audit of this report performed on March 22 to March 3, 2005, it was concluded that:

- "The statistical analyses were carried-out using very unusual methods completely different from the procedures described in the protocol"
- "The report did not comply with the recommendations of the ICH E3 guideline on Structure and Content of Clinical Study Reports "
- "The data should be analyzed as described in the protocol, according to a formal statistical analysis plan"
- "A new study report should be provided."

The sponsor hired new CRO in November 2006 and a second version of the protocol and statistical analysis plan (RAP) was created in June 2007, six years after the study closed. The redefined analysis plan led to the sponsor creating a second final study report submitted in the sBLA that was not finalized until November 21, 2007, more than 6 years after the study closed. The original study report was not included in the sBLA submission. It also seemed unusual that the study ended in March 2001 but the sponsor claims that the first blinded review of the data did not occur until June 2003 (more than a 2-year delay). Following the blinded review of the data, the sponsor changed the primary endpoint to the fast stretch Inter Medial Condyle (IMC) distance measured at week 4.

<u>The sponsor's chronology of the report and analysis for the second study RAP and analysis is summarized below:</u>

- 23 June 2003 Blind review meeting
- 30 September 2003 Blind review report
- 30 September 2003 Data base lock
- 20 October 2003 Unblinding
  - After unblinding, a statistical analysis was carried out by a contract research organization (CRO) on the basis of the statistical analysis plan contained in the blind review report.
- 16 March 2005 Draft study report by CRO
- 22 to 31 March 2005 Internal audit of this report, with the following findings:
  - The statistical analyses were carried out using methods different to the procedures described in the protocol.
  - The study report did not comply with the recommendations of the ICH E3 guideline on Structure and Content of Clinical Study Reports.

The conclusions were:

The data should be analyzed as described in the protocol, according to a formal report and analysis plan.

- A revised study report in ICH format should be provided.
- Discussions with the CRO concerned did not, however, lead to agreement and it was decided to entrust another CRO with the production of a new, ICH compliant report.

- 20 November 2006 Data base transferred to new CRO
- 13 June 2007 Report and analysis plan (RAP) drawn up
- 21 November 2007 Final report issued according to final RAP

Treatments

Patients received 30 U/kg of Dysport (0.12 mL/kg) or matching placebo injected into the adductor (2/3 of the total dose) and medial hamstring muscles (1/3 of the total dose). The maximum dose patients could receive was 2 injections per muscle with a maximal dose of 500 U per muscle group.

Study Populations (Table 30)

Safety Population-The safety population consists of the randomized subjects who were given at least one dose of the study medication and with at least one post baseline safety assessment.

Since there were 2 "primary" endpoints, two ITT populations were defined:

- The ITT ROM population defined as the subjects who were randomized, treated and were assessed at Week 0 and at Week 4 for the primary endpoint defined in the original protocol, Passive Abduction/Adduction Range Of Motion (ROM) at hip with knee extended.
- The ITT IMC (inter-medial condyli distance) population defined as the subjects, who were randomized, treated and were assessed at Week 0 and at Week 4 for the IMC (the "secondary "primary endpoint" defined after the blind review).

Per Protocol population (PP)-As for the ITT, there were two PP populations (PP ROM, PP IMC) are defined, consisting of the subjects in the corresponding ITT population with no major deviation.

Table 30: Analysis Populations

Population	Total N	Dysport N	Placebo N
Safety,	61	33	28
ITT ROM,	58	32	26
ITT IMC,	58	31	27
PP ROM,	56	30	26
PP IMC	56	29	27

Source: Ipsen

Endpoints

The original primary endpoint described in the original protocol was Passive abduction/adduction Range of motion (ROM) at hip at week 4. The primary endpoint was

changed following the blinded review to: the fast stretch Inter Medial Condyle (IMC) distance measured at week 4.

The main target criterion for the confirmatory analysis is the alteration of the abduction angle after 4-weeks of observation. "The question is whether Dysport is superior to placebo with respect to its action on the main target variable. Despite this one-sided formulation of the question, two sided statistical tests were to be performed to ensure neutrality."

The passive ROM at the hip was assessed using the "Neutral-Null" method. The Neutral-Null method for assessing abduction/adduction in the hip joint with hip and knee extended was used to measure and report the range of motion (ROM) of the joint. The results of both right and left sides were used for the analysis.

The Neutral Null method for describing joint range of motion (ROM) uses three numbers to describe ROM f a particular joint (Fujak, Kopschina, Gras, Forst, & Forst, 2011). Starting in the "neutral-null position" for example, the three numbers would describe flexion, neutral null position (0° if achieved) and the range of extension.

Secondary Endpoints:

- Flexion / extension of the hip
- Hip rotation
- Flexion / extension of the knee
- 90° bended hip knee flexion / extension
- Goal Attainment Scale (GAS)
- Pain scoring
- Parents' questionnaire
- Modified Ashworth Scale (MAS)
- Gross Motor Function Measure (GMFM)

Analysis Plan

The analysis methods for each endpoint in study 094 is listed in Table 31.

Table 31: Study 097 Analysis Populations and Analysis Methods

Parameter	Population	Method
ROM	PP ROM	ANCOVA[a]
IMC	PP IMC	ANCOVA[a]
Flexion/Extension of the hip	ITT ROM	ANCOVA[a]
Hip rotation	ITT ROM	ANCOVA[a]
Flexion/extension of the knee	ITT ROM	ANCOVA[a]
90° bended knee hip abduction / extension	ITT ROM	ANCOVA[a]
GAS[b]	ITT ROM	Wilcocon-Mann Whitney
Pain scoring[b]	ITT ROM	ANCOVA[c]
Parents' questionnaire[b]	ITT ROM	Non parametric ANCOVA[c]
MAS[b]	ITT ROM	Non parametric ANCOVA[c]
GMFM (goal area score)	ITT ROM	ANCOVA[c]

a Dependent=Randomization group + baseline value (cov) + height at inclusion (cov)

b At week 4 and 12 separately

c Dependent=Randomization group + baseline value (cov)

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(b) (4)

8. Safety

The ISS included safety information from four double blind placebo controlled and four open label studies of Dysport for the treatment of pediatric lower limb spasticity. The safety data for study 033 was not included in the efficacy or ISS safety datasets. The sponsor included a completed study report for study 033. In terms of safety, the 033 study report stated there were no deaths or SAE observed during the study. Five patients reported in the Dysport treated group and 1 patient in the placebo group reported an AE. The sponsor did not submit the clinical laboratory data.

Patient Exposure

The sponsor reported 62 patients were treated with 30 U/kg of Dysport for 4 consecutive treatments within 4 months in studiesY-55-52120-**141**, Y-55-52120-**147**, Y-97-52120-**702** and A-38-52120-**052**. The exposure figures in Table 35 included patients who received 4 injections within approximately 12 months but patients were not required to have a minimum interval between injections (i.e., every 16 weeks between injections). This reviewer found that 43 patients received 4 injections of 30 U/kg or more every 16 weeks (or sooner) for 4 consecutive treatments, regardless of the sequence (i.e., treatments 1 through 4 or 4 through 7) of the 4 consecutive treatments. The actual dose was used for each treatment session, the dose was rounded up or down to the nearest dose category (i.e., >=17.5 U/ kg rounded to 20 U/kg and 17.0 U/kg rounded down to 15 U/kg).

Table 35: Subject Exposure by Number of Consecutive Dysport Injections Within 6, 12 and 24 Months - Pooled Double Blind Placebo Controlled and Pooled Open Label Studies - Safety Population

Number of Consecutive Injections	Dysport			
	≥10 U/kg	≥15 U/kg	≥20 U/kg	≥30 U/kg
At least 2 consecutive injections within 6 months [a][b][c]	279	198	171	105
At least 4 consecutive injections within approximately 12 months [a][b][c][d]	142	119	106	62
At least 7 consecutive injections within a minimum of 24 months [a][b][e]	83	81	76	36

a Lowest of the consecutive doses
b Regardless of the place of the consecutive injections within the sequence of injections
c With a follow-up period of at least 28 days after the last of the consecutive injections
d Within 379 days (12 months + 2 weeks)
e At least 716 days (24 months – 2 weeks)
Source: Ipsen

In response to an information request, the sponsor revised the total number of patients treated with at least 30 U/kg for four consecutive sessions every 16 to 18 weeks to n=31 (Table 36). The sponsor's revised patient exposure using a more conservative method but they submitted the results of all 3 methods for calculating the long-term exposure for 6 and 12 months of treatment at the highest recommended dose (30 U/kg) proposed in labeling, and it is adequate.

