CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125274/105
Priority or Standard	Standard
Submit Date(s)	September 30, 2015
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PDUFA Goal Date	July 30, 2016
Division / Office	DNP/OND
Reviewer Name(s)	Susanne R. Goldstein, MD
Review Completion Date	July 8, 2016
Established Name	abobotulinumtoxinA
(Proposed) Trade Name	Dysport
Therapeutic Class	Purified Neurotoxin Complex
Applicant	Ipsen
Formulation(s)	Injection IM
Dosing Regimen	As needed
Indication(s)	Lower Limb Spasticity
Intended Population(s)	Pediatric

Template Version: March 6, 2009

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APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The results of the pivotal Phase III trial for lower limb (LL) spasticity in the pediatric population, Study Y-52120-0141, show substantial evidence of effectiveness without changing the known risk profile of Dysport (abobotulinumtoxinA). The studies leading to the approval of Dysport for the treatment of UL spasticity in adults (July 16, 2015) are supportive evidence of efficacy of Dysport in the treatment of spasticity in the pediatric population.

I recommend APPROVAL of Dysport for the treatment of lower limb spasticity in the pediatric population with a maximum recommended dose of 30 U/kg or 1000 U, whichever is lower, injected in the (b) (4) lower extremity. The PMC for the treatment of lower limb spasticity in pediatric population is fulfilled. The PMR for a long-term safety study in pediatric population treated for spasticity (half upper and half lower limb) cannot be fulfilled until the upper limb PMC submission is reviewed.

1.2 Risk Benefit Assessment

The efficacy results for the treatment of LL limb spasticity with Dysport (10 U/kg/leg and 15 U/kg/leg) in the pediatric population in the pivotal study 141, is statistically significant for the co-primary endpoints, the change in Modified Ashworth Scale (MAS) scores from Baseline to Week 4 for the gastrocnemius soleus complex (GSC) and the Physician's Global Assessment (PGA) compared to placebo. The PGA supports the clinical meaningfulness of Dysport's effect on spasticity as measured by the MAS.

Three additional double blind studies, Studies 040, 701, 094, were conducted (b) (4)

(b) (4)

Dysport was recently approved for the treatment of UL spasticity in adults. The results from the pivotal trial, Study 145, are considered supportive of efficacy for Dysport in the treatment of LL spasticity in pediatric patients (Please refer to sBLA 125274/102 Clinical Review July 14, 2015.)

Nine studies (4 DBPC, 5 OL) were submitted to evaluate the safety of Dysport in LL spasticity in the pediatric population, in the ISS. The overall exposure as well as the long term exposure, 6 months (2 consecutive treatments, and 12 months (4 consecutive treatments) Dysport 30 U/kg is adequate. Review of the Treatment Emergent Adverse

Events (TEAEs), Serious Adverse Events (SAEs) and deaths for Study 141, the ISS and postmarketing safety update did not reveal any new safety signals.

Dysport met the regulatory requirement for providing evidence of effectiveness for the treatment of lower limb spasticity in pediatric patients. The information in the sponsor's submission demonstrates that Dysport 10 U/kg/leg and 15 U/kg/leg are effective. The review of the safety information in this submission does not change the safety conclusions regarding use of Dysport for the treatment of spasticity in the pediatric population, ages 2-17 years old. Dysport, as studied, can be used safely for treatment of lower limb spasticity in the pediatric population at the recommended maximum dose of Dysport 15 U/kg/leg (30 U/kg) given no sooner than every 16-18 weeks. A risk mitigation strategy (REMS), additional PMR or PMC are not indicated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This supplement does not require a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of approval of Dysport for Cervical Dystonia and Glabellar lines (April 29, 2009), the FDA imposed Postmarketing Requirements (PMR) and Postmarketing Commitments (PMC) under FADAAA to study Dysport for the treatment of spasticity in adults and in the pediatric population. There was substantial evidence of use and adverse events including fatal and nonfatal serious adverse events reported in association with Dysport as well as other botulinum toxin products used in the treatment of spasticity in adults and children. As of July 14, 2015, the following modifications have been made to the PMRs and PMCs, issued at the time of initial approval of Dysport outlined below:

PMR

2933-1
A juvenile rat toxicology study is required to identify the unexpected serious risk of adverse effects on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Dysport (abobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

Final Report Submission: 08/15

2933-2

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

Study Completion: 05/18
Final Report Submission: 10/18

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.

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.

As of April 28, 2014, three clinical studies are ongoing, and 458 subjects have enrolled in the study. 7/14/15 Missed milestone letter sent; final study report not yet submitted. Original final report

PMC

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.
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.

The final report was submitted to FDA on 9/30/15

Additional PMRs or PMCs are not recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Dysport inhibits the release of the neurotransmitter acetylcholine, from peripheral cholinergic nerve endings. Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH –induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 lead to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction.

2.2 Tables of Currently Available Treatments for Proposed Indications

Treatments available for LL spasticity

Drug	**Preparation**
Systemic	
Baclofen*	Oral and Intrathecal
Dantrolene * (>5 years)	Oral
Diazepam *(>6 months)	Oral
Tizanidine	Oral
Local Injections	
Local anesthetics: Lidocaine, bupivacaine, Etidiocaine	

Ethyl Alcohol, Phenol, OnabotulinumtoxinA (BOTOX) *Approved April 17, 2015, January 21, 2016* abobotulinumtoxinA (Dysport) Approved *July 16, 2015*	I.M. for Adult upper limb including thumb, I.M. for Adult LL I.M. for Adult upper limb
Surgical	
Orthopedic procedures: Tendon release/lengthening.	

* FDA approved in pediatric patients for spasticity

2.4 Important Safety Issues with Consideration to Related Drugs

Potential distant spread of toxin (PDSOT) from the area of injection to other sites, producing symptoms consistent with the effects of botulinum toxin, i.e. weakness, is one of the main safety concerns for this class of drug. This effect is included in a boxed warning in the Dysport label (July 16, 2015.)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Dysport was first approved in the United States **April 29, 2009** for the treatment of cervical dystonia (spasmodic torticollis) by the Division of Neurology Products (DNP) and for the treatment of glabellar lines in adults by the Division of Dermatology and Dental Products (DDDP)

The sponsor received Orphan Designation on October 20, 1999 for the treatment of pediatric LL spasticity secondary to cerebral palsy.

During the filing review, it was noted that the sponsor proposed (b) (4) treatment of lower limb spasticity in pediatric patients (b) (4). The mechanism of action of botulinum toxin in the treatment of spasticity is not dependent on pathophysiology; it acts peripherally at the end organ, the neuromuscular junction rather than at the cortical or spinal motor neurons (b) (4)

In a letter dated December 11, 2015, the sponsor was asked:

Please provide a scientific justification for [redacted] (b) (4) propose labeling that incorporates a [redacted] indication ,i.e., "for the treatment of lower limb spasticity" in (all) pediatric patients.

You may consult the Office of Orphan Products Development regarding implications for orphan designation and orphan drug exclusivity.

After consulting with the Office of Orphan Products Development regarding orphan exclusivity [redacted] (b) (4) [redacted] (b) (4) indication for all pediatric patients (March 15, 2016), the sponsor agreed to revise labeling for the pediatric population (June 2, 2016) stating:

[redacted] (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the filing review, the following information was requested:

We request that you submit the following Biometrics information for study Y-55-52120-141:

1. We are unable to locate the effectiveness data presented by gender subgroup in your submission. Please identify the location of the effectiveness analyses by gender in your submission. If this information was not included in your submission, please submit this information as an amendment to your application no later than December 24, 2015.

2. Please provide the data unblinding date of the study and submit all versions of the protocol and SAP (initial and amendments) no later than December 24, 2015.

During the review cycle, an information request (IR) was sent to the sponsor on May 11, 2016

In the ISS, you have presented exposure for consecutive injections within 6 and 12 months (Table 12, p.41 of the ISS.) In order to better understand the dosing intervals (length between treatments) please recalculate and submit the

exposure table using actual dose received (not mean or median). Please use the following actual dosing intervals (i.e., ≥12 weeks but < 16 weeks, ≥16 weeks but less than 18 weeks, ≤ every 18 weeks) not the average or median interval between injections:

- *2 consecutive injections occurring every 12 weeks, 16 weeks and 18 weeks or sooner*
- *4 consecutive injections occurring every 12 weeks, 16 weeks and 18 weeks or sooner*

In addition, please calculate the exposure for subjects who received the maximum dose of Dysport 1000 U (actual dose=1000 U, not mean or median). Please present the data in tabular format, for consecutive cycles using actual weeks between treatments. Use the exposure intervals described above.

3.2 Compliance with Good Clinical Practices

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the ICH Consolidated Guideline on Good Clinical Practice.

The electronic data capture (EDC) was conducted in adherence to the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials [1, 2]. In addition, this study adhered to all local regulatory requirements. Ipsen included a Debarment Certification (module 1.3.3) stating that:

Ipsen Bipharm Limited hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal, Drug and Cosmetic Act in connection with this application.

This was signed by Zubair Hussam, VP Global Regulatory Affairs, 9/15/2015 and Gerard Hicky, Ph.D., US Agent, 9/16/2015.

3.3 Financial Disclosures

The sponsor submitted Certification: Financial Interests and Arrangements of Clinical Investigators: Form FDA 3454, signed by Zubair Hussain, SVP Global Regulatory Affairs, 9/15/2015 (module 1.3.4.)

On July 6, 2016, an information request was sent to the sponsor:

You have submitted FDA form 3454 attesting to financial disclosure for all investigators. However, you did not include either individual investigator forms of financial disclosure or evidence of due diligence in obtaining this information.

Would you either provide the individual investigator financial disclosure forms or evidence of due diligence on their part in obtaining this information, as required by CFR 54.4. This applies to all investigators who participated in Studies 141 and 147.

On July 11, 2016, the sponsor submitted Certification/Financial Disclosure forms for all investigators/sub-investigators who participated in studies 141 and 147. None of the investigators/sub-investigators had any financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

NONE

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Overview of Clinical Studies in Pediatric Lower Limb Spasticity

The sponsor has conducted a total of 10 prospective clinical studies with Dysport for the treatment of lower limb (LL) spasticity in pediatric patients.

The **five double blind, placebo controlled studies** conducted with Dysport in the treatment of PLL spasticity include:

- One pivotal double blind, placebo controlled single-treatment study: Y-55-52120-141 (Study 141);
- Four other double blind, placebo controlled single treatment legacy studies:
  - Y-97-52120-040 (Study 040);
  - Y-97-52120-701 (Study 701);
  - Y-97-52120-033 (Study 033);
  - A-94-52120-094 (Study 094).

Of note, Study 033 was terminated prematurely due to lack of recruitment, and is not included in the efficacy analyses.

These studies are outlined in Table 1.

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]	Number of	Study Duration
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.	Distal muscles: gastrocnemius, soleus (unilateral or bilateral injections)	1	12 to 28 weeks
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)	1	16 to 36 weeks
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)	1	16 to 36 weeks
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	1	2 to 24 weeks
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	1	12 weeks

CP=cerebral palsy; CSR=clinical study report; DB=double blind; ID-identification; N=number of randomized subjects; PC=placebo controlled; PLL= pediatric lower limb; U=unit.
Data Source: Study CSRs in Module 5.3.5.1 and Module 5 3 5.4.
a Muscles that have bulk of muscle distal or proximal to the knee joint line are considered distal and proximal muscles, respectively.
b Study 033 was terminated prematurely due to poor subject recruitment (40 subjects were recruited from a planned target of 100 subjects).

Source: Sponsor

The **five open label studies** conducted with Dysport in the treatment of PLL spasticity include:

- One open label extension study to the pivotal Study 141 with repeated treatment: Y-55-52120-147 (Study 147);

- Two studies with repeat treatment: Y-97-52120-702 (Study 702) and A-38-52120-052 (Study 052);
- One single-treatment study: A-38-52120-711 (Study 711);
- One single-treatment study with two active Dysport treatment arms: A-94-52120-062(Study 062).

These studies are summarized in Table 2.

Table 2 Summary of the Open Label Studies of Dysport for the Treatment of Pediatric 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[b] • Up to 15 U/kg for unilateral treatment; Up to 30 U/kg for	Treatment 1 Distal/proximal muscles: gastrocnemius, soleus ± hamstrings Treatments 2 to 4 Distal/proximal muscles: gastrocnemius, soleus ±	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	CP lower limb spasticity	• 30 U/kg at 12 month intervals • 30 U/kg at 4	Distal muscles: gastrocnemius (bilateral	3 to 7	28 months (112
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	Distal muscles: gastrocnemius (unilateral or bilateral	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	Distal muscles: gastrocnemius (unilateral or bilateral	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	Distal muscles: gastrocnemius + soleus if unilateral injections; only gastrocnemius if	1	36 weeks

CP=cerebral palsy; CSR=clinical study report; ID=identification; N=number of enrolled subjects; N/A=not applicable; OL=open label; PLL=pediatric lower limb; U=unit.
Data Source: Study CSRs in Module 5.3.5.2.
a Muscles that have bulk of muscle distal or proximal to the knee joint line are considered distal and proximal muscles, respectively.
b Study 147 permitted the concomitant treatment of pediatric upper limb spasticity but only PLL dose was used in analysis in this dossier. c Study 702 included subjects from Studies 040 and 701 and de novo subjects.

d 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 double blind with respect to low or high
Dysport dose, subjects received only active treatment so it is included in the open label study category.

Source: Sponsor

5.2 Review Strategy

In support of efficacy, the sponsor has included the results of a Phase III DBPC study, Y-55-52120-141(study 141); with an ongoing open label extension study Y-55-52120-147 (study 147.)

The information in the report for Study 141 provides the primary evidence of efficacy for pediatric lower limb spasticity and will be the focus of this review. The primary efficacy endpoint of Study 141 is change in the Modified Ashworth Score (MAS) from baseline to week 4 in the gastrocnemius-soleus complex (GSC). A key secondary endpoint, the Physicians Global Assessment (PGA), was included in the primary analysis of efficacy to assess the clinical meaningfulness of change in the primary endpoint, change in MAS. This study will be discussed in detail in Section 6.0.

(b) (4)

The Integrated summary of safety (ISS) contains data from both double blind and open label studies. Safety data from the ISS will be presented in Section 7.0. In addition, safety data from pivotal DBPC study 141 will be presented in Section 7.0.

6 Review of Efficacy

Efficacy Summary

(b) (4)

There was one pivotal double blind, placebo controlled single-treatment study, Y-55-52120-141 (Study 141) and four double blind placebo controlled single treatment legacy studies.

- One pivotal double blind, placebo controlled single-treatment study: Y-55-52120-141 (Study 141);

- (b) (4)

The pivotal study, Study 141, is the primary support of efficacy for the application and will be reviewed in detail. Studies 040, 701 and 094 will be summarized. Study 033 was terminated early due to lack of recruitment of subjects, and therefore, will not be reviewed other than for safety.