There were 43 patients (n=11 from US sites) in the 10-17 year old age category treated in one of the open label studies (Table 37). Thirty of these patients received at least one dose of 30 U/kg.

Table 36: The Revised ISS Exposure Requiring All Treatment Administered Within a Fixed Interval Between Treatments

Post Hoc Table EX.4.3: Subject Exposure by Number of Consecutive Dysport Injections Occurring Every 18 Weeks or Sooner
(Double-Blind Placebo-Controlled and Open-Label Studies Combined) - Safety Population

	Dysport >=10 U/kg	Dysport >=15 U/kg	Dysport >=20 U/kg	Dysport >=30 U/kg
At least 2 consecutive injections within 12 to 18 weeks (1) (2) (3)	245	183	155	102
At least 2 consecutive injections within 16 to 18 weeks (1) (2) (4)	161	133	124	95
At least 2 consecutive injections within 12 to 16 weeks (1) (2) (5)	123	78	57	17
At least 4 consecutive injections with all intervals between two injections within 12 to 18 weeks (1) (2) (3)	76	63	57	32
At least 4 consecutive injections with all intervals between two injections within 16 to 18 weeks (1) (2) (4)	51	50	47	31
At least 4 consecutive injections with all intervals between two injections within 12 to 16 weeks (1) (2) (5)	14	7	4	0

Included studies: Y-55-52120-141, Y-55-52120-147, Y-97-52120-702 and A-38-52120-052.

(1) Lowest of the consecutive doses. (2) Regardless of the place of the consecutive injections within the sequence of injections. (3) At least 84 days but not more than 126 days between two injections (4) At least 112 days but not more than 126 days between two injections (5) At least 84 days but less than 112 days between two injections

Subjects who had 2 consecutive injections within 12 to 16 weeks and also 2 consecutive injections within 16 to 18 weeks are counted only once, not twice in the 12 to 18 weeks exposure interval. Subjects who had 4 consecutive injections with exposure intervals within 12 to 16 weeks and also within 16 to 18 weeks are counted only in the 12 to 18 weeks exposure interval, not in the other two intervals.

Table 37: Exposure For The 10-17 Year Old Age Group in The ISS

STUDYID	AGEGR1>=10 years Dysport 10 U/kg	AGEGR1 >=10 years Dysport 15 U/kg	AGEGR1>=10 years Dysport 30 U/kg	AGEGR1>=10 years Placebo	AGEGR1>=10 years, ACTARM = All
A-94-52120-094	0	0	6	1	7
Y-55-52120-141	12	12	0	12	36
All	12	12	6	13	43

Safety Analysis for study 141

Table 38: Disposition DB PC Studies Included in The ISS Safety Population

	STUDYID				
DBCOMPFL	**A-94-52120-094**	**Y-55-52120-141**	**Y-97-52120-040**	**Y-97-52120-701**	**All**
N	2	13	1	0	16
Y	59	226	124	52	461
All	61	239	125	52	477

Source: CDTL

Relatively few patients in the placebo controlled trials of Dysport for the treatment of pediatric lower limb spasticity withdrew from any trial for any reason. In study 141 only 1 patient randomized to the placebo group, withdrew early form the study (Table 39).

Table 39: Study 141 Early Withdrawal

Reason	Dysport 10 U/kg	Dysport 15 U/kg	Dysport 20 U/kg	Dysport 30 U/kg	Placebo	Total
Consent Withdrawn	0	1	1	2	3	7
Adverse Events	0	0	0	0	1	1
Other	1	0	0	1	1	3

Source: CDTL

Table 40: Reasons for Early Withdrawal ISS DB PC Studies

		ACTARM				
	Unilateral		Bilateral			
Reason	**Dysport 10 U/kg**	**Dysport 15 U/kg**	**Dysport 20 U/kg**	**Dysport 30 U/kg**	**Tot Dysport**	**Placebo**
ADVERSE EVENT	0	0	0	1	1	1
LOST TO FOLLOW-UP	0	1	1	0	2	1
OTHER	1	1	0	0	2	1
PROTOCOL DEVIATION	0	0	0	1	1	0
WITHDRAWAL BY SUBJECT	1	3	0	0	4	3
Total by Dose	2	5	1	2	10	6

Source: CDTL

Of the two patients who withdrew because of an adverse event (Table 40), the patient in the placebo group of study 141 was diagnosed with Pelezaeus Merzbacher after enrollment. The patient who received Dysport withdrew from study 094 because of muscle weakness and dysarthria and the narrative for this patient is discussed under possible spread of toxin events. Of the 7 patients listed as "withdrawal by subject", 1 patient needed surgery and 6 parents withdrew consent for their children. The sponsor or investigator for noncompliance withdrew the three patients listed as "other".

Deaths

There were no deaths reported in any double blind trial.

Nonfatal Serious Adverse Events

Sixteen patients (Placebo=6 and Dysport-10) reported 25 nonfatal serious adverse events. The blue shaded cells are patients with nonfatal serious adverse events in study 141 only one patient with a SAE in study 141 was treated with Dysport 220 U, the remaining 4 patients received placebo.

Table 41: ISS Nonfatal Serious Adverse Events in All DB, PC Studies

STUDYID	USUBJID	SEX	AGE at BL	PHASE	TRT Units	AE Study Day	AE Preferred Term	AE Outcome
Y-97-52120-040	52120040-00000200037	F	6	DB	Pbo	8 68	Petit mal epilepsy Convulsion	Unknown Unknown
Y-97-52120-040	52120040-00000400066	M	4	DB	465	167	Abdominal pain Cholelithiasis Constipation	Unknown
Y-97-52120-040	52120040-00000400066	M	4	DB	465	167	Fever	Unknown
Y-97-52120-040	52120040-00000500082	M	7	DB	609	25	Lobar pneumonia	Unknown
Y-97-52120-040	52120040-00000400076	F	3	DB	Pbo	19	Localized infection	Unknown
Y-55-52120-141	52120141-61600100008	F	4	DB	Pbo	58	Upper limb fracture	Recovered
Y-55-52120-141	52120141-61600100015	F	2	DB	Pbo	51 59	Pneumonia Rotavirus infection	Recovered Recovered
Y-55-52120-141	52120141-61600200003	M	2	DB	Pbo	3	Head injury	Recovered
Y-55-52120-141	52120141-79200700012	M	4	DB	Pbo	21	Gastroenteritis	Recovered
Y-55-52120-141	52120141-25000200001	F	6	DB	220	72	Adenoidal hypertrophy	Recovered
A-94-52120-094	52120094-00000300034	M	2	DB	300	43	Pyrexia Upper respiratory tract infection	Recovered
A-94-52120-094	52120094-00000100025	M	1	DB	360	15	Pseudomonas bronchitis	Recovered
A-94-52120-094	52120094-00000200017	M	5	DB	420	57	Bronchitis Otitis media Pseudocroup	Recovered
A-94-52120-094	52120094-00001500089	M	10	DB	1290	17	Dysarthria Muscular weakness	Recovered
A-94-52120-094	52120094-00000300061	M	6	DB	450	23	Bronchopneumonia	Recovered
Y-97-52120-701	52120701-00000300018	M	4	DB	480	14	Bronchitis	Unknown

Source: CDTL

Table 42: Study Y-55-52120-141 Adverse Reactions Pivotal DB PC ≥4% and Greater in Any Dysport Group For Labeling

Adverse Reactions		Unilateral		Bilateral	
	Placebo (N=79) %	Dysport 10 units/kg N=43 %	Dysport 15 units/kg (N=50) %	Dysport 20 units/kg (N=37) %	Dysport 30 units/kg (N=30) %
Infections and infestations					
Upper respiratory tract infection	13	9	20	5	10
Nasopharyngitis	5	9	12	16	10
Influenza	8	0	10	14	3
Pharyngitis	8	5	0	11	3
Bronchitis	3	0	0	8	7
Rhinitis	4	5	0	3	3
Varicella	1	5	0	5	0
Ear infection	3	0	4	0	0
Gastroenteritis viral	0	2	4	0	0
Respiratory tract infection viral	0	5	2	0	0
Gastrointestinal disorders					
Vomiting	5	0	6	8	3
Nausea	1	0	2	5	0
Respiratory, thoracic and mediastinal disorders					
Cough	6	7	6	14	10
Oropharyngeal pain	0	2	4	0	0
General disorders and administration site conditions					
Pyrexia	5	7	12	8	7
Musculoskeletal and connective tissue disorders					
Pain in extremity	5	0	2	5	7
Muscular weakness	1	5	0	0	0
Nervous system disorders					
Convulsion/Epilepsy	0	7	4	0	7

Six of the 7 patients with adverse events of epilepsy or convulsion (Table 42) had a history of epilepsy or seizures at baseline. No medical history was provided for the remaining 3 year old patient who suffered a seizure.

Table 43: Adverse Reactions All DB PC Studies in the ISS ≥ 2% in The All Dysport Group and Greater Than Placebo

AEBODSYS	AEDECOD	Placebo N=164 %	Dysport 10 U/kg 1-leg (N=43) %	Dysport 15U/kg 1-leg (N=52) %	Dysport 10 U/kg 2-legs N=37 %	Dysport 20 U/kg 2-legs N=64 %	Dysport 30 U/kg 2-legs N=116 %	All Dysport (N=313) %
Infections and infestations	Upper respiratory tract infection	6	9	19	5	6	7	9
Infections and infestations	Nasopharyngitis	4	9	12	3	11	4	7
General disorders and administration site conditions	Pyrexia	4	7	12	8	6	4	7
Respiratory, thoracic and mediastinal disorders	Cough	6	7	6	11	8	3	6
Infections and infestations	Bronchitis	4	0	0	8	6	9	5
Infections and infestations	Pharyngitis	5	5	0	11	8	2	4
Infections and infestations	Influenza	4	0	10	0	9	1	4
Infections and infestations	Rhinitis	4	5	0	0	2	7	4
Gastrointestinal disorders	Vomiting	2	0	6	5	8	2	4
Musculoskeletal and connective tissue disorders	Muscular weakness	1	5	0	0	0	6	3
Infections and infestations	Varicella	1	5	0	8	3	0	2
Infections and infestations	Ear infection	1	2	4	0	0	2	2
General disorders and administration site conditions	Unevaluable event	1	0	0	0	0	6	2
Respiratory, thoracic and mediastinal disorders	Asthma	1	0	0	3	2	3	2
Gastrointestinal disorders	Diarrhoea	1	2	2	5	3	1	2
Nervous system disorders	Epilepsy/Convulsion	2	9	4	5	0	3	4
Nervous system disorders	Hypotonia	1	0	0	0	0	4	2
Injury, poisoning and procedural complications	Fall	1	0	0	3	3	3	2

Table 44: Disposition of Patient in Open label Studies Included in The ISS All Doses

	STUDYID					
Open Label Completers	**A-38-52120-052**	**A-38-52120-711**	**A-94-52120-062**	**Y-55-52120-147**	**Y-97-52120-702**	**All Studies**
N	0	0	0	19	37	56
Y	15	25	15	188	177	420
Total	15	25	15	207	214	476

The patients who withdrew early all came from studies 147 and 702.

Table 45: Reasons for Early Withdrawal from Pooled Open Label Studies –All Doses

	STUDYID		Total
Reason	**Y-55-52120-147**	**Y-97-52120-702**	
ADVERSE EVENT	1	2	3
LACK OF EFFICACY	1	0	1
LOST TO FOLLOW-UP	1	4	5
OTHER	10	8	18
PROTOCOL DEVIATION	0	3	3
WITHDRAWAL BY SUBJECT	6	20	26
Total	19	37	56

Table 46: Adverse Events Leading to Early Withdrawal From Open Label Studies

STUDYI	USUBJID	SEX	AG	TRTA2	AETERM	AEDECOD	Cycle	AEOUT
Y-55-2120-147	52120141-84000200001	F	5	Dysport 20 U/kg - 2 legs	Worsening Of Pre-Existing Pineal Region Cyst	Pineal gland cyst	Treatment Cycle 1	Not Recovered/Not Resolved
Y-97-2120-702	52120702-00001300053	M	2	Dysport 30 U/kg - 2 legs	Paresthesias In Legs After Maintaining Fixed Position	Paraesthesia	Treatment Cycle 3	Unknown
Y-97-2120-702	52120702-00001900207	F	3	Dysport 10 U/kg - 2 legs	Pain In Both Legs Weakness	Pain Muscular weakness	Treatment Cycle 3	Unknown Unknown

Three patients reported 4 adverse events that caused early withdrawal from an open label study (Table 45). None of the adverse events causing early withdrawal met criteria for a serious adverse event. One patient in study 147 withdrew early because of worsening of a pre-existing pineal region cyst (Table 46). The patient was last treated with Dysport 20 U/kg in both legs. The patient reported the adverse event one day after her first open label treatment. The patient had previously completed double blind treatment with 10 U/kg. Two patients in study 702 with drew for AE during treatment cycle 3. One patient had paresthesias in legs after maintaining fixed position and the other for pain in both legs weakness.

Of the 26 patients listed as "withdrew by subject" 6 patients had additional information, 1 additional patient withdrew because lack of efficacy, 1 elected to have surgical treatment for spasticity, 1 relocated to another area and the parents of the remaining 3 patients withdrew consent.

Deaths

There were no deaths in the open label studies of Dysport for the treatment of pediatric lower limb spasticity.

Nonfatal Serious Adverse Events

Thirty eight patients reported 58 nonfatal SAEs. The most common nonfatal SAEs were the related to the need for a surgical procedure (i.e., strabismus correction, hip surgery, tonsillectomy, orchidopexy, tenotomy etc.), or infectious disease (i.e., pneumonia, fever (pyrexia), otitis and tonsillitis.

Table 47: Nonfatal Serious Adverse Events Open label Studies in the ISS

		Unilateral Injection		Bilateral Injection		
AEBODSYS	**AEDECOD**	**Dysport 10 U/kg - 1 leg N=132**	**Dysport 10 U/kg - 2 legs N53**	**Dysport 20 U/kg - 2 legs N=146**	**Dysport 30 U/kg - 2 legs N=257**	**Total Dysport N=476**
Surgical and medical procedures	Surgery	0	0	0	6	6
Infections and infestations	Pneumonia	1	0	1	2	4
General disorders and administration site conditions	Pyrexia	0	0	0	3	3
Injury, poisoning and procedural complications	Injury	0	0	0	3	3
Surgical and medical procedures	Strabismus correction	0	1	0	2	3
Infections and infestations	Gastroenteritis	0	0	1	1	2
Infections and infestations	Otitis media	0	0	0	2	2
Nervous system disorders	Convulsion	0	0	0	2	2
Nervous system disorders	Epilepsy	0	0	0	2	2
Nervous system disorders	Hydrocephalus	0	0	0	2	2
Blood and lymphatic system disorders	Lymphadenopathy	0	0	1	0	1
Congenital, familial and genetic disorders	Cerebral palsy	0	0	0	1	1
Congenital, familial and genetic disorders	Patent ductus arteriosus	0	0	0	1	1

Eye disorders	Cataract	0	0	0	1	1
General disorders and administration site conditions	Drowning	0	0	0	1	1
General disorders and administration site conditions	Hypothermia	0	0	0	1	1
General disorders and administration site conditions	Unevaluable event	0	0	0	1	1
Infections and infestations	Appendicitis	0	0	0	1	1
Infections and infestations	Bronchitis	0	1	0	0	1
Infections and infestations	Bronchopneumonia	0	1	0	0	1
Infections and infestations	Pharyngitis	0	0	0	1	1
Infections and infestations	Pharyngotonsillitis	0	0	0	1	1
Infections and infestations	Sinusitis	0	0	1	0	1
Infections and infestations	Varicella	0	0	1	0	1
Injury, poisoning and procedural complications	Toxicity to various agents	0	0	0	1	1
Nervous system disorders	Ataxia	0	0	0	1	1
Nervous system disorders	Complex partial seizures	0	0	1	0	1
Nervous system disorders	Partial seizures	0	0	0	1	1
Nervous system disorders	Status epilepticus	0	0	1	0	1
Nervous system disorders	Syncope	0	0	0	1	1
Renal and urinary disorders	Renal colic	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Asthma	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	0	0	0	1	1
Skin and subcutaneous tissue disorders	Ecchymosis	0	0	0	1	1
Surgical and medical procedures	Hip surgery	0	0	0	1	1
Surgical and medical procedures	Limb operation	0	0	0	1	1
Surgical and medical procedures	Orchidopexy	0	0	0	1	1