6.1 Indication

Dysport was granted Orphan designation for lower limb spasticity in pediatric patients secondary to cerebral palsy October 20, 1999. The proposed labeling included with the submission, was for Dysport for the treatment of lower limb spasticity in pediatric patients (b) (4). On December 11, 2015, the Agency asked the sponsor to provide scientific justification for (b) (4) On June 2, 2016, after consultation with OOPD, (b) (4) (b) (4) indication for the treatment of LL spasticity in all pediatric patients.

6.1.1 Methods

The pivotal efficacy study 141 used the MAS to measure the treatment effect of Dysport on spasticity (muscle tone.) The MAS measures resistance to passive movement and is rated on a six point categorical scale (0,1,1+/1.5, 2, 3, 4.) A reduction of at least one grade in MAS is considered to be clinically relevant.

The key secondary efficacy endpoint (co-primary) was the Physicians Global Assessment (PGA). The PGA is a nine point scale ranging from -4 (markedly worse) to 4 (markedly improved.)

Of the 4 other DBPC studies submitted, only study 094 included the MAS, which was a secondary efficacy endpoint. The primary efficacy endpoint for study 094 was change in joint angle (range of passive motion) at the hip. Study 040, a dose ranging study, and Study 701 did not include MAS as an efficacy endpoint.

Pivotal Efficacy Study- Study 141

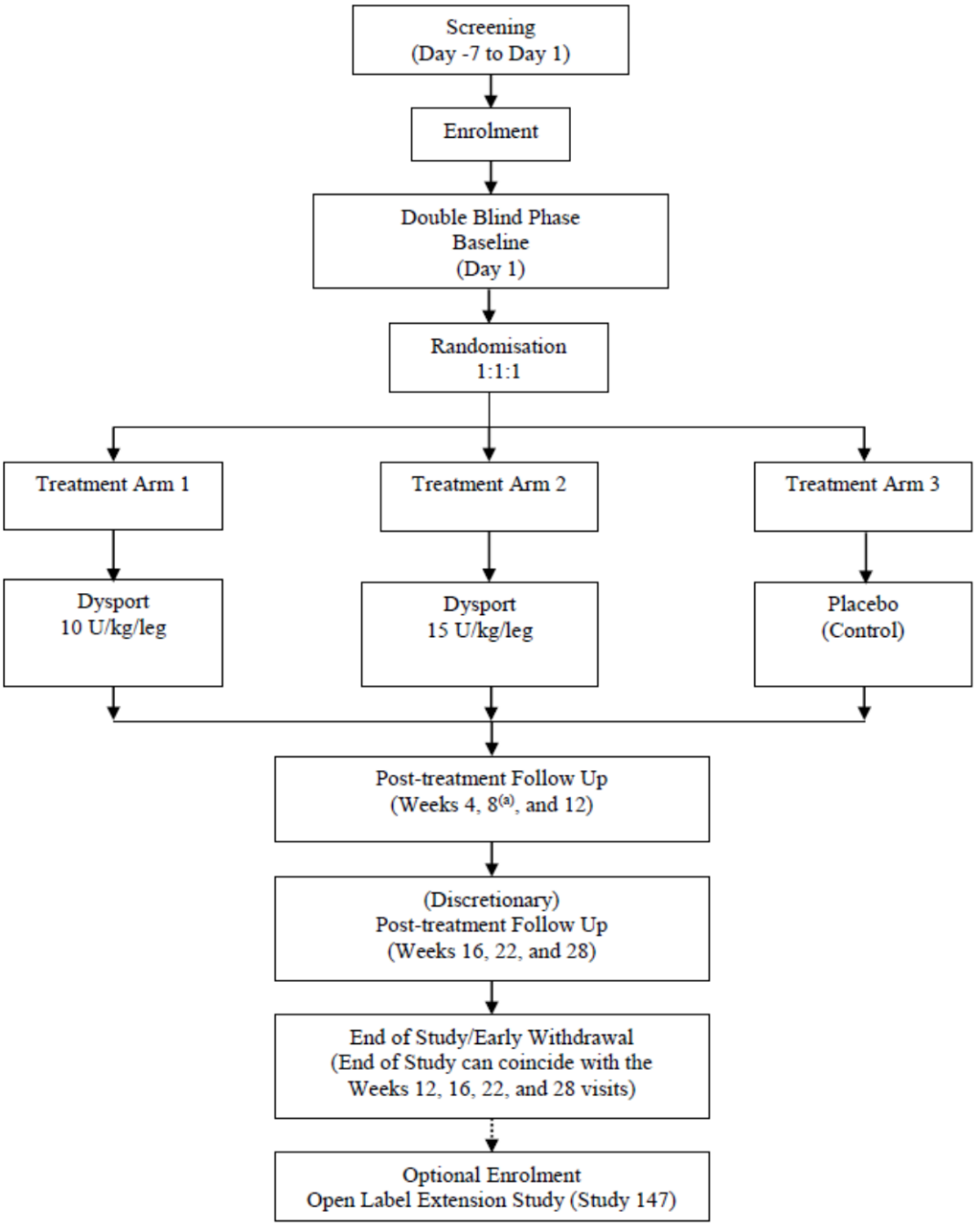
Design

The sponsor conducted a Phase III double blind placebo controlled, multicenter trial to evaluate the treatment effect of Dysport on pediatric patients with LL spasticity. The

study compared Dysport 10 U/kg/leg (10 U/kg for unilateral and 20 U/kg for bilateral), 15 U/kg/leg (15 U/kg for unilateral and 30 U/kg for bilateral) and placebo.

The study design is shown in Figure 1.

Figure 1 Study Flow Diagram



[a] Telephone contact.

Selection of Study Population

The inclusion/exclusion criteria for Study 141 are outlined below:

Inclusion Criteria

1. Provision of a signed informed consent obtained from the child's parent/guardian and a signed assent from the child when and where possible
2. Were from 2 to 17 years of age, inclusive
3. Had a diagnosis of CP as defined by Rosenbaum
4. Ambulatory with spasticity hemiparesis, paraparesis, diparesis or tetraparesis characterized by an equinus foot positioning during the stance phase of the gait
5. Able to walk (sufficient to complete video 2D motion analysis) with or without walking aids
6. Had a MAS score $\geq$2 at the ankle joint of the (most) affected lower limb to be injected
7. Had a spasticity grade (Y) between 2 and 4, inclusive on the TS assessed at the ankle joint of the most affected limb to be injected with a spasticity angle (X) of 10 degrees or more.
8. Were classified as the GMFCS Level I to III, inclusive
9. Botulinum toxin naïve subjects or subjects having received their last BTX treatment of any type more than 6 months prior to study entry for any condition.
10. If undergoing pre-study physiotherapy, it 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 a at least the Week 12 visit.
11. Be instructed and willing to use their casting/orthoses in the same way as before entry into the study until the end of the Week 12 visit.

Exclusion Criteria

1. Diagnosed as resistant to BTX treatment of any type
2. Evidence of non-ambulatory status
3. Major limitation in the passive range of motion at the ankle, as defined by maximum ankle dorsiflexion measured by the angle of arrest (XV1) at slow speed of <80 degrees (TS angle) in the most affected leg to be injected.
4. Subjects likely to be treated with BTX in the upper limbs during the course of this double blind study
5. Severe athetoid or dystonic movements in the targeted lower limb(s)
6. Significant difference (>2 cm) between the length of legs, defined clinically and confirmed, as required, by scanogram (A radiographic technique used for showing true dimensions by moving a narrow orthogonal beam of x-rays along the length of the structure being measured, the lower extremities.)
7. Current need for surgery or previous surgery for spasticity of the GSC and/or hamstring muscles (and tendons) in the most e affected leg to be injected.
8. Serial casting in the past 12 weeks

9. Previous injection of alcohol and/or phenol into the GSC and/or hamstrings in the most affected leg to be injected
10. Treatment with any drug that interferes either directly or indirectly with neuromuscular function (e.g. aminoglycoside antibiotics) or neuroblocking agents used during surgery (e.g. curare) within the last 30 days prior to study treatment
11. Be pregnant and/or lactating
12. Female subjects, not willing to use contraceptive measures throughout the course of the study if post-pubertal and sexually active.
13. In ability or unwillingness to comply with the protocol
14. Subjects with any clinical (or sub-clinical) evidence of marked defective neuromuscular transmission (e.g. Lambert-Eaton syndrome or myasthenia gravis) or persistent clinically significant neuromuscular disorders
15. Known sensitivity to BTX or to any of the components in the formulation or allergy to cow's milk protein
16. An infection at the injection site(s)
17. Ongoing treatment with intrathecal baclofen or previous/planned rhizotomy.
18. Treatment with a new investigational drug within 30 days prior to enrollment into the study or are scheduled to receive such a drug during the study periods
19. Any medical condition, laboratory or diagnostic procedure finding, which might compromise compliance with the objectives and procedures of this protocol or preclude administration of BTX-A, as judged by the Investigator.

REVIEWER COMMENT:

The study population includes pediatric patients with cerebral palsy. The prevalence of cerebral palsy is between 1.5 and 3 cases per 1000 live births with up to 80% of pediatric patients with CP having spasticity. The study population based on the inclusion/exclusion criteria is reasonable to support the indication of LL spasticity in pediatric patients.

Location:

The study was conducted as a multicenter study at 35 investigational sites:27 sites enrolled patients in France, Mexico, Turkey, Poland, and USA. Subjects were randomized into one of three treatment groups, Dysport 10 U/kg/leg, Dysport 15 U/kg/leg, or placebo in a ratio of 1:1:1, and stratified according to age range (2 to 9 years and 10 to 17 years) and botulinum toxin naïve or non-naïve status.

Number of Sites and Enrolled Patients in The ITT Population Per 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

Efficacy assessments:

The **primary efficacy endpoint** was mean change in the Modified Ashworth Score (MAS) in the Gastrocnemius-soleus Complex (GSC) at the ankle joint of the most affected lower limb between Baseline and Week 4, with the key secondary efficacy endpoint (co-primary in SAP for FDA) being the Physician Global Assessment (PGA) at week 4.

Other **secondary efficacy endpoints** included:

- Mean Physicians Global Assessment (PGA) score at Week 4.
- Mean Goal Attainment Scale (GAS) score at Week 4.

Tertiary Efficacy Endpoints included:

• 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 (XV3) at fast speed, X and Y derived from the Tardieu (TS) at the ankle joint of the (most) affected lower limb.
• Mean change from baseline to Week 4 (and Week 12) in the 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 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 Pediatric Quality of Life Inventory™ (PedsQL™) score.

Dose and Administration:

Subjects received either one of two Dysport doses or placebo injected into the gastrocnemius soleus complex (GSC) of each affected leg. The Dysport dose was either 10 U/kg or 15 U/kg for unilateral injections, or 20 U/kg or 30 U/kg for bilateral injections. The study treatment was injected intramuscularly into six injection sites per affected lower limb (four sites in the gastrocnemius muscle and two sites in the soleus muscle.) The total volume injected was 2.0 mL with a maximum concentration of 500 U/mL. (Table 3.)

Table 3 Injection Volume in Gastrocnemius-soleus Complex per Leg without Hamstring Injections

Muscle Injected	Upper Quadrant (No. of Sites)	Lower Quadrant (No. of Sites)	Total Volume
Gastrocnemius	0.4 mL (x2)	0.2 mL (x2)	1.2 mL
Soleus	N/A	0.4 mL (x2)	0.8 mL
Per leg			2.0 mL

Abbreviations: N/A=not applicable; No.=number.

Source: Sponsor

The maximum dose injected in subjects was not to exceed 30 U/kg or 1000 U, whichever was the lower value. The dose selection for the pivotal study, Study 141, was based upon the dose finding study, Study 040; which used 30 U/kg as the maximum dose. The 30 U/kg dose was both efficacious and well tolerated (see detailed description in section 6.1.10.)

6.1.2 Demographics

The demographic characteristics for subjects enrolled in Study 141 are presented in Tables 4 and 5, by treatment received.

Table 4 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.
Data Source: Table 14.1.5.1, Listing 16.2.4.1 and Listing 16.2.9.2.
Note: The denominator is the number of subjects in the given column (N).

Source: Sponsor

Table 5 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)
Neutralizing 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 neutralizing antibodies were not assessed.
Data Source: Table 14.1.5.1, Table 14.2.4.3, Listing 16.2.4.4, Listing 16.2.4.5, Listing 16.2.5.1, Listing 16.2.6.1, Listing 16.2.6.5 and Listing 16.2.9.4.
Note: The denominator is the number of subjects in the given column (N). Tanner grading scale was only collected for female subjects so the denominator is the number of female subjects in the given column (n).

Source:Sponsor

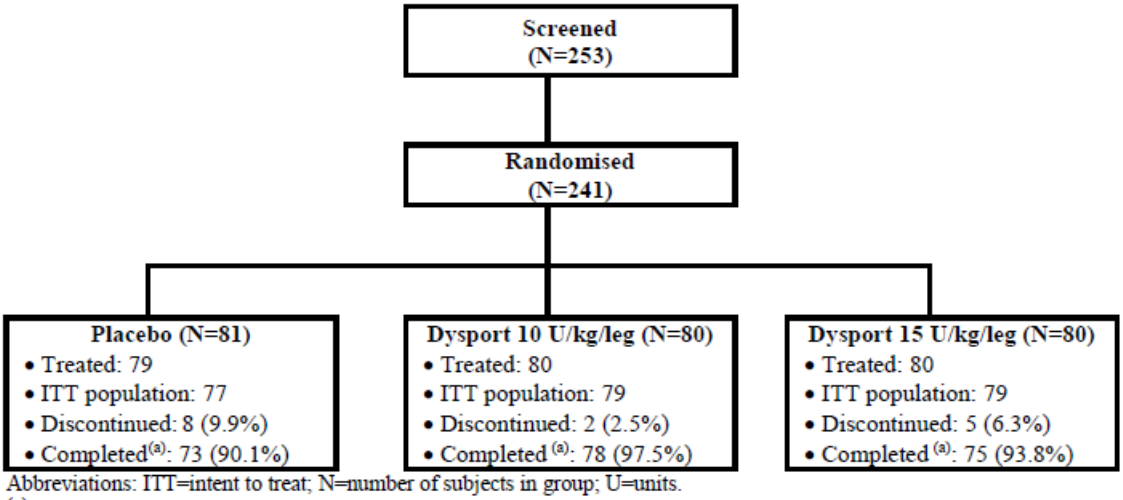
REVIEWER COMMENT:

The majority of subjects (approximately 85%) were in the age range of 2-9 years old, with approximately 50% male, 50% female and 75% Caucasian. This was similar across treatment groups. In addition the mean BMI was 15.0, approximately 50% were botulinum toxin (BTX) naïve, 50-60% was injected unilaterally and approximately 85% had MAS score of 2 in the most affected limb. Of note, only 20% of the subjects were enrolled in sites in the United States.

6.1.3 Subject Disposition

A total of 253 subjects were screened, of whom 241 were enrolled into the study and were randomized into one of three treatment groups in a 1:1:1 ratio (Figure 2)

Figure 2 Subject Disposition, by Dose per Leg - Screened Population



Abbreviations: ITT=intent to treat; N=number of subjects in group; U=units.
[a] Were either identified as eligible for retreatment or were not eligible for retreatment by Week 28.
Data Source: Table 14.1.1.2 and Table 14.1.2.1.

Source:Sponsor

REVIEWER COMMENT:

Overall , 15 (6.2%) of subjects discontinued the study prematurely: 14 subjects prior to or at Week 12 (8 in the placebo group, 2 in the Dysport 10 U/kg/leg treatment group, and 3 in the Dysport 15 U/kg/leg treatment group) and 2 subjects after Week 12, both of whom were in Dysport 15 U/kg/leg treatment group. Overall, Dysport 10 U/kg/leg had the highest completion rate.

The reasons for discontinuation are outlined in Table 6.

Table 6 Subjects Discontinuing the Study by Reason, by Dose per Leg - Randomized Population

Total Withdrawals Reason for Withdrawal, n (%)	**Placebo (N=81)**	**Dysport 10 U/kg/leg (N=80)**	**Dysport 15 U/kg/leg (N=80)**	**All Subjects (N=241)**
Total number of withdrawals	8 (9.9)	2 (2.5)	5 (6.3)	15 (6.2)
Does not meet entry criteria	1 (12.5)	0	0	1 (6.7)
Adverse event	1 (12.5)	0	0	1 (6.7)
Protocol violation	0	0	0	0
Consent withdrawn	3 (37.5)	1 (50.0)	3 (60.0)	7 (46.7)
Lost to follow up	1 (12.5)	0	1 (20.0)	2 (13.3)
Other	2 (25.0)	1 (50.0)	1 (20.0)	4 (26.7)

Abbreviations: N=number of subjects in group; n=number of subjects with data; U=Units.
Data Source: Table 14.1.2.4, Listing 16.2.1.1 and Listing 16.2.1.2.1.
Note: Percentages for total number of withdrawals are based on the total number of subjects who were randomized to the study. For individual reasons, percentages are based on the number of subjects who discontinued the study overall or at that visit, as applicable.

Source:Sponsor

REVIEWER COMMENT:

Only one subject, enrolled in the placebo group, withdrew due to adverse events.

Major protocol deviations by treatment group are presented in Table 7.

Table 7 Major Protocol Deviations, by Treatment Group (Dose per Leg) - Randomized Population

Major Deviations Deviation type, n (%)	**Placebo (N=81)**	**Dysport 10 U/kg/leg (N=80)**	**Dysport 15 U/kg/leg (N=80)**	**All Subjects (N=241)**
Subjects with at least one major protocol deviation	14 (17.3)	12 (15.0)	14 (17.5)	40 (16.6)
Eligibility criteria violation	2 (2.5)	2 (2.5)	1 (1.3)	5 (2.1)
GCP Breach	6 (7.4)	7 (8.8)	11 (13.8)	24 (10.0)
Procedures violation	0	1 (1.3)	0	1 (0.4)
Prohibited medication/therapy/surgery	1 (1.2)	1 (1.3)	0	2 (0.8)
Randomization/treatment allocation process violation	1 (1.2)	0	0	1 (0.4)
Study treatment non-compliance	3 (3.7)	1 (1.3)	2 (2.5)	6 (2.5)
Test/examination not done	4 (4.9)	1 (1.3)	1 (1.3)	6 (2.5)

Abbreviations: GCP=good clinical practice; N=number of subjects in group; n=number of subjects with data; U=Units.
Data Source: Table 14.1.3.1, Listing 16.2.2.2.
Note: The denominator is the number of subjects in the given column (N). Subjects may have more than one deviation.

Source:Sponsor

REVIEWER COMMENT:

There were a total of 51 major protocol deviations reported for 40 subjects during the study. The types of protocol violations were similar across treatment groups with breach in good clinical practices being the most common, Dysport 15 U/kg/leg>Dysport 10 U/kg/leg> placebo.

6.1.4 Analysis of Primary Endpoint(s)

Two different statistical strategies for the primary efficacy analysis were applied for the registrations in the USA and non USA countries. In the USA, the superiority of Dysport to placebo was demonstrated if any Dysport dose was superior to placebo for both the primary (change in MAS at week 4) and first secondary (PGA at week 4) efficacy endpoints. A hierarchical testing procedure was applied to test for superiority.

Mean data for the Dysport and placebo groups were compared using two contrast analyses within a single analysis of covariance (ANCOVA) model, controlled for the baseline MAS score, the randomization stratification factors (age range and BTX

treatment status at baseline) and the center, all as fixed effects. The least squares (LS) mean and the associated 95% confidence intervals were calculated for the Dysport and placebo groups, plus the differences in the LS means between these groups and the associated p-values.

The results of the change in MAS from baseline to week 4 are presented in Table 8.

Table 8 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.
Data Source: Table 14.2.1.1, Table 14.2.1.2 and Listing 16.2.6.1.
Note: MAS is displayed on derived scale. LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANCOVA on the change from baseline with treatment, baseline MAS score, age range at baseline, BTX status at baseline and center as covariates.

Source:Sponsor

The first secondary efficacy endpoint, mean PGA score at Week 4, was analyzed using an analysis of covariance (ANCOVA) model, controlling for randomization stratification factors (age range and BTX treatment status at baseline) and the center, all as fixed effects (Table 9).

Table 9 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.
Data source: Table 14.2.2.1, Table 14.2.2.2 and Listing 16.2.6.2.
Note: LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BTX status at baseline and center as covariates.

Source:Sponsor

REVIEWER COMMENT:

Both the change in MAS from baseline to Week 4 and the PGA score at Week 4 were statistically significantly improved for Dysport 10 U/kg/leg and 15 U/kg/leg compared to placebo.

The statistical reviewer checked the normality of the residuals of the primary analysis ANCOVA model for the MAS and did not find any violations of the normality assumption. (Dr. X. Zhang, 07//6/2016)

6.1.5 Analysis of Secondary Endpoints(s)

The second secondary efficacy endpoint as the Goal Attainment Scale score at Week 4. The GAS, Goal Attainment Scale, is a functional scale. Individual goals (one to three goals) were defined for each patient by the physician and the patients' parents where applicable. The goals were ranked according to their importance to the parent/child. The overall GAS score is based on the weighted average ratings of the goals, with weights calculated from importance ratings scores and difficulty rating scores. The results are presented in Table 10.

Table 10 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.
Data source: Table 14.2.3.1, Table 14.2.3.2 and Listing 16.2.6.3.
Note: LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BTX status at baseline and center as covariates.

Source:Sponsor

REVIEWER COMMENT:

Although, the GAS score was not part of the primary efficacy analysis hierarchy, it was nominally significant for both Dysport treatment groups compared to placebo.

6.1.6 Other Endpoints

Tertiary Efficacy Endpoints:

The change from Baseline in MAS Scores at all-time points **except Week 4** are presented in Table 11 and shown graphically in Figure 3.

Table 11 Modified Ashworth Scale Score in the (Most) Affected Leg, Change from Baseline at all Time points (except Week 4), by Treatment Group (Dose per Leg) - ITT Population

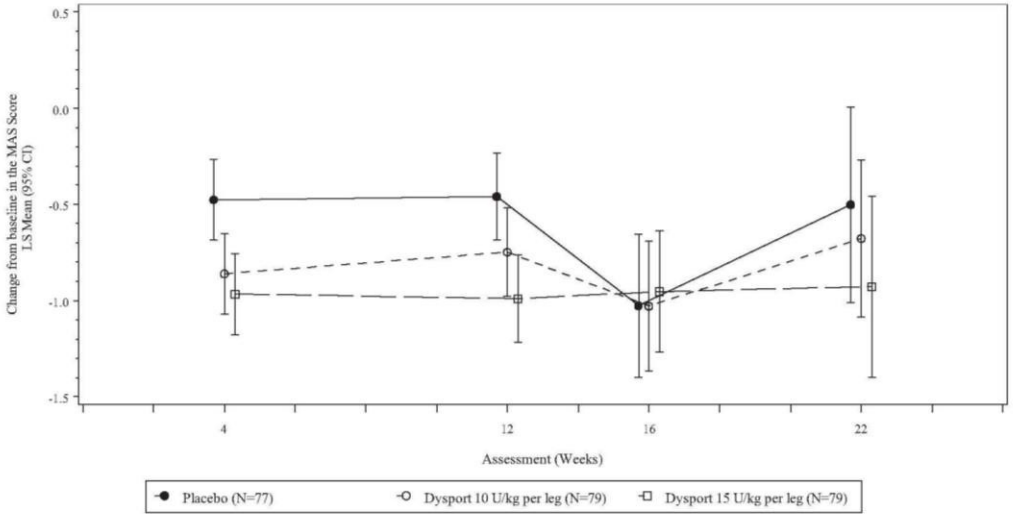
Visit Statistic	Placebo (N=77)	Dysport 10 U/kg/leg (N=79)	Dysport 15 U/kg/leg (N=79)
Week 12	n=70	n=69	n=74
Mean change (SD)	-0.5 (0.8)	-0.7 (0.8)	-1.1 (0.9)
LS mean change (95% CI)	-0.5 (-0.7, -0.2)	-0.8 (-1.0, -0.5)	-1.0 (-1.2, -0.8)
LS mean change vs placebo (95% CI)	N/A	-0.3 (-0.6, -0.0)	-0.5 (-0.8, -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
Source: Table 14.2.4.1, Table 14.2.4.2 and Listing 16.2.6.1.
Note: MAS is displayed on derived scale. LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANCOVA on the change from baseline with treatment, baseline MAS score, age range at baseline, BTX status at baseline and center as covariates.

Source:Sponsor

The results for change from Baseline in MAS are shown graphically in Figure 3.

Figure 3 Change from Baseline in the Modified Ashworth Scale Score in the (Most) Affected Leg, by Treatment Group - ITT Population



Data Source: Figure 14.2.1.1.

Source:Sponsor

REVIEWER COMMENT:
The change in MAS at Week 12 was nominally significant for both active treatment groups compared to placebo.

A responder analysis for the MAS by week is presented in Table 12. Responders were defined as, the number of subjects with ≥1 grade reduction in their MAS score compared to their baseline score.

Table 12 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 Source: Table 14.2.4.4 and Listing 16.2.6.1.
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:Sponsor

REVIEWER COMMENT:

The responder analysis for the MAS was nominally significant for Dysport 15 U/kg/leg at Weeks 4 and 12, while Dysport 10 U/kg/leg showed a positive trend at Week 4, only.

The PGA of treatment response at all-time points **except Week 4** is presented in Table 13.

Table13 Physician's Global Assessment of Treatment Response at all Time points (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 score (SD)	0.5 (1.0)	0.8 (1.4)	1.1 (1.2)
LS mean (95% CI)	0.4 (0.0, 0.7)	0.8 (0.5, 1.2)	1.0 (0.7, 1.3)
LS mean vs placebo (95% CI)	N/A	0.5 (0.1, 0.9)	0.7 (0.3, 1.0)
p-value	N/A	0.0212	0.0013
Week 16	n=30	n=41	n=47
Mean score (SD)	0.5 (1.0)	1.5 (1.4)	1.0 (1.1)
LS mean (95% CI)	0.6 (0.0, 1.1)	1.4 (0.9, 1.9)	1.1 (0.6, 1.5)
LS mean vs placebo (95% CI)	N/A	0.9 (0.3, 1.5)	0.5 (-0.1, 1.1)
Week 22	n=18	n=32	n=30
Mean score (SD)	0.8 (0.9)	1.1 (1.0)	0.9 (1.2)
LS mean (95% CI)	1.0 (0.4, 1.6)	1.2 (0.7, 1.7)	1.3 (0.7, 1.9)
LS mean vs placebo (95% CI)	N/A	0.2 (-0.5, 0.8)	0.3 (-0.4, 1.0)
Week 28	n=3	n=19	n=14
Mean score (SD)	-0.7 (0.6)	1.4 (1.4)	0.7 (1.1)

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.
Data source: Table 14.2.5.1, Table 14.2.5.2 and Listing 16.2.6.2.
Note: LS means for each treatment group and treatment comparisons, as well as the p-values are obtained from an ANOVA on the visit value with treatment, age range at baseline, BTX status at baseline and center as covariates.

Source:Sponsor

REVIEWER COMMENT:

The PGA was nominally significant for both active treatment groups at Week 12.

6.1.7 Subpopulations

In Study 141 (pivotal study) there were two age groups defined as 2-9 and 10-17 years of age. The majority of subjects in all treatment groups were 2-9 years old (about 85%). In the subgroup analyses, the sponsor calculated the change in MAS for Dysport treatment groups (Dysport 10 U/kg/leg and Dysport 15 U/kg/leg) versus placebo for the 2-9 year old group, which was nominally significant.

DYSPORT (Y-55-52120-141) Page 1 of 2

Table 14.2.13.1: Modified Ashworth Scale in (Most) Affected Leg (Summary Statistics on Raw Data with Change from Baseline at Week 4, by Age Group and Dose per Leg)
ITT Population

AGE GROUP = 2 - 9 Years

		Placebo (N=65)		Dysport 10 U/kg per leg (N=67)		Dysport 15 U/kg per leg (N=67)		Total Dysport (N=134)		All Subjects (N=199)	
VISIT	STATISTIC	RAW	CHANGE FROM BASELINE	RAW	CHANGE FROM BASELINE	RAW	CHANGE FROM BASELINE	RAW	CHANGE FROM BASELINE	RAW	CHANGE FROM BASELINE
BASELINE	n	65		67		67		134		199	
	Missing	0		0		0		0		0	
	Mean	3.1		3.1		3.1		3.1		3.1	
	SD	0.4		0.3		0.4		0.4		0.4	
	Median	3.0		3.0		3.0		3.0		3.0	
	Range	(3, 5)		(3, 4)		(3, 4)		(3, 4)		(3, 5)	
WEEK 4	n	65	65	67	67	67	67	134	134	199	199
	Missing	0	0	0	0	0	0	0	0	0	0
	Mean	2.6	-0.5	2.3	-0.8	2.1	-1.0	2.2	-0.9	2.3	-0.8
	SD	0.9	0.8	0.9	0.9	0.8	0.9	0.9	0.9	0.9	0.9
	Median	3.0	0.0	2.0	-1.0	2.0	-1.0	2.0	-1.0	2.0	-1.0
	Range	(1, 4)	(-2, 1)	(0, 4)	(-3, 1)	(0, 4)	(-3, 0)	(0, 4)	(-3, 1)	(0, 4)	(-3, 1)

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Table 14.2.13.2: Modified Ashworth Scale in (Most) Affected Leg (Analysis of Covariance of Change from Baseline at Week 4, by Age Group and Dose per Leg)
ITT Population

AGE GROUP = 2 - 9 Years

STATISTIC	Placebo (N=65)	Dysport 10 U/kg per leg (N=67)	Dysport 15 U/kg per leg (N=67)
n	65	67	67
LS Mean (SE)	-0.49 (0.10)	-0.90 (0.10)	-1.11 (0.10)
95% CI of LS Mean	(-0.69, -0.29)	(-1.09, -0.70)	(-1.31, -0.91)
Dysport dose compared to Placebo			
Difference (Dysport dose - Placebo) in LS Means (95% CI)		-0.41 (-0.68, -0.14)	-0.62 (-0.89, -0.34)
p-value		0.0032	<0.0001

Source: Data listing 16.2.6.1 Analysis dataset: ADEFF
Note: 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, centre, and treatment by age range at baseline interaction as covariates.
MAS is displayed on derived scale.
Program: Ipsen_Ltd Y_55_52120_141\Final Run\TLF\t14-2-13-2.sas (13OCT2014 13:29); Analysis dataset run: 13OCT2014 9:15

The statistical reviewer independently calculated the change in MAS and PGA by age subgroups, confirming the sponsor's results.