Surgical and medical procedures	Tenotomy	0	0	0	1	1
Surgical and medical procedures	Tonsillectomy	0	0	0	1	1
Total		**1**	**3**	**7**	**47**	**58**

Table 48: Seizure/Epilepsy Related Nonfatal Serious Adverse Events ISS Open Label Studies

AEBODSYS	**AEDECOD**	**Dysport 10 U/kg - 1 leg N=132**	**Dysport 10 U/kg - 2 legs N=53**	**Dysport 20 U/kg - 2 legs N=146**	**Dysport 30 U/kg - 2 legs N=257**	**Total By PT N=476**
Nervous system disorders	Complex partial seizures	0	0	1	0	1
Nervous system disorders	Convulsion	0	0	0	2	2
Nervous system disorders	Epilepsy	0	0	0	2	2
Nervous system disorders	Partial seizures	0	0	0	1	1
Nervous system disorders	Status epilepticus	0	0	1	0	1
Total by Dose ARM		0	0	2 (1%)	5 (2%)	7 (2%)

In the open label studies, 25 patients had an adverse (serious and non-serious) event of epilepsy, seizure or convulsion, 11 of these patients had a previous history of epilepsy. All of the 25 patients with an epilepsy related adverse event while participating in an open label study were enrolled in study 702 (Table 48).

Table 49: ISS Adverse Events Pneumonia Related Terms

AEBODSYS	AEDECOD	Dysport 10 U/kg - 1 leg N=132	Dysport 10 U/kg - 2 legs N=53	Dysport 20 U/kg - 2 legs N=146	Dysport 30 U/kg - 2 legs N=257	Total By PT N=476
Infections and infestations	Bronchopneumonia	0	1	0	0	1
Infections and infestations	Pneumonia	1	0	1	2	4
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	0	0	0	1	1
Total by Dose Arm		1 (1%)	1 (2%)	1 (1%)	3 (1%)	6 (1%)

The proportion of patients with an adverse event related to pneumonia while enrolled in an open label study was similar for all doses of Dysport (Table 49).

Table 50: All Adverse Reactions For Dysport ISS All Open Studies Frequency ≥ 2%

AEBODSYS	AEDECOD	Percent 10 U/kg 1-leg N=132	Percent 15 U/kg 1-leg N=53	Percent 20 U/kg 1-leg N=13	Percent 10 U/kg - 2 legs N=17	Percent 20 U/kg - 2 leg N=146	Percent 30 U/kg - 2 legs N=257	Percent 40 U/kg – 2 legs N=2
Infections and infestations	Bronchitis	4	4	8	29	8	25	0
Infections and infestations	Pharyngitis	7	4	0	12	7	23	0
Infections and infestations	Nasopharyngitis	16	8	0	29	9	14	0
Infections and infestations	Upper respiratory tract infection	11	2	0	6	10	7	0
Infections and infestations	Influenza	6	2	0	0	8	5	0
Infections and infestations	Viral infection	0	0	0	6	1	12	0
Infections and infestations	Rhinitis	2	0	0	0	1	11	0
Infections and infestations	Tonsillitis	2	0	0	6	1	10	50
Infections and infestations	Varicella	5	0	8	6	3	7	50
Infections and infestations	Respiratory tract infection	0	0	0	0	1	8	0
Infections and infestations	Otitis media	1	0	0	6	3	5	0
Infections and infestations	Acute tonsillitis	1	0	0	6	1	4	0
Infections and infestations	Pneumonia	2	2	0	6	1	4	0
Infections and infestations	Ear infection	2	0	0	6	1	3	0
Infections and infestations	Laryngitis	1	0	8	0	0	3	0
Infections and infestations	Sinusitis	0	0	0	0	1	3	0
Infections and infestations	Gastroenteritis	1	0	0	0	3	1	0
Infections and infestations	Urinary tract infection	0	2	0	0	0	2	0
Infections and infestations	Viral upper respiratory tract infection	2	2	0	0	1	0	0
Infections and infestations	Acute sinusitis	2	0	0	0	1	0	0
Infections and infestations	Gastroenteritis viral	2	2	0	0	0	0	0
Infections and infestations	Pharyngotonsillitis	2	0	0	0	0	1	0

Infections and infestations	Bronchopneumonia	0	0	0	6	0	1	0
Infections and infestations	Upper respiratory tract infection bacterial	0	0	0	0	2	0	0
Infections and infestations	Viral pharyngitis	0	0	0	6	1	0	0
Infections and infestations	Hand-foot-and-mouth disease	0	2	0	0	0	0	0
Infections and infestations	Hepatitis viral	0	2	0	0	0	0	0
Infections and infestations	Herpes simplex	0	0	0	6	0	0	0
Musculoskeletal and connective tissue disorders	Pain in extremity	6	0	0	0	1	13	0
Musculoskeletal and connective tissue disorders	Muscular weakness	0	0	0	12	2	12	0
Musculoskeletal and connective tissue disorders	Arthralgia	1	0	0	0	0	2	0
Musculoskeletal and connective tissue disorders	Myalgia	0	0	0	0	0	2	0
Musculoskeletal and connective tissue disorders	Limb deformity	0	0	0	6	0	0	0
General disorders and administration site conditions	Pyrexia	7	2	0	6	9	9	0
General disorders and administration site conditions	Gait disturbance	0	0	0	18	1	4	0
General disorders and administration site conditions	Injection site pain	4	2	0	0	1	1	0
General disorders and administration site conditions	Pain	0	0	0	12	1	3	0
General disorders and administration site conditions	Influenza like illness	2	0	0	0	1	0	0
General disorders and administration site conditions	Injection site papule	1	2	0	0	1	0	0
Gastrointestinal disorders	Diarrhoea	5	2	0	0	3	5	0

Gastrointestinal disorders	Vomiting	2	2	0	6	3	3	0
Gastrointestinal disorders	Nausea	3	0	0	0	1	1	0
Gastrointestinal disorders	Toothache	2	2	0	0	0	0	0
Gastrointestinal disorders	Salivary hypersecretion	0	2	0	0	0	0	0
Gastrointestinal disorders	Gastrooesophageal reflux disease	0	2	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Cough	2	0	0	18	4	10	0
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	2	2	0	6	2	1	0
Respiratory, thoracic and mediastinal disorders	Nasal congestion	0	0	0	6	0	0	0
Nervous system disorders	Epilepsy	0	0	0	6	1	5	0
Nervous system disorders	Convulsion	1	2	0	0	1	2	0
Nervous system disorders	Headache	2	0	0	0	0	1	0
Injury, poisoning and procedural complications	Fall	3	0	0	0	1	0	0
Injury, poisoning and procedural complications	Injury	0	0	0	6	0	2	0
Injury, poisoning and procedural complications	Skin abrasion	2	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	Rash	0	0	0	6	1	4	0
Surgical and medical procedures	Strabismus correction	0	0	0	6	0	2	0
Surgical and medical procedures	Surgery	0	0	0	0	0	3	0
Immune system disorders	Hypersensitivity	0	0	0	0	0	3	0
Immune system disorders	Seasonal allergy	1	2	0	0	0	0	0
Investigations	Body temperature increased	0	2	0	0	0	1	0
Psychiatric disorders	Depression	0	0	0	6	0	0	0

Blood and lymphatic system disorders	Lymphadenitis	0	0	0	0	0	2	0
Ear and labyrinth disorders	Ear pain	0	0	0	6	0	0	0
Metabolism and nutrition disorders	Iron deficiency	0	2	0	0	0	0	0
Vascular disorders	Phlebitis	0	0	8	0	0	0	0

The most common adverse events in the pooled open label studies were related to infectious diseases or physical disabilities frequently seen in children with CP (Table 50).

Adverse Events of Special Interest

Distant Spread of Toxin

Ten patients had "Remote Spread of Toxin" adverse events, two of the event met criteria for an SAE (Table 51).