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

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

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

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

Source: Stats reviewer

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

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

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

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

Source: Stats reviewer

REVIEWER COMMENT:

For the 2-9 year old population, the mean change in MAS at Week 4 for Dysport 10 U/kg/leg and Dysport 15 U/kg/leg was -0.4 and -0.6 respectively, which was nominally significant (p= 0.0032, p<0.0001.) For the 10-17 year old population, the mean change in MAS at Week 4 for Dysport 10 U/kg/leg and Dysport 15 U/kg/leg was -1.1 and -0.6 respectively. However, the sponsor did not calculate it for the 10-17 year old age group, stating that there were too few subjects (<20) as defined in the RAP.

(b) (4)

Study 040- Dose Range Study

Design:
Study 040 was a double-blind prospective, randomized, placebo controlled **dose ranging** study to compare the efficacy and safety of Dysport 10 U/kg, 20 U/kg and 30 U/kg, with placebo in pediatric LL spasticity. Subjects were randomly allocated to the treatment groups. Randomization was stratified according to the baseline dynamic component.

The primary efficacy variables were:

- decrease in dynamic component compared to baseline,
- duration of time over which this decrease was observed (duration of response), and
- change in active gastrocnemius muscle length compared to baseline.

Both the dynamic component and active muscle length were obtained by use of electrogoniometry. The dynamic component is calculated by subtracting active muscle length from passive muscle length, where muscle lengths are expressed as a percentage of the normal muscle length with the leg in the anatomical position.

DOSE AND ADMINISTRATION

Subjects were treated with Dysport 10 U/kg, Dysport 20 U/kg, Dysport 30 U/kg and placebo injected into medial and lateral gastrocnemius and soleus, bilaterally.

Demographics

The demographic data for subjects is presented in Table 17, by treatment group**.**

Table 17 Demographic characteristics

		Placebo	10 U/kg	20 U/kg	30 U/kg
Age (years)	Mean ± SD	5.5 ± 2.2	5.4 ± 2.0	4.9 ± 1.9	4.8 ± 2.1
	Median	5.3	5.3	4.8	4.5
	Range	2-9	2-9	2-9	2-9
Gender	Male, n (%)	17 (55)	23 (64)	13 (46)	14 (47)
Race	Caucasian	30 (97)	34 (94)	28 (100)	29 (97)
Weight (kg)	Mean ± SD	18.7 ± 4.7	17.7 ± 4.4	17.3 ± 4.2	17.3 ± 4.5
	Median	18.0	17.0	16.5	16.8
	Range	11-29	11-29	10-27	11-30
Height (cm)	Mean ± SD	109 ± 13	108 ± 16	104 ± 13	105 ± 13
	Median	106	107	103	104
	Range	85-136	77-140	85-140	80-132

Source of data: Appendix 9 (statistical report)
Source:Sponsor

REVIEWER COMMENT:

The demographics data was similar across treatment groups except Dysport 10 U/kg/leg had a higher percentage of male subjects.

Subject Disposition

A total of 126 patients entered the study. The disposition of the subjects is presented in Table 18.

Table 18 Patient disposition

	Placebo	10 U/kg	20 U/kg	30 U/kg
Entered	31	36	28	31
Randomized	31	36	28	31
Treated	31	36	28	30
Week 4	31	36	28	30
Week 8	31	36	28	30
Withdrawn before week 16	0	0	1	0
Week 16 (Study Completion)	31	36	27	30
Continued after week 16	8	6	8	9

Data presented as number of patients in each treatment group
Source:Sponsor

REVIEWER COMMENT

One subject in the Dysport 20 U/kg treatment group withdrew before study completion, Week 16 and one subject in the Dysport 30 U/kg treatment group withdrew consent prior to study medication administration (randomized n=31, treated n=30.)

Protocol Deviations:

The protocol deviations are summarized in Table 19.

Table 19 Protocol deviations

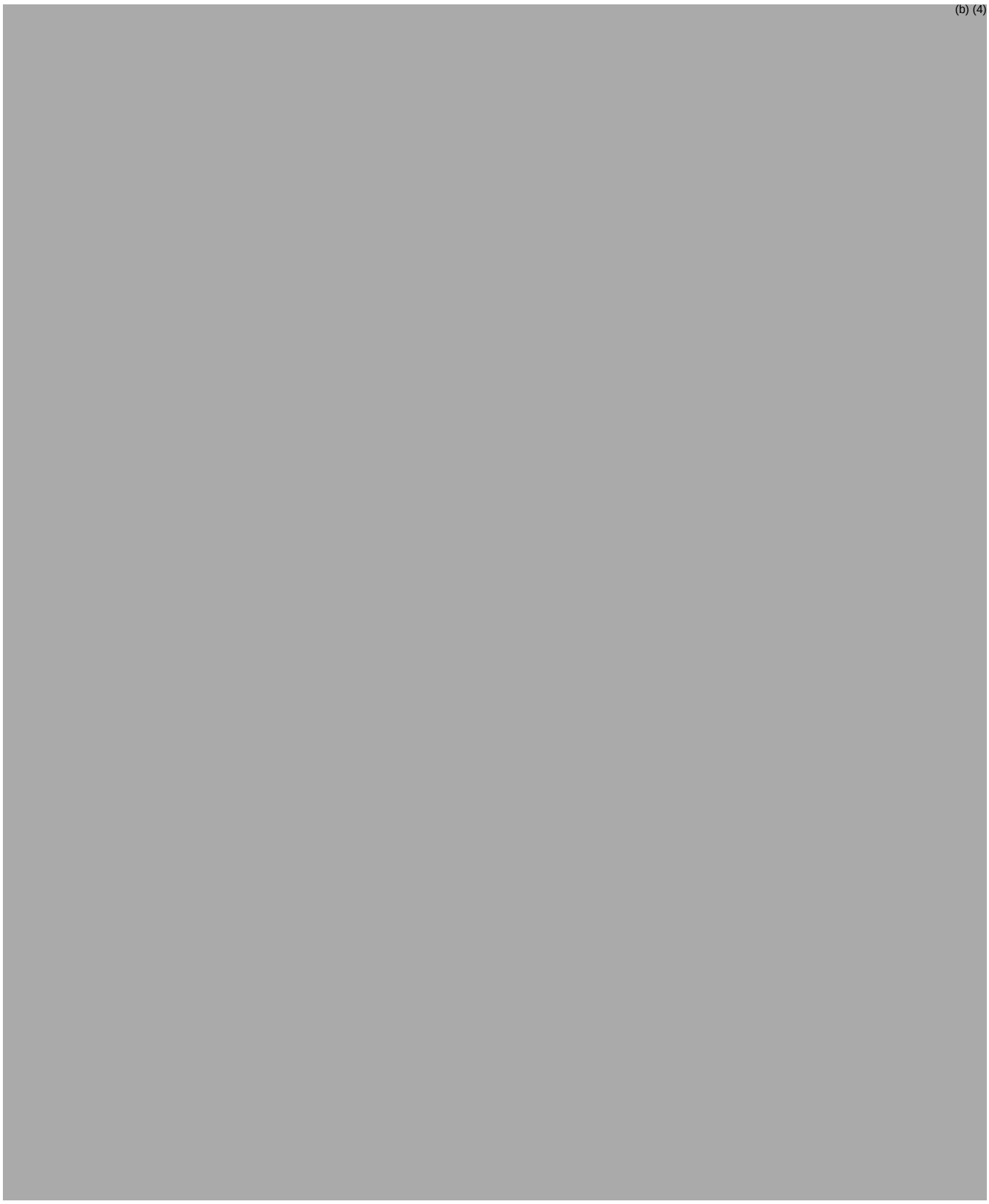
	Placebo	10 U/kg	20 U/kg	30 U/kg
Patients deviating from protocol	16 (52)	17 (47)	15 (54)	8 (27)
Protocol deviations (n)	19	24	18	13
Dynamic component not >1.5 for at least one leg (Major)	4 (12.9)	1 (2.8)	1 (3.6)	2 (6.7)
Did not attend one or more scheduled visits	0	2 (5.6)	2 (7.1)	0
One or more visits outside +/- 7 days of scheduled visit	9 (29.0)	8 (22.2)	4 (14.3)	5 (16.7)
Randomization stratification / errors	5 (16.1)	12 (33.3)	10 (35.7)	5 (16.7)
Weight at study entry >25 kg	1 (3.2)	1 (2.8)	1 (3.6)	1 (3.3)

Data presented as number (%) of patients in each treatment group
Source of data: Appendix 9 (statistical report)**Source:Sponsor**

REVIEWER COMMENT:

The protocol deviations were similar across treatment groups, with the lowest

(b) (4)



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Study 701

Design

Study 701 was a prospective, multicenter, double blind, placebo-controlled study comparing the efficacy and safety of a single administration of Dysport, 30 U/kg, or placebo in the treatment of pediatric dynamic equinus spasticity associated with cerebral palsy.

Efficacy Variables

The **primary efficacy variable** was Gross Motor Function Measure (GMFM) overall score at week 4. The GMFM is a standardized observational instrument designed to measure changes in gross motor function over time in children with cerebral palsy. It is comprised of an 88 item questionnaire subdivided into 5 dimensions:

A. Lying and Rolling
B. Sitting
C. Crawling and Kneeling
D. Standing
E. Walking, Running and Jumping

Each activity item is scored as follows:

0 = does not initiate
1 = initiates
2 = partially completes
3 = completes

Secondary efficacy variables included:

- 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

Dose and Administration:

All subjects received one treatment with either Dysport 30 U/kg or placebo, injected into medial and lateral gastrocnemius.

Demographics

The demographic characteristics of the subjects are outlined in Table 21.

All patients treated (APT) population: Comprised all patients randomized to the study who received some study medication. This population has been used for (b) (4) safety summaries and analyses.

Per-protocol (PP) population: Comprised all patients, in the APT population, who were not major protocol violators. (b) (4)

Table 23 Demographic details

		APT Population		PP Population	
		Placebo	**DYSPORT**	**Placebo**	**DYSPORT**
Patients	n	26	26	18	15
Age	Mean	4.2 ± 1.5	5.1 ± 1.3	3.9 ± 1.4	5.1 ± 1.5
	Median	3.9	5.1	3.9	4.9
	Range	2-7	3-8	2-7	3-8
Gender	Male, n (%)	13 (50.0)	16 (61.5)	10 (55.6)	9 (60.0)
Weight (kg)	Mean	15.7 ± 3.7	17.9 ± 4.2	15.3 ± 3.8	17.5 ± 4.3
	Median	15.0	18.0	14.5	18.0
	Range	10-24	10-27	10-24	10-27
Height (cm)[a]	Mean	104 ± 14	116 ± 17	101 ± 13	116 ± 19
	Median	103	113	101	110
	Range	80-142	85-154	80-124	87–154

[a]Height not recorded for one patient in the APT placebo group. Source of data: Appendix 9 (statistical report)

Source: Sponsor

REVIEWER COMMENT:

The subjects in the Dysport treatment group were on average slightly older than those in the placebo group (5.1 versus 4.2 years.) The age difference is likely related to the differences in mean weight and height as well.

Subject Disposition

A total of 52 patients were randomized. There were no withdrawals and all patients completed up to week 16 (Table 24).

Table 24 Patient disposition

	Placebo		DYSPORT	
Patients entered	26		26	
Patients randomised	26		26	
	APT Population	PP Population	APT Population	PP Population
Baseline assessment	26	18	26	15
Week 4 assessment	26	18	26	15
Week 8 assessment	26	18	26	15
Week 16 assessment	26	18	26	15
Week 24 assessment	8	5	8	4
Week 36 assessment	7	5	7	4

Source:Sponsor

Protocol Deviations

The protocol deviations are outlined in Table 25.

Table 25 Protocol Deviations

	Placebo	DYSPORT
No videographic proof of dynamic equinus deformity at baseline (major)	8 (30.8)	10 (38.5)
Study medication not administered in accordance with the protocol (major)	1 (3.8)	2 (7.7)
Attended one or more visits outside of visit window (minor)	9 (34.6)	7 (26.9)
Aged more than 7 years (minor)	0	1 (3.8)

Data presented as number (%) of patients in each treatment group

NB. Some patients had more than one protocol deviation

Source:Sponsor

REVIEWER COMMENT:

There were 9 major protocol violations in the placebo treatment group and 12 in the Dysport treatment group. The majority of the violations were "No videographic proof of dynamic equinus deformity at baseline."

(b) (4)

(b) (4)

STUDY 094

Design

Study 094 was a Phase II, multicenter, double-blind, prospective, randomized, placebo-controlled study, to assess the efficacy and safety of Dysport 30 U/kg for the treatment of hip adductor spasticity.

Primary Efficacy Variable

The protocol defined primary efficacy variable was the change in the **slow passive ROM** at the hip, from Baseline to Week 4.

According to the sponsor, "…it became apparent during the study that the originally planned primary efficacy parameter, **passive range of motion at the hip joint**, no longer represented the state of the art and that dynamic effects are much more suitable efficacy parameters for direct effects during one treatment cycle."
During the Blind Review meeting, and before un-blinding, it was decided to change the primary efficacy endpoint. According to the sponsor, this was justified by the fact that spasticity is a motor disorder characterized by a **velocity-dependent** increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks,

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resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome. Due to this velocity-dependence, an improvement of spasticity can only be evaluated using a dynamic parameter, assessed with a fast movement, either active or passive. The static position was therefore considered not suitable to demonstrate the efficacy of the therapy and it was decided to use the **fast passive hip abduction**, measured as the distance between both knees (inter medial condyli [IMC]) in cm as primary efficacy endpoint.

The study was initiated on January 18, 1999 and was completed on March 26,2001.

Report and Analysis Plan

The chronology of the report and analysis of this study is summarized below:

- 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

In the Final Study Report (November 21, 2007), the sponsor presented both primary efficacy analyses; one for the protocol defined primary endpoint, change in **slow**

passive ROM at the hip, and a second one for the primary efficacy endpoint defined during the blind review, change **fast passive hip abduction**,

Secondary efficacy variables are summarized in Table 27

Table 27 Secondary Efficacy Analyses

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	Wilcoxon-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)

Source:Sponsor

Dose and Administration

Patients were administered either Dysport 30 U/kg (with a maximum of 500 U/muscle group) or placebo. **Two thirds** of the total dose was injected into adductor muscles and **one third** into the medial hamstrings.