Table 51: All Studies in ISS Remote (Distant) Spread of Toxin Events

Study ID	USUBJID	Sex	Age years	Preferred Term	Serious AE	Outcome	Study Day	Total Dose U/kg
040	52120040-00001100207	M	6	Muscular weakness	N	Unknown	14	30
094	52120094-00000300034	M	2	Dysphagia	N	Recovered	6	30
094	52120094-00000500003	M	2	Muscular weakness	N	Recovered	15	30
094	52120094-00000500049	F	3	Dysphagia	N	Recovered	15	Pbo
094	52120094-00000500050	M	9	Dysarthria Muscular weakness	N N	Not Recovered Not Recovered	10 10	30 30
094	52120094-00001200014	F	3	Dysphagia	N	Recovered	Unknown	30
094	52120094-00001500089	M	10	Dysarthria Muscular weakness	Y Y	Recovered Recovered	17 17	30 30
141	52120141-84000700004	M	4	Dysphagia	N	Recovered	4	15
702	52120702-00002200061	F	4	Constipation	N	Unknown	3	30
702	52120702-00002700236	F	3	Muscular weakness Muscular weakness	N N	Unknown Unknown	3 246	27.5 20

Source CDTL

Most of the cases 6 of 10 were from study 094 that injected proximal (adductor and medial hamstring) muscles, five were treated with Dysport and one patient received Placebo. Most of

the patients with Remote Spread events received a dose that was the highest dose 30 U/kg or close to that dose and only two patients had events on lower doses. The one patient who had an event that met criteria for an SAE recovered from the event. Patient with constipation with other symptoms of weakness or dysarthria a not clearly cases of spread of toxin events. One patient developed muscular weakness following injection with placebo. Six of the remaining patients had isolated weakness or dysarthria. They could potentially have been cases of distant spread of toxin based on the review of their case narratives. Two patients 52120094-00000500050 and 52120094-00001500089, had dysarthria and generalized weakness both cases are potential cases of distant spread of toxin. After reviewing the narratives, it is still unclear why the event was classified as a SAE.

Clinical Laboratory Evaluations

Blood samples for clinical laboratory testing were taken at baseline (pretreatment), at Week 4 and at the end of study or early withdrawal visit. Data for clinical laboratory parameters were only systematically collected for the double blind placebo controlled Study 141 and in open label Study 147.

There were no significant changes in the mean values for any of the hematology or chemistry tests from baseline. There was no significant trends over time for changes in mean hematology or chemistry parameters. There were no patients that met the criteria for a Hy's Law casein study 141 or 147.

Hematology Parameters

In study 141 a single patients had a clinically significant abnormal hemoglobin HGB (and) hematocrit (HCT) at baseline , both values were low however, the HGB and HCT returned to the normal range by week 4 (Table 52). The clinically abnormal criteria for each laboratory was not established in the protocol instead, investigators were to use their medical judgment.

Table 52: Study 141 Clinically Significant Hematology Abnormality

USUBJID	VISIT	TRTA	AGEGR1	SEX	PARAMCD	AVAL	ANRLO	ANRHI
52120141-79200100004	VISIT 2 BASELINE/DAY 1	Dysport 15 U/kg	2 - 9 YEARS	F	HB	93	102	127
52120141-79200100004	VISIT 2 BASELINE/DAY 1	Dysport 15 U/kg	2 - 9 YEARS	F	HCT	0.286	0.312	0.378
52120141-79200100004	VISIT 2 BASELINE/DAY 1	Dysport 15 U/kg	2 - 9 YEARS	F	RBC	3.43	3.84	4.92

Source: CDTL

Clinical Chemistry

Table 53: Study 141 Summary of Biochemistry Abnormalities – Safety Population

Subject No	Laboratory Abnormality	Time of Laboratory Abnormality	Associated Adverse Event
15200300006	High triglycerides	Baseline	None

84000200002	Low glucose	Baseline	Hypoglycaemia
84000500006	High glucose	Week 4	Blood glucose increased
48400500003	Low bicarbonate	Baseline, Week 4 and Week 16	Blood bicarbonate decreased
	High phosphate	Baseline, Week 4 and Week 16	Hyperphosphataemia
48400500005	Low bicarbonate	Baseline, Week 4 and Week 16	Blood bicarbonate decreased
	High phosphate	Baseline, Week 4 and Week 16	Hyperphosphataemia
79200700002	High conjugated bilirubin	Baseline, Week 4 and Week 12	Gilbert's Syndrome
	High total bilirubin	Baseline, Week 4 and Week 12	
79200700003	High bone specific alkaline phosphatase	Baseline, Week 4 and Week 12	Hypothyroidism from Day 30 and Vitamin D deficiency from Day 72

Source: Ipsen

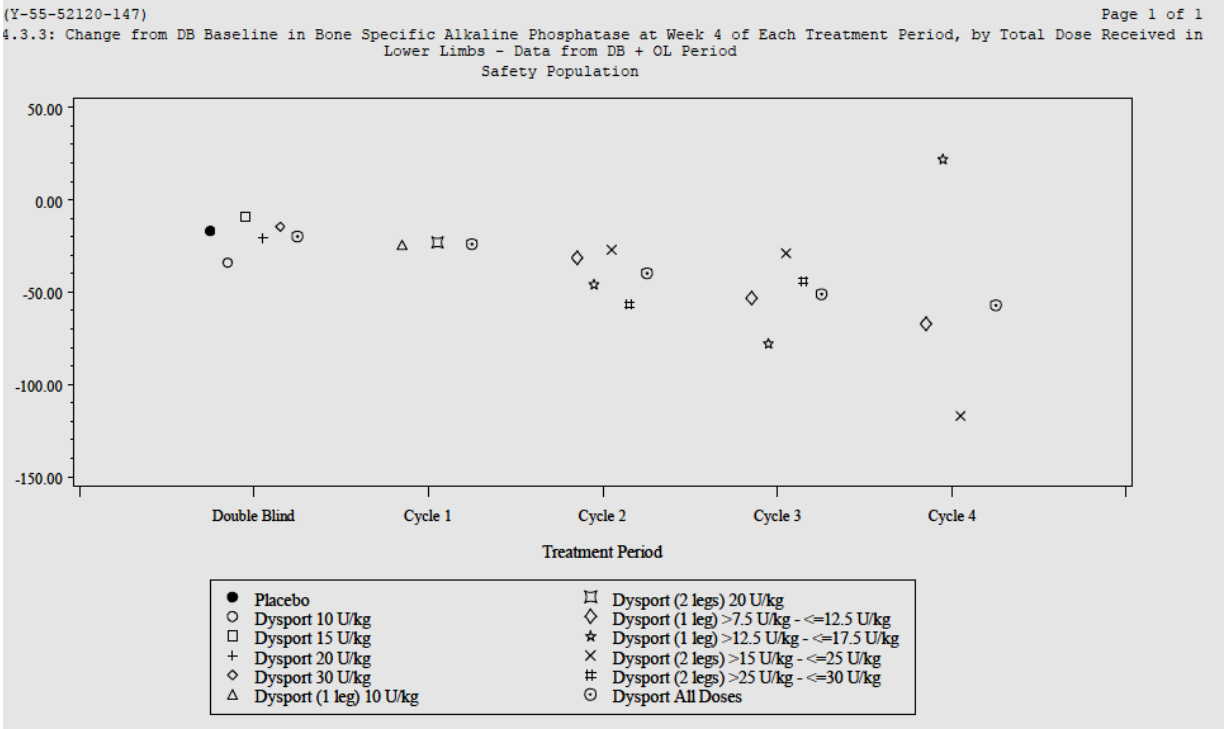
The abnormal and clinical significant chemistry results shown in Table 53 was reviewed and confirmed using the sponsor laboratory datasets. There was no evidence of trend for chemistry abnormality, including glucose favoring a higher level in patients randomized to Dysport. All but one of the abnormal chemistry values were detected at the baseline visit that remained persistently abnormal throughout the study. Patient #84000500006 had a normal glucose at baseline, a high glucose at Week 4 (random glucose level). The patient's glucose returned to the normal 5.27 mmol/L (near the ULN of 5.83mmol/L) by Week 22 and remained within the normal range through the remainder of study 147.

Study 147

There were no significant change in the mean values for any hematology or chemistry parameters in study 147. An individual patient had intermittently raised eosinophil count that started in study 141 and continued in study 147. There were no adverse events associated with the patient's increased eosinophil count. Glucose measurements revealed small changes ranging from -0.720 to 0.504 mmol/L throughout the study, both high and low. There were no meaningful changes in fasting glucose or non-fasting glucose measurement. There was no clear relationship to dose or treatment cycle.

Alkaline Phosphatase trended downward during studies 141 and 147 with successive treatment cycles, however, there were fewer patients in each treatment cycle especially in cycles 4 (n=8) and 5-7 (Figure 3).

Figure 3: Change from DB Baseline in Bone Specific Alkaline Phosphatase at Week 4 of Each Treatment Period, by Total Dose Received in Lower Limbs - Data from DB + OL Period Safety Population



Source: Ipsen

ECG

In Study 141, there were two patients who had an ECG abnormality that was considered to be clinically significant. A 6-year-old female in the Dysport 10 U/kg group, had an episode of sinus tachycardia >150 bpm recorded at Week 16. A 2-year-old female in the Dysport 15 U/kg group, had a technically poor ECG tracing at Week 12 which showed a sinus tachycardia that was potentially significant. Her heart rate recorded during the vital signs measurements was 85 bpm at this visit. Three patients had a change from baseline of QTcF (prolonged) of between 30ms and 50 ms but no patients had a QTcF interval >450 ms.

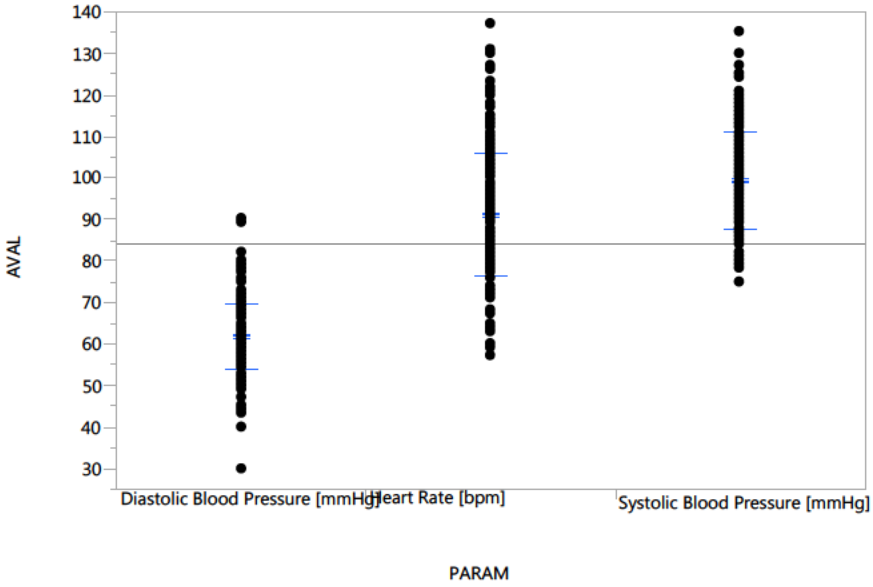
In study 147, 3 patients had similar change (prolonged) in QTcF compared to baseline of 30ms to 40 ms that were asymptomatic. The QTcF was inconsistently prolonged during one or more treatment visits in these patients. One additional patient was found to have a cardiac murmur that was unrelated to study treatment.

Vital Signs

The were no clinical significant changes in mean systolic or diastolic blood pressure or pulse during studies 141 or 147 (Figure 4). There were a small number of patients with high or low vital sign measurement that varied from visit to visit. The patients with abnormal values were few in number generally, only 1 to 4 patients for pulse or blood pressure per visit. The sponsor had prespecified the normal/abnormal ranges of pulse, systolic and diastolic blood pressure according to age in the analysis plan. The range that defined abnormal vital signs was acceptable. None of the vital sign changes were judged to be clinically significant events.

Figure 4: Pooled Studies 141 and 147 Vital Signs by Treatment Arm

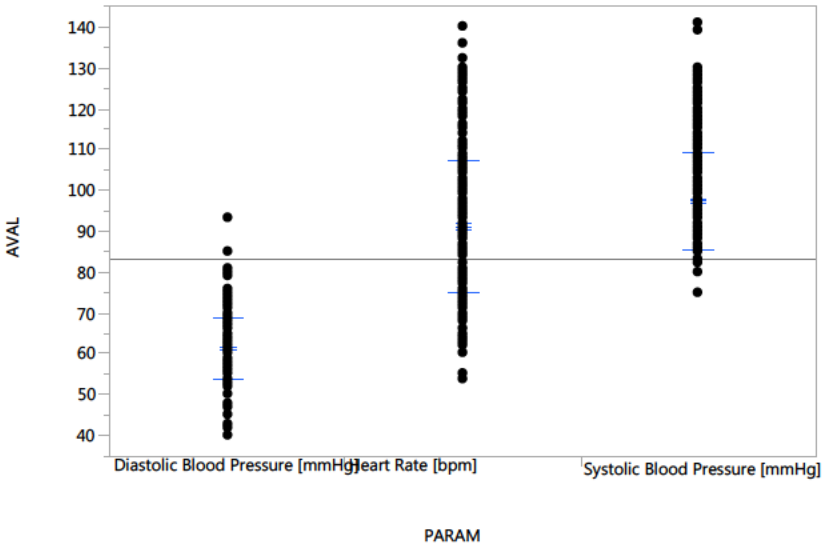
Oneway Analysis of AVAL By PARAM TR01PG1=Dysport 10 U/kg



Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Diastolic Blood Pressure [mmHg]	548	61.8704	7.8972	0.33735	61.208	62.53
Heart Rate [bpm]	548	91.1077	14.6567	0.62611	89.878	92.34
Systolic Blood Pressure [mmHg]	548	99.4507	11.7263	0.50092	98.467	100.43

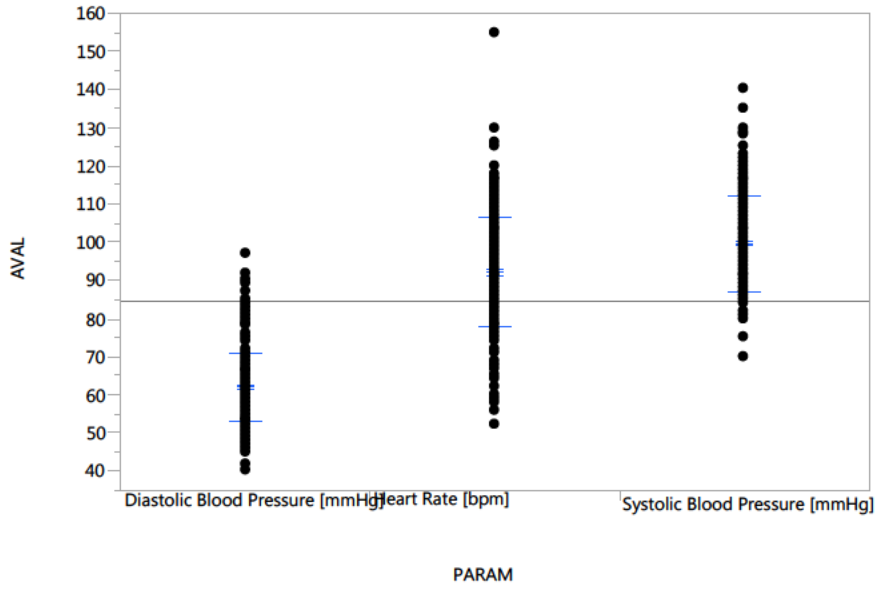
Oneway Analysis of AVAL By PARAM TR01PG1=Dysport 15 U/kg



Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Diastolic Blood Pressure [mmHg]	551	61.3775	7.5459	0.32147	60.746	62.009
Heart Rate [bpm]	552	90.9946	16.2623	0.69217	89.635	92.354
Systolic Blood Pressure [mmHg]	551	97.4773	11.9386	0.50860	96.478	98.476

Oneway Analysis of AVAL By PARAM TR01PG1=Placebo



Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Diastolic Blood Pressure [mmHg]	606	62.0627	8.7669	0.35613	61.363	62.76
Heart Rate [bpm]	606	92.0429	14.3424	0.58262	90.899	93.19
Systolic Blood Pressure [mmHg]	606	99.5578	12.3946	0.50350	98.569	100.55

Source CDTL

CDTL Safety Conclusions

Pediatric patients injected with the high dose in the proximal muscles of both legs were more likely to experience symptoms of remote spread of toxin. The information in the label does not include the use of Dysport for treatment of spasticity in the proximal lower limb muscles. The other adverse effects are similar in type, upper respiratory infections and musculoskeletal pain as those reported by adults treated with Dysport for upper limb spasticity. Dysport provides benefit for the treatment of lower limb spasticity in children with no change in the known adverse event profile.