DEMOGRAPHICS

The demographic characteristics of the subjects is presented in Table 26

Table 28 Demographic data at baseline (safety population)

		Dysport® (N= 33)	Placebo (N= 28)	All subjects (N=61)
Age (years)	Mean	6.02	5.78	5.91
	SD	3.03	2.24	2.67
	Median	5.89	5.64	5.78
	Range	(2.0 , 10.8)	(2.4 , 10.0)	(2.0 , 10.8)
Height (cm)[a]	Mean	104.6	105.6	105.0
	SD	18.3	13.9	16.3
	Median	105.0	105.0	105.0
	Range	(73 , 146)	(79 , 132)	(73 , 146)
Weight (kg)	Mean	18.2	17.0	17.6
	SD	8.4	6.6	7.6
	Median	15.0	16.0	16.0
	Range	(10 , 43)	(9 , 35)	(9 , 43)
Sex[b]	Female	11 (33.3)	14 (50.0)	25 (41.0)
Race[b]	Caucasian	31 (93.9)	27 (96.4)	58 (95.1)
	Asian	0 (0.0)	1 (3.6)	1 (1.6)
	Other	2 (6.1)	0 (0.0)	2 (3.3)

Data source: Table 14.1.7, page 85

a One data missing: ID 83-15 (placebo)

b N (%)

Source:Sponsor

REVIEWER COMMENT:

The age, height and race were similar across treatment groups. There were more males in the Dysport treatment group compared to 50:50 distribution in the placebo group.

Subject Disposition

A total of 61 patients were enrolled in the study, 33 to Dysport group and 28 to the placebo group, Table 29.

Table 29 Disposition of patients (screened patients)

		Dysport® (N=33)	Placebo (N=28)	All subjects (N=61)
Attended visit[a]	Screening	33 (100.0)	28 (100.0)	61 (100.0)
	Week 0	33 (100.0)	28 (100.0)	61 (100.0)
	Week 4	33 (100.0)[b]	28 (100.0)	61 (100.0)[b]
	Week 12	32 (97.0)	28 (100.0)	60 (98.4)
Last attended visit[c]	Week 4	1 (3.0)	0	1 (1.6)
	Week 12	32 (97.0)	28 (100.0)	60 (98.4)

Data source: Table 14.1.5, page 81

a N (%)

b Data from patient ID 3-5 are recorded at week 4 even though he did not actually attend this visit.

Source:Sponsor

REVIEWER COMMENT:

Two patients from the Dysport group did not complete the follow-up period as planned in the protocol. One patient dropped out secondary to SAE of dysarthria and muscle weakness. The second patient completed visits week 4 and 12 out of window (protocol deviations.)

Protocol Deviations

The protocol deviations by treatment group are presented in Table 30.

Table 30 Patients excluded from the ITT and PP populations

Treatment	Subject ID	Age/Sex	ITT ROM	PP ROM	ITT IMC	PP IMC	Reason for exclusion
Dysport®	3-5	2.8/M	No	No	No	No	No W4 value for passive abduction/adduction at hip No W4 value for distance condyli Visit window at W4 > 42 days
	28-1	10.7/F	Yes	No	Yes	No	No spasticity
	52-5	3.0/M	Yes	Yes	No	No	No W4 value for distance condyli
	89-15	10.8/M	Yes	No	Yes	No	Unblinding due to SAE
Placebo	1-5	3.8/M	No	No	Yes	Yes	No W4 value for hip passive slow stretch
	26-1	2.4/F	Yes	Yes	No	No	No baseline value for distance condyli No W4 value for distance condyli
	60-9	5.7/M	No	No	Yes	Yes	No baseline value for hip passive abduction/adduction at hip No W4 value for hip passive slow stretch

Data source: Listing 16.2.3.1, page 785, Listing 16.2.3.2, page 787

Source:Sponsor

REVIEWER COMMENT:

There were 4 protocol violations in the Dysport treatment group and 3 in the placebo treatment group.

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7 Review of Safety

Safety Summary

7.1 Methods

The safety information included in the submission to support the approval of Dysport for the treatment of lower limb (LL) spasticity in pediatric patients, 2 years of age and older, is from prospective clinical studies (double blind and open label) in pediatric patients

with spasticity secondary to cerebral palsy, solicited and spontaneous post marketing adverse event (AE) data from the applicant's Adverse Reaction Information System global (ARISg) pharmacovigilance database (presented in Section 8.0):

Double Blind Placebo Controlled Studies

Four prospective double blind placebo controlled clinical studies are included in the application (Table 35):

Table 35 Summary of Clinical Studies of Dysport for the Treatment of Pediatric Lower Limb Spasticity – Double Blind Placebo Controlled Studies

Study Number	Number of Subjects Randomized	Design	Population	Number of Subjects Treated per Dose Group	Muscles Injected[a]	Number of Treatments	Duration
Study 141 (pivotal)	241	Multicenter, randomized, DBPC	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 (N=80) • 15 U/kg/leg i.e. 15 U/kg for unilateral treatment; 30 U/kg for bilateral treatment (N=80) • Placebo (N=79)	Distal muscles: gastrocnemius, soleus (unilateral or bilateral injections)	1	12 to 28 weeks
Study 040	126	Multicenter, randomized, DBPC	Dynamic equinus foot deformity due to CP	• 10 U/kg (N=36) • 20 U/kg (N=28) • 30 U/kg (N=30) • Placebo (N=31)	Distal muscles: gastrocnemius (bilateral injections)	1	16 to 36 weeks
Study 701	52	Multicenter, randomized, DBPC	Dynamic equinus foot deformity due to CP	• 30 U/kg (N=26) • Placebo (N=26)	Distal muscles: gastrocnemius (bilateral injections)	1	16 to 36 weeks
Study 094	61	Multicenter, randomized, DBPC	Adductor muscle spasticity due to CP	• 30 U/kg (N=32[b]) • Placebo (N=28)	Proximal muscles: adductor, medial hamstrings (bilateral injections)	1	12 weeks

CP=cerebral palsy; DBPC=double blind placebo controlled; GSC=gastrocnemius soleus complex; NA=not applicable; PLL= pediatric lower limb; U=units.
Data Source: All Study CSRs Module 5.3.5.1.
a Muscles that have the bulk of muscle distal or proximal to the knee joint line are considered distal and proximal muscles, respectively

b The scheduled Dysport dose in Study 094 was 30 U/kg. One subject (00000900057) was not treated with this dose and only appears in the All Doses column of the safety tables. The subject was treated with 23 U/kg administered bilaterally (Listing EX.1.1)

Source:Sponsor

Studies 141, 040 and 701 included injections in distal muscles of the lower extremities (gastrocnemius or GSC.) In study 094, subjects were injected with Dysport into the proximal muscles of the hip adductors and medial hamstrings.

Open Label Studies

Five prospective open label studies conducted in PLL spasticity were included in the submission (Table 36).

Table 36 Summary of Clinical Studies of Dysport for the Treatment of Pediatric Lower Limb Spasticity – Open Label Studies

Study Number (abbreviated study	Number of Subjects	Design	Population	Number of Subjects Treated per Dose	Muscles Injected[a]	Number of Treatments	Duration
Study 147 (extension to pivotal Study 141)	221	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 The number of subjects per dose group varied per Treatment Cycle.	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)
Study 702	214[b]	Multicenter, OL (assessor blinded)	CP lower limb spasticity	• 30 U/kg at 12 month intervals (N=104) • 30 U/kg at 4 month intervals (N=110)	Distal muscles: gastrocnemius (bilateral injections)	3 to 7	28 months (112 weeks)
Study 052	15	Multicenter, OL	CP equinus foot deformity	• 10 U/kg if unilateral treatment (N=4) • 20 U/kg if bilateral treatment (N=11)	Distal muscles: gastrocnemius (unilateral or bilateral injections)	Up to 2	32 weeks

Study 711	25	Multicenter, OL	CP equinus foot deformity	• 10 U/kg if unilateral treatment (N=10) • 20 U/kg if bilateral treatment (N=15)	Distal muscles: gastrocnemius (unilateral or bilateral injections)	1	16 weeks
Study 062	15	Multicenter	Dynamic equinus foot deformity due to CP	• Low dose: 15 U/kg if unilateral treatment; 20 U/kg if bilateral treatment (N=7) • Standard dose: 25 U/kg if unilateral treatment; 30 U/kg if bilateral treatment (N=8)	Distal muscles: gastrocnemius + soleus if unilateral injections; only gastrocnemius if bilateral injections	1	36 weeks

CP=cerebral palsy, CSR=clinical study report, OL=open label, U=units
Data Source: All Study CSRs Module 5.3.5.2 and ISS Appendix 2a Table DP.2 2

a Muscles that have the bulk of muscle distal or proximal to the knee joint line are considered distal and proximal muscles, respectively

b Study 702 included subjects from Studies 040 and 701 and de novo subjects

c Study 062 , a single-treatment study with two active Dysport treatment arms, was terminated prematurely due to poor subject recruitment (15 subjects were recruited from a planned target of 280 subjects). Although conducted as a double blind study, this was not included in the pooled double blind placebo controlled population because both the investigators and study subjects were blind only to the dose of study drug but not to which study drug was administered.

Source:Sponsor

The open label studies varied in the number of treatment cycles, dose and duration. In Study 702, subjects could receive up to 30 U/kg into the gastrocnemius at a fixed interval of every 4 months for up to 28 months (7 treatment cycles.) All open label studies, distal muscles were injected, except in Study 147 where proximal muscles could also be injected.

Pooling of Data across Studies/Clinical Trials

Safety analyses for LL spasticity in pediatric patients are presented for:

- **Double Blind Placebo Controlled Studies** – contains safety data from four double blind placebo controlled studies who received a single cycle of study treatment,
    - **Overall Safety Population –** Studies 141, 040, 701 and 094
    - **Safety Population Distal Muscles**- Studies 141, 040 and 701, a subgroup of the **Overall Safety Population,** which excludes Study 094.

- **Open Label Studies-** contains data from 5 prospective open label clinical studies. All subjects received at least one treatment with Dysport

    - **Dysport All Doses group** – Studies 147, 702, 052, 711 and 062.

Pooling for Post marketing and Supportive Data

A single **ARISg** extraction was performed for the PMSD dataset according to following specifications:

- If an event was present under different versions of a case, only the last version was extracted;
- The reported (suspect) drug was Dysport, Dyslor, Reloxin, Azzalure or BTX-A NOS;
- Multiple records for the same event (e.g. representing different suspect drugs or dosing schedules) were verified and treated as one event.

All adverse events (AEs) and medical history data were recoded using the MedDRA version 17.1.

An overview of safety variables and the time points assessed Pooled Double Blind Placebo Controlled and Open Label Studies is summarized in Table 37.

Table 37 Overview of Safety Variables and Time points Assessed in the Pooled Double Blind Placebo Controlled and Pooled Open Label Studies

Study	Safety Variables				
	AE	Vital Signs	Laboratory Data	ECG	Antibodies
Double Blind Placebo Controlled Studies					
141	Throughout	SC, BL, W4, W12, W16[a], W22[a], W28[a], EOS/EW	BL, W4, EOS/EW	SC, W4, EOS/EW	BL, EOS/EW
040	Throughout	W0, W16, EOS/EW	Not assessed	Not assessed	Not assessed
701	Throughout	W0, W16, W24, W36, EOS/EW	Not assessed	Not assessed	Not assessed
094	Throughout	W-2, W0, W4, W12	Not assessed	Not assessed	Not assessed
Open Label Studies					

147	Throughout	BL, W4, W12, W16[a], W22[a], W28[a], W34[a], W40[a]for each cycle, EOS/EW	BL, W4	BL, W4, EOS/EW	BL, EOS/EW
702	Throughout	M0, M28	Not assessed	Not assessed	M0, M28
052	Throughout	BL, W2, W4, W8, W16, W24, W32	Not assessed	Not assessed	Not assessed
711	Throughout	BL, W2, W4, W8, W16	Not assessed	Not assessed	Not assessed
062	Throughout	Not assessed	Not assessed	Not assessed	Not assessed

BL=baseline, defined as the last visit prior to the first study drug administration, CSR=clinical study report, EOS/EW=end of study/early withdrawal, M=month, SC=screening, W=week
Data Source: All Study CSRs: Module 5.3.5.1 and Module 5.3.5.2
a The visit only occurred if the subject was not eligible/received retreatment

Source:Sponsor

REVIEWER COMMENT:

Study 141 and open label extension study 147 were the only studies that collected data for vital signs, laboratory and ECG recordings, throughout the study.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

According to the sponsor the total number of subjects who received at least two injections of the highest dose (30 U/kg) over 6 months was reported as 105, while the total number of subjects who received at least 4 injections of the highest dose (30 U/kg) over 12 months was 62 (Table 38)

Table38 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

Data Source: Appendix 2a, Table EX.4.1
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:Sponsor

The reviewer was unable to generate a table with the same exposure numbers as the sponsor. An information request (IR) was sent to the sponsor on May 11, 2016

In the ISS, you have presented exposure for consecutive injections within 6 and 12 months (Table 12, p.41 of the ISS.) In order to better understand the dosing intervals (length between treatments) please recalculate and submit the exposure table using actual dose received (not mean or median). Please use the following actual dosing intervals (i.e., ≥12 weeks but < 16 weeks, ≥16 weeks but less than 18 weeks, ≤ every 18 weeks) not the average or median interval between injections:

- *2 consecutive injections occurring every 12 weeks, 16 weeks and 18 weeks or sooner*
- *4 consecutive injections occurring every 12 weeks, 16 weeks and 18 weeks or sooner*

In addition, please calculate the exposure for subjects who received the maximum dose of Dysport 1000 U (actual dose=1000 U, not mean or median). Please present the data in tabular format, for consecutive cycles using actual weeks between treatments. Use the exposure intervals described above.

The sponsor generated the tables as requested and submitted them on May 18, 2016. The subject exposure by number of consecutive Dysport injections for 6 months and 12 months is presented in Table 39.

Post Hoc Table 39: 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 two injections within 12 to 18 weeks (1) (2) (3)	76	63	57	**32**
At least 4 consecutive injections with two injections within 16 to 18 weeks (1) (2) (4)	51	50	47	31
At least 4 consecutive injections with 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.

Source:Sponsor

The number of subjects exposed to Dysport 1000 U on repeat injections for 6 and 12 months is summarized in Table 40.

Post Hoc Table 40: Subject Exposure by Number of Consecutive Dysport Injections Occurring Every 18 Weeks or Sooner (Double-Blind Placebo-Controlled and Open-Label Studies Combined) –

Post Hoc Table EX.4.4: Subject Exposure by Number of Consecutive Dysport Injections Occurring Every 18 Weeks or Sooner (Double-Blind Placebo-Controlled and Open-Label Studies Combined) - Subjects Who Received the Maximum Dose of Dysport 1000 U

	Dysport 1000 U
At least 2 consecutive injections within 12 to 18 weeks (1) (2) (3)	8
At least 2 consecutive injections within 16 to 18 weeks (1) (2) (4)	1
At least 2 consecutive injections within 12 to 16 weeks (1) (2) (5)	7
At least 4 consecutive injections with all intervals between two injections within 12 to 18 weeks (1) (2) (3)	1
At least 4 consecutive injections with all intervals between two injections within 16 to 18 weeks (1) (2) (4)	0
At least 4 consecutive injections with all intervals between two injections within 12 to 16 weeks (1) (2) (5)	1

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.

Source:Sponsor

REVIEWER COMMENT:

There were 102 subjects exposed to two treatment cycles over 6 months and 31 subjects exposed to four treatment cycles over 12 months at the highest dose of Dysport, 30 U/kg. The majority of subjects who received repeat injections at 6 and 12 months at all doses had treatment intervals between 16-18 weeks.

Only 8 subjects were injected with maximum total dose, Dysport 1000 U, for two treatment cycles over 6 months and only 1 subject was injected with Dysport 1000 U for 4 treatment cycles over 12 months.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the double blind placebo controlled and open label studies conducted in pediatric subjects with lower limb spasticity due to cerebral palsy.

7.3.2 Nonfatal Serious Adverse Events

In the double blind studies 10 subjects (3.2%) who received Dysport and 6 (3.7%) subjects who received placebo, experienced SAEs (Table 41).

Table 41 Treatment Emergent Serious Adverse Events - Pooled Double Blind Placebo Controlled Studies– Overall Safety Population

System Organ Class Preferred Term	Placebo (N=164) n (%)	Subjects treated unilaterally		Subjects treated bilaterally		Dysport All Doses[a,b] (N=313) n (%)
		Dysport 10 U/kg (N=43) n (%)	Dysport 15 U/kg (N=52) n (%)	Dysport 20 U/kg (N=64) n (%)	Dysport 30 U/kg (N=116) n (%)	
Any Treatment Emergent SAE	**6 (3.7%)**	**0**	**0**	**1 (1.6%)**	**8 (6.9%)**	**10 (3.2%)**
Infections and Infestations	**3 (1.8%)**	**0**	**0**	**0**	**6 (5.2%)**	**6 (1.9%)**
Bronchitis	0	0	0	0	2 (1.7%)	2 (0.6%)
Bronchopneumonia	0	0	0	0	1 (0.9%)	1 (0.3%)
Lobar pneumonia	0	0	0	0	1 (0.9%)	1 (0.3%)
Otitis media	0	0	0	0	1 (0.9%)	1 (0.3%)
Pseudocroup	0	0	0	0	1 (0.9%)	1 (0.3%)
Pseudomonas bronchitis	0	0	0	0	1 (0.9%)	1 (0.3%)
Upper respiratory tract infection	0	0	0	0	1 (0.9%)	1 (0.3%)
Gastroenteritis	1 (0.6%)	0	0	0	0	0
Localised infection	1 (0.6%)	0	0	0	0	0
Pneumonia	1 (0.6%)	0	0	0	0	0
Rotavirus infection	1 (0.6%)	0	0	0	0	0
Nervous System Disorders	**1 (0.6%)**	**0**	**0**	**0**	**1 (0.9%)**	**2 (0.6%)**
Dysarthria	0	0	0	0	1 (0.9%)	1 (0.3%)
Epilepsy	0	0	0	0	0	1 (0.3%)
Convulsion	1 (0.6%)	0	0	0	0	0
Petit mal epilepsy	1 (0.6%)	0	0	0	0	0
Gastrointestinal Disorders	**0**	**0**	**0**	**0**	**1 (0.9%)**	**1 (0.3%)**
Abdominal pain	0	0	0	0	1 (0.9%)	1 (0.3%)
Constipation	0	0	0	0	1 (0.9%)	1 (0.3%)
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**0**	**1 (0.9%)**	**1 (0.3%)**
Pyrexia	0	0	0	0	1 (0.9%)	1 (0.3%)
Hepatobiliary Disorders	**0**	**0**	**0**	**0**	**1 (0.9%)**	**1 (0.3%)**
Cholelithiasis	0	0	0	0	1 (0.9%)	1 (0.3%)
Investigations	**0**	**0**	**0**	**0**	**1 (0.9%)**	**1 (0.3%)**

Body temperature increased	0	0	0	0	1 (0.9%)	1 (0.3%)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**0**	**0**	**1 (0.9%)**	**1 (0.3%)**
Muscular weakness	0	0	0	0	1 (0.9%)	1 (0.3%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**1 (1.6%)**	**0**	**1 (0.3%)**
Adenoidal hypertrophy	0	0	0	1 (1.6%)	0	1 (0.3%)
Injury, Poisoning and Procedural Complications	**2 (1.2%)**	**0**	**0**	**0**	**0**	**0**
Head injury	1 (0.6%)	0	0	0	0	0
Upper limb fracture	1 (0.6%)	0	0	0	0	0

N=number of subjects in group, n=number of subjects with observation, SAE=serious adverse event, U=units
Data Source: Appendix 2a, Table AE.3.1.1.1.2
a Studies included: 141, 040, 701 and 094
b Data from subjects who received 10 U/kg administered bilaterally (5 U/kg/leg) are included in the All Doses column but are not summarised by dose in the table.

Source:Sponsor

One SAE occurred in a subject who received Dysport 20 U/kg cohort and 8 SAEs occurred in the Dysport 30 U/kg cohort. The 10th SAE occurred in a subject who received Dysport 5 U/kg.

The individual subjects are summarized in Table 42

Table 42 Listing of Serious Treatment Emergent Adverse Events - Pooled Double Blind Placebo Controlled Studies – Overall Safety Population

Subject ID/ Study	Gender/ Age	MedDRA Preferred Term/Verbatim Term	Treatment received/Muscle(s) injected	Treatment Cycle/ Dysport Exposure	Last (Cumulative) Dysport Dose Injected Prior	Event Onset (days) [a]	Duration of event (days)
61600100008 / Study 141	Female/4	Upper limb fracture/Broken	Placebo/unilateral, GSC	NA/N A	N A	58	29
61600100015 / Study 141	Female/2	Pneumonia/ Pneumonia	Placebo/ bilateral, GSC	NA/N A	N A	51	9
		Rotavirus infection/Rota virus	Placebo/ bilateral, GSC	NA/N A	N A	59	4
61600200003 / Study 141	Male/2	Head injury/Head	Placebo/ bilateral, GSC	NA/N A	N A	3	6
79200700012 / Study 141	Male/4	Gastroenteritis/gastro enteritis (the semptoms started on 12.09.2013 with nausea and vomiting	Placebo/ unilateral, GSC	NA/N A	N A	21	7
00001100219 / Study 040	Female/3	Epilepsy/Lost o	Dysport 5 U/kg / bilateral, gastroc.	NA/10.6	10 U/kg	74	<1
25000200001 / Study 141	Female/6	Adenoidal hypertrophy/adenoid	Dysport 10 U/kg/ bilateral, GSC	NA/10.3 weeks	20 U/kg	72	<1
00000200037 / Study 040	Female/6	Petit mal epilepsy/Petite	Placebo/bilateral, gastroc.	NA/N A	N A	8	<1
		Convulsio n/Seizure	Placebo/bilateral, gastroc.	NA/ NA	N A	68	2
00000400066 / Study 040	Male/4	Abdominal p	Dysport 15 U/kg / bilateral, gastroc.	NA/23.9	30 U/kg	167	4
		Constipation/ Constipation	Dysport 15 U/kg / bilateral, gastroc.	NA/23.9	30 U/kg	167	4

		Cholelithiasis	Dysport 15 U/kg / bilateral, gastroc.	NA/23.9	30 U/kg	167	4
		Bodyte	Dysport 15 U/kg/ bilateral, gastroc.	NA/23.9	30 U/kg	167	4
00000400076 / Study 040	Female/3	Localised infection/Infection	Placebo/bilateral, gastroc.	NA/ NA	NA	19	24
00000500082 / Study 040	Male/7	Lobar pneumonia/Pneumoni	Dysport 15 U/kg / bilateral, gastroc.	NA/3.6	30 U/kg	25	3
00000300018 / Study 701	Male/4	Bronchitis/Bronchitis AC	Dysport 15 U/kg / bilaterally in the GSC	NA/2 weeks	30 U/kg	14	2
00000100025 / Study 094	Male/1	Pseudosomonas bronchitis/ Obstructive	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/2.1 weeks	30 U/kg	15	14

Subject ID/ Study	Gender/ Age	MedDRA Preferred Term/Verbatim Term	Treatment received/Muscle(s) injected	Treatment Cycle/ Dysport Exposure	Last (Cumulative) Dysport Dose Injected Prior	Event Onset (days) [a]	Duration of event (days)
00000200017 / Study 094	Male/5	Bronchitis/Otitis media	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/8.1 weeks	30 U/kg	57	8
		Otitis media/ Otitis	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/8.1 weeks	30 U/kg	57	8
		Pseudocroup/Otitis media/	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/8.1 weeks	30 U/kg	57	8
00000300034 / Study 094	Male/2	Pyrexia/Upper airway infection/Fever	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/6.1 weeks	30 U/kg	43	7
		Upper respiratory tract infection/Up	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/6.1 weeks	30 U/kg	43	7
00000300061 / Study 094	Male/6	Bronchopneumonia/ Broncho pneumonia	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/3.3 weeks	30 U/kg	23	4
00001500089 / Study 094	Male/10	Muscular weakness/ Articulation	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/2.4 weeks	30 U/kg	17	≤56
		Dysarthria/Articulation	Dysport 15 U/kg / bilateral, adductors/ hamstrings	NA/2.4 weeks	30 U/kg	17	≤56

gastroc.= gastrocnemius, GSC=gastrocnemius soleus complex, MedDRA=Medical Dictionary for Regulatory Activities, NA=not applicable, -=not recorded, ID=identification, U=units
Studies included: 141, 040, 701 and 094
Data Source: Appendix 3a, Listings AE.2.1 and EX.2.1

a Days since last dose

The case reports of patients treated with Dysport, who experienced SAEs are summarized below.

Study 141

Patient 25000200001 treated with **Dysport 10 U/kg** had an SAE of adenoid hypertrophy during the study.

Study 040

Patient 066 ,male patient (aged 4 years) experienced severe abdominal pain and raised temperature almost six months after receiving **DYSPORT (30 units/kg)**. The patient was hospitalized and an ultrasound scan and X-ray showed evidence of **gallstones and constipation**. The patient was treated with oral Augmentin (dose unknown), and also received an enema. These events resolved after four days.

Patient 082,male patient (aged 7 years) developed a temperature and shortness of breath of moderate intensity 24 days after treatment with **DYSPORT (30 units/kg)**. The patient was hospitalized, and a **diagnosis of right lobar pneumonia** was made following chest X-ray. The event resolved after three days following treatment with intravenous and oral erythromycin.

Patient 219,female patient (aged 3 years) experienced an **epileptic fit** ten weeks after treatment with **DYSPORT (10 units/kg)**. The patient was hospitalized, and received intravenous treatment with clonazepam (95 mg), phenobarbital (40 mg), mannitol 20% (50 ml), and dexamethasone (2 mg). The event fully resolved after two days. The patient had a history of epilepsy.

Study 701

Patient No. 018 (4½ year old boy) was randomized to the **DYSPORT (30 U/kg)** group and became ill with **bronchitis** thirteen days after receiving study medication. The patient had not suffered with bronchitis prior to the study. He was hospitalized overnight for monitoring purposes and received clarithromycin, ambroxol hydrochloride and dextromethorphan hydrobromide. The event lasted two days in total and the patient recovered without sequelae.

Study 094

All patients received **Dysport 30 U/kg**

Patient 00000100025 a 1 year old subject experienced **obstructive bronchitis** 15 days after Dysport treatment and recovered after 14 days. The subject was hospitalized and a throat smear test revealed **pseudomonas aeruginosa** infection.

Patient 00000200017 a 5 year old subject experienced three events, **Otitis media, Pseudocroup, Bronchitis ,**57 days after Dysport injection lasting for 8 days and received antibiotics as corrective therapy.

Patient 00000300034, a 2 year old subject experienced **upper respiratory tract infection** and primary atypical pneumonia with symptoms of fever, rhinitis and dyspnea 43 days after Dysport treatment. The subject recovered after 7 days following corrective therapy.

Patient 00000300061, a 6 year old subject experienced event of **bronchopneumonia** with symptoms of cough, fever and sinusitis 23 days after Dysport treatment and recovered after 4 days. This subject had history of pulmonary stenosis, adenoid hyperplasia, chronic recurrent tonsillitis and peritonsillitis with tonsillohyperplasia, chronic bronchitis and sinusitis.

Patient 00001500089, a 10 year old subject experienced **dysarthria and muscular weakness** (generalized, i.e. not localized to the site of injection), 17 days after Dysport treatment. The events lasted for ≤56 days.

REVIEWER COMMENT:
In the double blind studies, the most frequent SAEs, by SOC, were Infections and Infestations (pneumonia.) With the exception of the last subject described above, the SAEs are most likely related the patients' underlying disorder, cerebral palsy. The adverse events experienced by Subject 000015000089 are consistent with remote spread of toxin.

In the **open label studies**, 38 subjects (8.0%) experienced SAEs. The most frequent SAE was Surgery and Medical Procedures, followed by Nervous Conditions (epilepsy/convulsions) and Infections and Infestations (pneumonia.)