9. Advisory Committee Meeting

The application did not meet criteria to convene an Advisory Committee before acting on this sBLA application.

10. Pediatrics

The Division met with PeRC on July 13, 2016, and there was agreement that the pediatric lower limb spasticity PMC is fulfilled and the same portion of the PMR is also fulfilled. However, the PMR will not be completely fulfilled until all studies described in the PMR for the treatment of spasticity are fulfilled.

11. Other Relevant Regulatory Issues

Financial Disclosures
The placebo controlled study 141 and open label study 147 were the only studies that included sites in the US and that were conducted under an IND. The remaining legacy studies were all completed at sites outside the US. The sponsor provided financial disclosures for all of the investigators and staff for the foreign and domestic sites in studies 141 and 147. None of the investigators or study personnel disclosed a reportable financial relationship with Ipsen.

DSI Audits
Study audits were not requested for clinical sites for the studies included in this BLA supplement.

Outstanding Regulatory Issues
None.

12. Labeling

The sponsor agreed to (b) (4) indication to "the treatment of lower limb spasticity in pediatric patients 2 years of age and older" (b) (4) The sponsor was notified that a user fee was required (b) (4) The User Feed was submitted by the sponsor.

Justine Harris, RPh in DMEPA and LaShawn Griffiths, MSHS-PH, BSN, RN in DMPP reviewed proposed changes to the Prescribing Information (PI) and the Medication Guide (MG), respectively. The recommendations included in their reviews were incorporated into the PI and MG sent to the sponsor.

Dhara Shah, PharmD, Regulatory Review Officer review the PI and MG. The OPDP's recommendations were incorporated into both documents.

Key changes in the final versions of the PI and MG are provided below.

Key Changes to the Prescribing Information

Lower Limb Spasticity in Pediatric Patients
DYSPORT® is indicated for the treatment of lower limb spasticity in pediatric patients 2 years of age and older.

Dosing in Lower Limb Spasticity in Pediatric Patients

Pediatric Lower Limb Spasticity Patients 2 years of age and older

DYSPORT® dosing for pediatric lower limb spasticity is based on Units per kilogram of body weight. Table 3 describes the recommended Units/kg dose of DYSPORT® per muscle of the Gastrocnemius-Soleus Complex (GSC). The recommended total DYSPORT® dose per treatment session is 10 to 15 Units/kg for unilateral lower limb injections or 20 to 30 Units/kg for bilateral lower limb injections. However, the (b) (4) total dose of DYSPORT® administered per treatment session must not exceed 15 Units/kg for unilateral lower limb injections or 30 Units/kg for bilateral lower limb injections or 1000 units, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s). When possible, the dose should be distributed across more than 1 injection site in any single muscle (see Table 3). No more than 0.5 mL of DYSPORT® should be administered in any single injection site.

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins.

Table 3: DYSPORT® Dosing by Muscle for Lower Limb Spasticity in Pediatric Patients

Muscle Injected	**Recommended DYSPORT® Dose Range per muscle per leg (Units/kg Body Weight)**	**Recommended number of injections per muscle**
Gastrocnemius	6 to 9 Units/kg[a]	Up to 4
Soleus	4 to 6 Units/kg[a]	Up to 2
Total	10 to 15 Units/kg divided across both muscles	Up to 6

Note: a – the listed individual doses to be injected in the muscles can be used within the range mentioned without exceeding
15 Units/kg total dose for unilateral injection or 30 Units/kg for bilateral injections.

Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography or electrical stimulation, is recommended to target the injection sites.

Repeat DYSPORT® treatment should be administered when the effect of a previous injection has diminished but no sooner than 12 weeks after the previous injection. A majority of patients in the clinical studies were retreated between 16-22 weeks, however; some had a longer duration of response. The degree and pattern of muscle spasticity and overall clinical benefit at the time of re-injection may necessitate alterations in the dose of DYSPORT® and muscles to be injected.

Pediatric Patients less than 2 years of age

The safety and effectiveness of DYSPORT® in the treatment of lower limb spasticity in pediatric patients of less than 2 years of age has not been evaluated.

Pediatric Patients 0 to 17 years of age
The safety and effectiveness of DYSPORT® injected into upper limb muscles or proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established.

Adult Patients
The safety and effectiveness of DYSPORT® in the treatment of lower limb spasticity in adult patients has not been demonstrated.

Instructions for Preparation and Administration for the Treatment of Lower Limb Spasticity in Pediatric Patients 2 years and older

DYSPORT® is supplied as single-use 300Unit or 500Unit vials. Only use sterile preservative-free 0.9% Sodium Chloride Injection, USP for reconstitution of DYSPORT®. Each 500 Unit vial of DYSPORT® is to be reconstituted with 2.5 mL of preservative-free 0.9% Sodium Chloride Injection, USP prior to injection. Each 300 Unit vial of DYSPORT® is to be reconstituted with 1.5 mL of preservative-free 0.9% Sodium Chloride Injection, USP prior to injection. The concentration of the resulting solution will be 20 Units per 0.1 mL. Further dilution with preservative-free 0.9% Sodium Chloride Injection, USP, may be required to achieve the final volume for injection. No more than 0.5 mL of DYSPORT® should be administered in any single injection site.

To calculate the total units of DYSPORT® required for treatment of one leg, select the dose of DYSPORT® in Units/kg/leg and the body weight (kg) of the patient (see Table 3). Using an appropriately sized sterile syringe (e.g., 3 mL syringe), needle and aseptic technique, draw up 2.5 mL of preservative-free 0.9% Sodium Chloride Injection, USP. Insert the needle into the DYSPORT® 500 Unit vial. The partial vacuum will begin to pull the saline into the vial. Any remaining required saline should be expressed into the vial manually. Do not use the vial if no vacuum is observed. Swirl gently to dissolve. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted DYSPORT® should be a clear, colorless solution, free of particulate matter; otherwise it should not be injected.

Draw the required patient dose of DYSPORT® into a sterile syringe and dilute with additional preservative-free 0.9% Sodium Chloride Injection, USP, if required, to achieve the final volume for injection. Expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach an appropriately sized new sterile needle.

Use immediately after reconstitution in the syringe.

Discard the vial and needle in accordance with local regulations.

Lower Limb Spasticity in Pediatric Patients

Table 8 reflects exposure to DYSPORT® in 160 patients, 2 to 17 years of age, who were evaluated in the randomized, placebo-controlled clinical study that assessed the use of DYSPORT® for the treatment of unilateral or bilateral lower limb spasticity in pediatric cerebral palsy patients *[see Clinical Studies (14.4)]*. The most commonly observed adverse reactions (≥10% of patients) are: upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough and pyrexia.