Table 43 Treatment Emergent Serious Adverse Events - Pooled Open Label Studies – Overall Safety

Population

System Organ Class Preferred Term	Subjects treated unilaterally		Subjects treated bilaterally		Dysport All Doses[a,b] (N=476) n (%)
	Dysport 10 U/kg (N=132) n (%)	Dysport 15 U/kg (N=53) n (%)	Dysport 20 U/kg (N=146) n (%)	Dysport 30 U/kg (N=257) n (%)	
Any Treatment Emergent SAE	**1 (0.8%)**	**0**	**6 (4.1%)**	**29 (11.3%)**	**38 (8.0%)**
Infections and Infestations	**1 (0.8%)**	**0**	**3 (2.1%)**	**8 (3.1%)**	**14 (2.9%)**
Pneumonia	1 (0.8%)	0	1 (0.7%)	2 (0.8%)	4 (0.8%)
Gastroenteritis	0	0	1 (0.7%)	1 (0.4%)	2 (0.4%)
Otitis media	0	0	0	2 (0.8%)	2 (0.4%)
Appendicitis	0	0	0	1 (0.4%)	1 (0.2%)
Bronchitis	0	0	0	0	1 (0.2%)
Bronchopneumonia	0	0	0	0	1 (0.2%)
Pharyngitis	0	0	0	1 (0.4%)	1 (0.2%)
Pharyngotonsillitis	0	0	0	1 (0.4%)	1 (0.2%)
Sinusitis	0	0	1 (0.7%)	0	1 (0.2%)
Varicella	0	0	1 (0.7%)	0	1 (0.2%)

Surgical and Medical Procedures	**0**	**0**	**0**	**13 (5.1%)**	**14 (2.9%)**
Surgery	0	0	0	6 (2.3%)	6 (1.3%)
Strabismus correction	0	0	0	2 (0.8%)	3 (0.6%)
Hip surgery	0	0	0	1 (0.4%)	1 (0.2%)
Limb operation	0	0	0	1 (0.4%)	1 (0.2%)
Orchidopexy	0	0	0	1 (0.4%)	1 (0.2%)
Tenotomy	0	0	0	1 (0.4%)	1 (0.2%)
Tonsillectomy	0	0	0	1 (0.4%)	1 (0.2%)
Nervous System Disorders	**0**	**0**	**2 (1.4%)**	**9 (3.5%)**	**10 (2.1%)**
Convulsion	0	0	0	2 (0.8%)	2 (0.4%)
Epilepsy	0	0	0	2 (0.8%)	2 (0.4%)
Hydrocephalus	0	0	0	2 (0.8%)	2 (0.4%)
Ataxia	0	0	0	1 (0.4%)	1 (0.2%)
Complex partial seizures	0	0	1 (0.7%)	0	1 (0.2%)
Partial seizures	0	0	0	1 (0.4%)	1 (0.2%)
Status epilepticus	0	0	1 (0.7%)	0	1 (0.2%)
Syncope	0	0	0	1 (0.4%)	1 (0.2%)
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**6 (2.3%)**	**6 (1.3%)**
Pyrexia	0	0	0	3 (1.2%)	3 (0.6%)
Drowning	0	0	0	1 (0.4%)	1 (0.2%)
Hypothermia	0	0	0	1 (0.4%)	1 (0.2%)
Injury, Poisoning and Procedural Complications	**0**	**0**	**0**	**4 (1.6%)**	**4 (0.8%)**
Injury	0	0	0	3 (1.2%)	3 (0.6%)
Toxicity to various agents	0	0	0	1 (0.4%)	1 (0.2%)
Congenital, Familial and Genetic Disorders	**0**	**0**	**0**	**2 (0.8%)**	**2 (0.4%)**
Cerebral palsy	0	0	0	1 (0.4%)	1 (0.2%)
Patent ductus arteriosus	0	0	0	1 (0.4%)	1 (0.2%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**2 (0.8%)**	**2 (0.4%)**
Asthma	0	0	0	1 (0.4%)	1 (0.2%)
Pneumonia aspiration	0	0	0	1 (0.4%)	1 (0.2%)
Blood and Lymphatic System Disorders	**0**	**0**	**1 (0.7%)**	**0**	**1 (0.2%)**

System Organ Class Preferred Term	**Subjects treated unilaterally**		**Subjects treated bilaterally**		**Dysport All Doses[a,b] (N=476) n (%)**
	Dysport 10 U/kg (N=132) n (%)	**Dysport 15 U/kg (N=53) n (%)**	**Dysport 20 U/kg (N=146) n (%)**	**Dysport 30 U/kg (N=257) n (%)**	
Lymphadenopathy	0	0	1 (0.7%)	0	1 (0.2%)
Eye Disorders	**0**	**0**	**0**	**1 (0.4%)**	**1 (0.2%)**
Cataract	0	0	0	1 (0.4%)	1 (0.2%)
Renal and Urinary Disorders	**0**	**0**	**0**	**1 (0.4%)**	**1 (0.2%)**
Renal colic	0	0	0	1 (0.4%)	1 (0.2%)
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**0**	**1 (0.4%)**	**1 (0.2%)**
Ecchymosis	0	0	0	1 (0.4%)	1 (0.2%)

N=number of subjects in group, n=number of subjects with observation, PT=preferred term, SAE=serious adverse event,
Data Source: Appendix 2a, Table AE.3.1.2.1.2
a Studies included: 147, 702, 052, 711 and 062

b PT of Unevaluable event was coded for side effects (Study 094); multiple verbatim terms with no specific diagnosis; for terms with no corresponding MedDRA code or terms confirmed as duplicates (i.e. same subject reporting TEAEs with exact same PT)

Source:Sponsor

REVIEWER COMMENT:

In the pooled open label studies, the majority of patients experiencing SAEs were related to SOC infections and infestations, and surgical and medical procedures.

7.3.3 Dropouts and/or Discontinuations

Double Blind Placebo Controlled Studies

In the Pooled Double Blind Studies, 313 subjects were treated with Dysport, of whom 95.2% completed the study. 164 subjects were treated with placebo, of which 95.1% completed the study (Table 44)

Table 44 Subject Disposition by Lower Limb Dose in U/kg Injected Unilaterally or Bilaterally – Pooled Double Blind Placebo Controlled Studies - Safety Population

	Placebo (N=164)	Subjects Treated Unilaterally		Subjects Treated Bilaterally		Dysport All Doses (N=313)[a]
		Dysport 10 U/kg (N=43)	Dysport 15 U/kg (N=52)	Dysport 20 U/kg (N=64)	Dysport 30 U/kg (N=116)	
Number of subjects that received study treatment:						
Study 141	79	43	50	36	30	160
Study 040	31	0	0	28	30	94
Study 701	26	0	2	0	24	26
Study 094	28	0	0	0	32[b]	33[b]
Overall	164	43	52	64	116	313
Number of subjects completed (n (%)	156 (95.1%)	42 (97.7%)	51 (98.1%)	61 (95.3%)	108 (93.1%)	298 (95.2%)
Number of subjects withdrawn after having received study treatment	8 (4.9%)	1 (2.3%)	1 (1.9%)	3 (4.7%)	8 (6.9%)	15 (4.8%)
Reason for premature withdrawal:						
Adverse event	1 (0.6%)	0	0	0	1 (0.9%)	1 (0.3%)
Lack of efficacy	0	0	0	0	0	0
Protocol violation	0	0	0	0	1 (0.9%)	1 (0.3%)
Lost to follow-up	1 (0.6%)	0	0	1 (1.6%)	1 (0.9%)	2 (0.6%)
Withdrawal by subject	3 (1.8%)	0	1 (1.9%)	1 (1.6%)	2 (1.7%)	4 (1.3%)
Other reason	1 (0.6%)	1 (2.3%)	0	0	1 (0.9%)	2 (0.6%)

N=number of subjects in group
Data Source: Appendix 2a, Table DP.1.2
a An additional 37 subjects were treated with Dysport 10 U/kg bilaterally are included only in the Dysport All Doses column. b The scheduled Dysport dose in Study 094 was 30 U/kg. One subject (00000900057) was not treated with this dose and only

appears in the All Doses column. The subject was treated with 23 U/kg administered bilaterally (Appendix 3a, Listing EX.1.1)

Source:Sponsor

REVIEWER COMMENT:

The reason for withdrawal was similar between Dysport and placebo, with the highest overall rate of withdrawal in patients treated with Dysport 30 U/kg.

7.3.5 Submission Specific Primary Safety Concerns

Possible Distant Spread of Toxin (PDSOT)

PDSOT is defined as a possible pharmacologic effect of botulinum toxin at sites that are either contiguous or distant from the site of injection.

The sponsor compiled a list of AEs of special interest (AESIs)

comprised primarily of AEs reflecting potential spread of effect of the toxin The list of MedDRA preferred terms used to identify AESI that required further review for inclusion as remote spread effects of Dysport, were based on the terms used for all licensed BTX-A products. A list of the MedDRA preferred terms used to identify the AESI for inclusion as spread of effects is provided below:

Accommodation disorder
Bradycardia
Botulism
Constipation
Diplopia
Dry mouth
Dysarthria
Dysphagia
Dysphonia
Eyelid ptosis
Facial palsy
Facial paresis*
Muscular weakness
Paralysis
Paralysis flaccid
Paresis cranial nerve
Pelvic floor muscle weakness
Peripheral nerve palsy
Peripheral paralysis

Pneumonia aspiration
Pupillary reflex impaired
Respiratory depression
Respiratory failure
Speech disorder

*(in MedDRA version 17.0, term is VIIth nerve paralysis)

TEAEs related to PDSOT or Remote Spread of Effects in double blind placebo controlled studies are presented by dose in Table 45

Table 45 Treatment Emergent Adverse Events Indicative of Remote Spread of Effect of Toxin by Lower Limb Dose in U/kg Injected Unilaterally or Bilaterally - Pooled Double Blind Placebo Controlled Studies – Overall Safety Population

System Organ Class Preferred Term	Placebo (N=164) n (%)	Subjects Treated Unilaterally		Subjects Treated Bilaterally		Dysport All Doses[a] (N=313) n (%)
		Dysport 10 U/kg (N=43)	Dysport 15 U/kg (N=52)	Dysport 20 U/kg (N=64)	Dysport 30 U/kg (N=116)	
Any TEAE Indicative of Remote Spread of Effect of Toxin	**1 (0.6)**	**0**	**1 (1.9%)**	**0**	**6 (5.2%)**	**7 (2.2%)**
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**0**	**0**	**4 (3.4%)**	**4 (1.3%)**
Muscular weakness	0	0	0	0	4 (3.4%)	4 (1.3%)
Gastrointestinal Disorders	**1 (0.6%)**	**0**	**1 (1.9%)**	**0**	**2 (1.7%)**	**3 (1.0%)**
Dysphagia	1 (0.6%)	0	1 (1.9%)	0	2 (1.7%)	3 (1.0%)
Nervous System Disorders	**0**	**0**	**0**	**0**	**2 (1.7%)**	**2 (0.6%)**
Dysarthria	0	0	0	0	2 (1.7%)	2 (0.6%)

N=number of subjects in group, n=number of subjects with observation, TEAE=treatment emergent adverse event, U=units
Data Source: Appendix 2a, Table AESI.1.1.2.
a Studies included: 141, 040, 701 and 094

Source:Sponsor

In the double blind placebo controlled studies there was one patient treated with Dysport 15 U/kg in GSC in Study 141, one patient treated with Dysport 30 U/kg in GSC in Study 040, and 6 patients (1 on placebo, 5 treated with Dysport 30 U/kg) in proximal (hip adductors) as well as distal (medial hamstring) muscles. These subjects are summarized in Table 46.

Table 46 Listing of Treatment Emergent Adverse Events of Special Interest Relating to Remote Spread of Effect of Toxin by Subject - Pooled Double Blind Placebo Controlled Studies – Overall Safety Population

Subject ID	Sex/ Age (years)	MedDRA PT/Verbatim Text	Onset Within 1st 4 Weeks/1st 12 Weeks/ Days From Prior Injection	Dysport Dose at Event (U/kg)/ Muscle Injected	Study Participation Duration at the First Event Onset (weeks)	Event Duration (days)	Outcome
84000700004	Male/4	Dysphagia/ Patient was having difficulty swallowing	Y/Y/4	15 GSC	<1	8	Recovered /Resolved
00001100207	Male/6	Muscular weakness/ Weakness of all muscles. he didn't want to make any action	Y/Y/14	30 Gastroc-nemius	2	16	Not recorded
00000500049	Female/ 3	Dysphagia/ Swallowing difficulty	Y/Y/15	NA	NA	11	Recovered /Resolved
00000300034	Male/2	Dysphagia/ Swallowing difficulties	Y/Y/6	30 HA/MH	<1	47	Recovered /Resolved
00000500003	Male/2	Muscular weakness/ Generalised muscular weakness	Y/Y/15	30 HA/MH	2.1	8	Resolved
00000500050	Male/9	Muscular weakness/ Generalised muscular weakness in the sense of premature fatigue	Y/Y/10	30 HA/MH	1.4	76	Not Resolved
		Dysarthria/ Dysarthria increasing	Y/Y/10	30 HA/MH	1.4	76	Not Recovered /Not Resolved

Subject ID	Sex/ Age (years)	MedDRA PT/Verbatim Text	Onset Within 1st 4 Weeks/1st 12 Weeks/ Days From Prior Injection	Dysport Dose at Event (U/kg)/ Muscle Injected	Study Participation Duration at the First Event Onset (weeks)	Event Duration (days)	Outcome
00001200014	Female/ 3	Dysphagia/ Swallowing difficulties, child could swallow less well. didn't like to have food in the mouth as well	Y/Y/25	30 HA/MH	3.6	≤62	Recovered /Resolved
00001500089	Male/10	Dysarthria/ articulation difficulty / Muscular weakness	Y/Y/17	30 HA/MH	2.4	≤56	Recovered /Resolved
		Muscular weakness/ articulation difficulty / Muscular weakness	Y/Y/17	30 HA/MH	2.4	≤56	Recovered /Resolved

CSR=clinicl study report, GSC=gastrocnemius soleus complex, HA/MH=hip adductors/medial hamstring, ID=identification, MedDRA=medical dictionary for regulatory activities, NA=not applicable,
PT=preferred term
Data Source: Study CSRs and Appendix 3a, Listing AESI.1.1

Source:Sponsor

All **double blind placebo controlled studies** except Study 094 involved injection of study treatment into the distal muscles (GSC or gastrocnemius only). In Study 094, Dysport 30 U/kg or placebo was injected bilaterally into the proximal

muscles (hip adductors and medial hamstrings) since the study enrolled subjects with hip adductor spasticity. The sponsor performed a focused evaluation of the TEAE profile between subjects injected in the proximal muscles in Study 094 and subjects treated with Dysport 30 U/kg administered bilaterally into the distal muscles. A comparison of TEAEs of the two groups, distal versus proximal muscle injections, is presented in Table 47.

Table 47 Treatment Emergent Adverse Events Reported in at Least 2% of Subjects in any Individual Dysport Dose Group (and >1 Subject) - Comparison of Double Blind Placebo Controlled Studies by Distal and Proximal Muscle Groups Injected

System Organ Class/ Preferred Term	Subjects Injected in Distal Muscles		Subjects Injected in Proximal Muscles	
Any TEAE[d]	**Placebo N=136**	**Dysport 30 U/kg [b] Administered Bilaterally N=84**	**Placebo N=28**	**Dysport 30 U/kg [b,c] Administered Bilaterally N=32**
	65 (47.8%)	**44 (52.4%)**	**13 (46.4%)**	**19 (59.4%)**
Infections and Infestations	**44 (32.4%)**	**31 (36.9%)**	**6 (21.4%)**	**11 (34.4%)**
Upper respiratory tract infection	10 (7.4%)	5 (6.0%)	0	3 (9.4%)
Nasopharyngitis	5 (3.7%)	4 (4.8%)	2 (7.1%)	1 (3.1%)
Bronchitis	5 (3.7%)	7 (8.3%)	1 (3.6%)	3 (9.4%)
Pharyngitis	9 (6.6%)	2 (2.4%)	0	0
Rhinitis	7 (5.1%)	6 (7.1%)	0	2 (6.3%)
Viral infection	7 (5.1%)	4 (4.8%)	0	0
Otitis media	4 (2.9%)	1 (1.2%)	2 (7.1%)	2 (6.3%)
[b]Ear infection	2 (1.5%)	2 (2.4%)	0	0
Tonsillitis	1 (0.7%)	2 (2.4%)	1 (3.6%)	0
General Disorders and Administration Site Conditions	**9 (6.6%)**	**9 (10.7%)**	**2 (7.1%)**	**11 (34.4%)**
Pyrexia	7 (5.1%)	3 (3.6%)	0	2 (6.3%)
Gait disturbance	0	2 (2.4%)	0	1 (3.1%)
Respiratory, Thoracic and Mediastinal Disorders	**14 (10.3%)**	**6 (7.1%)**	**1 (3.6%)**	**4 (12.5%)**
Cough	9 (6.6%)	3 (3.6%)	1 (3.6%)	0
Asthma	1 (0.7%)	2 (2.4%)	0	2 (6.3%)
Nervous System Disorders	**4 (2.9%)**	**8 (9.5%)**	**6 (21.4%)**	**7 (21.9%)**
Hypotonia	0	1 (1.2%)	1 (3.6%)	4 (12.5%)
Speech disorder	0	0	2 (7.1%)	3 (9.4%)
Musculoskeletal and Connective Tissue Disorders	**9 (6.6%)**	**9 (10.7%)**	**1 (3.6%)**	**6 (18.8%)**
Pain in extremity	7 (5.1%)	7 (8.3%)	0	0
Muscular weakness	1 (0.7%)	1 (1.2%)	1 (3.6%)	6 (18.8%)
Injury, Poisoning and Procedural Complications	**7 (5.1%)**	**4 (4.8%)**	**0**	**0**
Fall	2 (1.5%)	3 (3.6%)	0	0
Renal and Urinary Disorders	**1 (0.7%)**	**3 (3.6%)**	**0**	**2 (6.3%)**
Enuresis	1 (0.7%)	2 (2.4%)	0	0

N=number of subjects in group, n=subjects with observation, TEAE=treatment emergent adverse event, U=units
Data Source: Appendix 2a Tables SUB-AE-2.2.2 and Study 094 Table 14.3.1.2
a Studies included are Study 141, 040 and 701
b Administered as 15 U/kg/leg

c The scheduled Dysport dose in Study 094 was 30 U/kg. However, one subject (00000900057) was not treated with this dose and therefore only appears in the All Doses column. The subject was treated with 23 U/kg administered bilaterally (Appendix 3a Listing EX.1.1)

d PT of Unevaluable event was coded for side effects (Study 094); multiple verbatim terms with no specific diagnosis; for terms with no corresponding MedDRA code or terms confirmed as duplicates (i.e. same subject reporting TEAEs with exact same PT).