Table 8: Adverse Reactions Observed in ≥ 4% of Patients Treated in the Double-Blind Trial of Pediatric Patients with Lower Limb Spasticity and Reported More Frequently than with Placebo

Adverse Reactions		Unilateral		Bilateral	
	Placebo (N=79) %	Dysport 10 units/kg (N=43) %	Dysport 15 units/kg (N=50) %	Dysport 20 units/kg (N=37) %	Dysport 30 units/kg (N=30) %
Infections and infestations					
Nasopharyngitis	5	9	12	16	10
Upper respiratory tract infection	13	9	20	5	10
Influenza	8	0	10	14	3
Pharyngitis	8	5	0	11	3
Bronchitis	3	0	0	8	7
Rhinitis	4	5	0	3	3
Varicella	1	5	0	5	0
Ear infection	3	2	4	0	0
Respiratory tract infection viral	0	5	2	0	0
Gastroenteritis viral	0	2	4	0	0
Gastrointestinal disorders					
Vomiting	5	0	6	8	3
Nausea	1	0	2	5	0
Respiratory, thoracic and mediastinal disorders					
Cough	6	7	6	14	10
Oropharyngeal pain	0	2	4	0	0
General disorders and administration site conditions					
Pyrexia	5	7	12	8	7
Musculoskeletal and connective tissue disorders					
Pain in extremity	5	0	2	5	7
Muscular weakness	1	5	0	0	0
Nervous system disorders					
Convulsion/Epilepsy	0	7	4	0	7

14.4 Pediatric Patients with Lower Limb Spasticity

The efficacy of DYSPORT® was evaluated in a double-blind, placebo-controlled multicenter study in patients 2 to 17 years of age treated for lower limb spasticity because of cerebral palsy causing dynamic equinus foot deformity. A total of 235 (158 DYSPORT and 77 Placebo) toxin naïve or non-naïve patients with a Modified Ashworth Score (MAS) of grade 2 or greater at the ankle plantar flexor were enrolled to receive DYSPORT® 10 Units/kg/leg (n=79), DYSPORT® 15 Units/kg/leg (n=79) or placebo (n=77) injected into the gastrocnemius and soleus muscles. Forty one percent of patients (n=66) were treated bilaterally and received a total lower limb DYSPORT® dose of either 20 Units/kg (n=37) or 30 Units/kg (n=29). The primary efficacy endpoint was the mean change from baseline in MAS in ankle plantar flexor at Week 4; a co-primary endpoint was the mean Physician's Global Assessment (PGA) score at Week 4 (Table 17).

Table 17: MAS and PGA Change from Baseline at Week 4 in Pediatric Patients with Lower Limb Spasticity (ITT Population)

		Placebo (N=77)	DYSPORT® 10 U/kg/leg (N=79)	DYSPORT® 15 U/kg/leg (N=79)
LS Mean Change from Baseline in Ankle plantarflexor Muscle Tone on the MAS	Week 4	-0.5	-0.9 *	-1.0 *
	Week 12	-0.5	-0.8 *	-1.0 *
LS Mean PGA of Response to Treatment	Week 4	0.7	1.5*	1.5 *
	Week 12	0.4	0.8 *	1.0 *

LS=Least Square
*p<0.05

16 HOW SUPPLIED/STORAGE AND HANDLING

DYSPORT® for Injection is supplied in a sterile, single-use, glass vial. Unopened vials of DYSPORT® must be stored under refrigeration at 2°to 8°C (36°°F to 46°F). Protect from light.

Do not use after the expiration date on the vial. All vials, including expired vials, or equipment used with DYSPORT® should be disposed of carefully as is done with all medical waste.

DYSPORT® contains a unique hologram on the carton. If you do not see the hologram, do not use the product. Instead contact 877-397-7671.

Cervical Dystonia, Upper Limb Spasticity in Adults, and Lower Limb Spasticity in Pediatric Patients

Key Changes to the Medication Guide

What is DYSPORT®?
DYSPORT® is a prescription medicine that is injected into muscles and used:
- to treat cervical dystonia (CD) in adults
- to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary)
- to treat increased muscle stiffness in, elbow, wrist, and finger muscles in adults with upper limb spasticity
- to treat increased muscle stiffness in calf muscles in children 2 years of age and older with lower limb spasticity.

CD is caused by muscle spasms in the neck. These spasms cause abnormal position of the head and often neck pain. After DYSPORT® is injected into muscles; those muscles are weakened for up to 12 to 16 weeks or longer. This may help lessen your symptoms.
Frown lines (wrinkles) happen because the muscles that control facial expression are used often (muscle tightening over and over). After DYSPORT® is injected into the muscles that control facial expression, the medicine stops the tightening of these muscles for up to 4 months.
Upper limb spasticity is caused by muscle spasms in the elbow, wrist, and finger muscles. These spasms cause an abnormal position of these muscles. After DYSPORT® is injected into muscles, those muscles are weakened for up to 12 to 16 weeks or longer. This may help lessen your symptoms.
Lower limb spasticity is caused by muscle spasms in calf muscles. These spasms cause an abnormal position of these muscles. After DYSPORT® is injected into muscles, those muscles are weakened for up to 16 to 22 weeks or longer. This may help lessen your symptoms.
- For the treatment of cervical dystonia, glabellar lines, and upper limb spasticity in adults, it is not known whether DYSPORT® is safe or effective in children under 18 years of age.
- For the treatment of lower limb spasticity, it is not known whether DYSPORT is safe or effective in children under 2 years of age.
- It is not known whether DYSPORT® is safe or effective for the treatment of other types of muscle spasms.

It is not known whether DYSPORT® is safe or effective for the treatment of other wrinkles.

How should I take DYSPORT®?
- DYSPORT® is an injection that your doctor will give you
- DYSPORT® is injected into the affected muscles
- If you are an adult, your doctor may give you another dose of DYSPORT® after 12 weeks or longer, if it is needed

- If you are an adult being treated for CD or upper limb spasticity or you are a child (2 to 17 years of age) being treated for lower limb spasticity, your doctor may change your dose of DYSPORT®, until you and your doctor find the best dose for you. Children should not be retreated sooner than every 12 weeks.

The dose of DYSPORT® is not the same as the dose of any other botulinum toxin product

What are the possible side effects of DYSPORT®?
DYSPORT® can cause serious side effects. See "What is the most important information I should know about DYSPORT®?"

The most common side effects of DYSPORT® in children (2 to 17 years of age) with lower limb spasticity include:

- upper respiratory infection
- flu
- fever
- stuffy or runny nose and sore throat
- cough

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval

Risk Benefit Assessment

The results of study 141 show that Dysport is a safe and effective treatment for lower limb spasticity in children age 2 to 17 years. Supporting evidence comes from the fact that Dysport and other botulinum toxins have been shown to be safe and effective treatment for limb spasticity in adults. This is the first application of any botulinum toxin for the treatment of pediatric spasticity. Dysport is shown to be effective at 10 U/kg/Leg and 15 U/kg/Leg but the difference in the effect size is not substantially different on the MAS and PGA for the higher dose compared to the low dose. However, the proportion of responders on the MAS at the high dose was greater than the low dose. Numerically, the treatment difference compared to placebo is greater for the 15 U/kg/Leg compared to the 10 U/KG/Leg. In this reviewer's opinion, the statutory requirement for demonstrating effectiveness has been met.

Pediatric patients injected with the high dose Dysport (30 U/kg) in the proximal muscles of both legs were more likely to experience symptoms of remote spread of toxin. The information in the label does not include the use of Dysport for treatment of spasticity in the proximal lower limb muscles none. The other adverse effects are similar in type upper respiratory infections and musculoskeletal pain as those reported by adults treated with Dysport for upper limb spasticity. Dysport provides benefit for the treatment of lower limb spasticity in children with no change in the known adverse event profile described I the current Dysport label. The clinical trials data adds important information for the proper dosing and administration of Dysport for pediatric patients treated for lower limb spasticity.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not need to safely and effectively use of Dysport based review on the information in this supplement and the postmarketing history of Dysport.

Postmarketing Requirements and Commitments

Postmarketing Commitment 2564-6: is *FULFILLED*

6. A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with lower extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

PMC Establishment Date, 04/29/2009
Final Protocol Due Date 11/30/2009
Final Report Due Date 09/30/2013

Postmarketing Requirement 2564-5: Remains unfulfilled until all of the required studies are completed and reviewed by the FDA. The portion of the PMR related to the safety of Dysport for the treatment of lower limb spasticity in children ages 2 to 17 years is fulfilled.

5. Submit safety data assessing distant spread of toxin effects after multiple administrations of Dysport (abobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years) (approximately half upper, and half lower extremity spasticity). In addition, submit data assessing the effects of Dysport (abobotulinumtoxinA) on blood glucose and alkaline phosphatase as a marker of bone metabolism. These safety data could come from open-label extensions of the clinical studies specified under #5-8 below, from separate long-term open-label safety studies, or from a long-term controlled safety and efficacy study. The doses evaluated must be at least as high as those shown effective in studies specified under #5-8 below, or those commonly used to treat spasticity.

Final Protocol Due Date 07/31/2010
Final Report Due Date 05/31/2015

Recommended Comments to Applicant

None outside of the Comments in the Approval Letter (routine).

Cited Publications

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/s/

GERALD D PODSKALNY
07/26/2016