Source:Sponsor

REVIEWER COMMENT:

The number of TEAEs related to muscular weakness (dysarthria/dysphagia and/or generalized muscle weakness) was greater for patients treated with Dysport 30 U/kg in proximal and distal muscles of the LE, compared to patients treated with Dysport 30 U/kg in distal muscles of the LE alone.

An SMQ Broad search of double blind placebo controlled studies included in the ISS, with MAED revealed 2 events in one subject treated with Dysport 10 U/kg defined as Guillain Barre, which is consistent with spread of toxin.

Table 48 SMQ Broad Search for PDSOT

SMQ (Broad Search)		*Dysport 10 U/kg (N = 116)*			*Dysport 15 U/kg (N = 84)*			*Dysport 20 U/kg (N = 72)*		
Level 1	*Level 2*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
(1) Agranulocytosis		18	13	11.21	8	6	7.14	0	0	0
(1) Oropharyngeal disorders		20	15	12.93	9	7	8.33	0	0	0
(1) Oropharyngeal disorders	**(2) Oropharyngeal infections**	19	14	12.07	9	7	8.33	0	0	0
(1) Noninfectious diarrhoea		3	3	2.59	0	0	0	1	1	1.39
(1) Systemic lupus erythematosus		5	3	2.59	2	1	1.19	0	0	0
(1) Convulsions		5	3	2.59	2	1	1.19	0	0	0
(1) Noninfectious encephalitis		1	1	0.86	2	1	1.19	0	0	0
(1) Noninfectious encephalopathy/delirium		2	2	1.72	2	1	1.19	0	0	0
(1) Noninfectious meningitis		1	1	0.86	2	1	1.19	0	0	0
(1) Accidents and injuries		1	1	0.86	1	1	1.19	0	0	0

(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions		9	7	6.03	15	10	11.9	2	2	2.78
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	8	6	5.17	15	10	11.9	2	2	2.78
(1) Generalised convulsive seizures following immunisation		4	3	2.59	0	0	0	0	0	0
(1) Hepatic disorders		1	1	0.86	1	1	1.19	0	0	0
(1) Hepatic disorders	(2) Liver infections	1	1	0.86	1	1	1.19	0	0	0
(1) Severe cutaneous adverse reactions		1	1	0.86	1	1	1.19	0	0	0
(1) Anaphylactic reaction		16	12	10.34	9	8	9.52	0	0	0
(1) Acute pancreatitis		6	4	3.45	14	9	10.71	1	1	1.39
(1) Asthma/bronchospasm		2	1	0.86	0	0	0	0	0	0
(1) Depression and suicide/self-injury		0	0	0	1	1	1.19	0	0	0
(1) Depression and suicide/self-injury	(2) Depression (excl suicide and self injury)	0	0	0	1	1	1.19	0	0	0
(1) Haemorrhages		1	1	0.86	0	0	0	0	0	0
(1) Haemorrhages	(2) Haemorrhage terms (excl laboratory terms)	1	1	0.86	0	0	0	0	0	0
(1) Neuroleptic malignant syndrome		1	1	0.86	0	0	0	0	0	0
(1) Retroperitoneal fibrosis		0	0	0	0	0	0	0	0	0
(1) Pseudomembranous colitis		2	2	1.72	0	0	0	1	1	1.39
(1) Extrapyramidal syndrome		2	2	1.72	0	0	0	0	0	0
(1) Extrapyramidal syndrome	(2) Dyskinesia	1	1	0.86	0	0	0	0	0	0
(1) Extrapyramidal syndrome	(2) Dystonia	1	1	0.86	0	0	0	0	0	0
(1) Extrapyramidal syndrome	(2) Parkinson-like events	2	2	1.72	0	0	0	0	0	0
(1) Oropharyngeal disorders	(2) Gingival disorders	1	1	0.86	1	1	1.19	0	0	0
(1) Oropharyngeal disorders	(2) Oropharyngeal	1	1	0.86	0	0	0	0	0	0

	conditions (excl neoplasms, infections and allergies)									
(1) Thrombophlebitis		0	0	0	0	0	0	0	0	0
(1) Guillain-Barre syndrome		2	1	0.86	0	0	0	0	0	0
(1) Extravasation events (injections, infusions and implants)		0	0	0	0	0	0	0	0	0
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	(2) Gastrointestinal nonspecific inflammation	1	1	0.86	0	0	0	0	0	0
(1) Eosinophilic pneumonia		4	3	2.59	1	1	1.19	0	0	0
(1) Hearing and vestibular disorders		0	0	0	0	0	0	0	0	0
(1) Hearing and vestibular disorders	(2) Vestibular disorders	0	0	0	0	0	0	0	0	0
(1) Conjunctival disorders		0	0	0	1	1	1.19	0	0	0
(1) Ocular infections		0	0	0	1	1	1.19	0	0	0
(1) Hypersensitivity		3	2	1.72	1	1	1.19	0	0	0

Source: Reviewer

An SMQ Narrow search of all DBPC studies did not produce any terms that are consistent with spread of toxin.

Open Label Studies

There were two additional patients treated with Dysport (one patient was treated with 15 U/kg/leg and one patient was treated with 13 U/kg/leg on the first injection and 10 U/kg/leg on the second injection), in distal muscles of the leg (gastrocnemius) in the open label study 702, who experienced possible distant spread of toxin effects. These cases are outlined in Table 49.

Table 49 Listing of Treatment Emergent Adverse Events of Special Interest Relating to Remote Spread of Effect of Toxin by Subject - Pooled Open Label Studies

Study/ Subject ID	Sex/ Age (years)	MedDRA PT/Verbatim Text	Onset Within 1st 4 Weeks/1st 12 Weeks/ Days/Weeks From Prior Injection	Last (U/kg/leg) (Cum. (U/kg)) Dysport Dose Injected in the LL Prior to the Event Onset/Muscle Injected	Treatment Cycle/Total Dysport Exposure Duration at the First Event Onset (weeks)	Event Duration (days)	Outcome
00002200061	Female/ 4	Constipation/ Constipation	Y/Y/3/<1	15 (30)/ Gastrocnemius	OL-C1/ <1/	85	-
00002700236	Female/ 3	Muscular weakness/ Muscle weakness (generalized)	Y/Y/3/<1	13.8 (28)/ Gastrocnemius	OL-C1/ <1/	26	-
		Muscular weakness/ Muscle weakness (general)	Y/Y/8/1.1	10 (68)/ Gastrocnemius	OL-C3/ 35.1/	80	-

-=not recorded, C=Treatment Cycle, CSR=clinical study report, Cum.=cumulative, ID=identification, LL=lower limb, MedDRA=Medical Dictionary for Regulatory Activities, OL=open label,
PT=preferred term, U=units, Y=yes
Data Source: Study CSRs and Appendix 3a, Listing AESI1.2
a Subjects were injected in the gastrocnemius/soleus complex

Source:Sponsor

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An analysis of the common adverse events by PT was conducted for Study 141, using MAED. All PT terms that occurred in at least 2% (rounded to the nearest percent) of patients treated with Dysport 10 U/kg/leg and/or Dysport 15 U/kg/leg are included. The PT terms are ranked from highest to lowest percentage for Dysport 15 U/kg/leg.

Table50 Common Adverse Events for pivotal study, Study 141

	Dysport 10 U/kg/leg (N = 80)			*Dysport 15 U/k/leg (N = 80)*			*Placebo (N = 81)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Upper respiratory tract infection	5	3	**3.8**	11	10	**12.5**	10	9	**11.1**
Cough	8	6	**7.5**	6	6	**7.5**	5	5	**6.2**
Vomiting	2	2	**2.5**	4	3	**3.8**	3	3	**3.7**
Bronchitis	4	3	**3.8**	2	2	**2.5**	1	1	**1.2**
Headache	0	0	**0**	3	2	**2.5**	1	1	**1.2**

Nasopharyngitis	0	0	**0**	2	2	**2.5**	4	2	**2.5**
Pharyngitis	6	5	**6.2**	1	1	**1.2**	8	5	**6.2**
Nausea	3	2	**2.5**	3	1	**1.2**	2	1	**1.2**
Rhinitis	2	2	**2.5**	1	1	**1.2**	1	1	**1.2**
Urinary tract infection	2	2	**2.5**	1	1	**1.2**	2	2	**2.5**

Source: Reviewer

REVIEWER COMMENT:

The most common adverse event was upper respiratory tract infection, cough and nasopharyngitis.

A similar analysis was conducted using the safety data from the ISS for all double blind placebo controlled trials.

Table 51 Common Adverse Events from ISS for all double blind placebo controlled trials

	Dysport 10 U/kg (N = 116)			*Dysport 15 U/kg (N = 84)*			*Dysport 20 U/kg (N = 72)*			*Dysport 30 U/kg (N = 92)*			*Placebo (N = 166)*		
PT	*Events*	*N*	*(%)*	*Events*	*N*	*(%)*	*Events*	*N*	*(%)*	*Events*	*N*	*(%)*	*Events*	*N*	*(%)*
Bronchitis	11	9	**7.8**	12	9	**10.7**	4	4	**5.6**	2	2	**2.8**	4	4	**2.4**
Rhinitis	4	2	**1.7**	4	3	**3.6**	0	0	**0**	2	2	**2.8**	3	3	**1.8**
Gastroenteritis	0	0	**0**	0	0	**0**	0	0	**0**	3	2	**2.8**	4	4	**2.4**
Upper respiratory tract infection	13	9	**7.8**	22	14	**16.7**	2	2	**2.8**	3	1	**1.1**	19	13	**7.8**
Pharyngitis	16	11	**9.5**	5	4	**4.8**	0	0	**0**	1	1	**1.1**	16	9	**5.4**
Otitis media	2	2	**1.7**	1	1	**1.2**	1	1	**1.4**	1	1	**1.1**	7	4	**2.4**
Tonsillitis	1	1	**0.9**	2	1	**1.2**	0	0	**0**	1	1	**1.1**	7	4	**2.4**
Constipation	0	0	**0**	1	1	**1.2**	0	0	**0**	1	1	**1.1**	0	0	**0**
Ear infection	1	1	**0.9**	0	0	**0**	0	0	**0**	1	1	**1.1**	3	3	**1.8**
Fatigue	1	1	**0.9**	0	0	**0**	1	1	**1.4**	1	1	**1.1**	0	0	**0**
Urinary incontinence	1	1	**0.9**	0	0	**0**	0	0	**0**	1	1	**1.1**	0	0	**0**
Convulsion	0	0	**0**	0	0	**0**	0	0	**0**	1	1	**1.1**	0	0	**0**
Head injury	0	0	**0**	0	0	**0**	0	0	**0**	1	1	**1.1**	1	1	**0.6**
Cough	14	11	**9.5**	9	8	**9.5**	0	0	**0**	0	0	**0**	10	9	**5.4**
Nausea	4	3	**2.6**	7	5	**6.0**	0	0	**0**	0	0	**0**	3	2	**1.2**
Vomiting	2	2	**1.7**	7	5	**6.0**	1	1	**1.4**	0	0	**0**	4	4	**2.4**
Nasopharyngitis	1	1	**0.9**	6	4	**4.8**	0	0	**0**	0	0	**0**	5	3	**1.8**
Headache	0	0	**0**	4	3	**3.6**	0	0	**0**	0	0	**0**	2	2	**1.2**
Toothache	0	0	**0**	2	2	**2.4**	0	0	**0**	0	0	**0**	0	0	**0**
Urinary tract infection	3	3	**2.6**	2	1	**1.2**	0	0	**0**	0	0	**0**	2	2	**1.2**
Pneumonia	2	2	**1.7**	1	1	**1.2**	0	0	**0**	0	0	**0**	2	2	**1.2**

Source:Reviewer

REVIEWER COMMENT:

Similar results for common adverse events were identified for pooled double blind studies compared to pivotal Study 141. Upper respiratory tract infection, bronchitis, pharyngitis, cough and Nasopharyngitis along with nausea and vomiting were the most common adverse events.

Dysport Label (Approval UL spasticity in Adults, July 16, 2015)

The common TEAEs (≥2%) in patients receiving Dysport 500 or Dysport 1000 U versus placebo in double blind clinical trials for UL spasticity in adults is shown in Table 2 from the Dysport label.

Table 2: Most Common Adverse Reactions Observed in at Least 2% of Patients Treated in Pooled, Double-Blind Trials of Patients with Upper Limb Spasticity Reported More Frequently than with Placebo

Adverse Reaction Preferred Term	DYSPORT® 500 Units (N=197) %	DYSPORT® 1000 Units (N=194) %	Placebo (N=279) %
Infections and infestations			
Nasopharyngitis	4	1	1
Urinary tract infection	3	1	2
Influenza	1	2	1
Infection	1	2	1
Musculoskeletal and connective tissue disorders			
Muscular weakness	2	4	1
Pain in extremity	0	2	1
Musculoskeletal pain	3	2	2
Back pain	1	2	1
Nervous system disorders			
Headache	1	2	1
Dizziness	3	1	1
Convulsion	2	2	1
Syncope	1	2	0
Hypoaesthesia	0	2	<1
Partial seizures	0	2	0
General disorders and administration site conditions			
Fatigue	2	2	0
Asthenia	2	1	<1
Injury, poisoning and procedural complications			
Fall	2	3	2
Injury	2	2	1
Contusion	1	2	<1
Gastrointestinal disorders			
Diarrhea	1	2	<1
Nausea	2	1	1
Constipation	0	2	1
Investigation			
Blood triglycerides increased	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough	1	2	1
Vascular disorders			
Hypertension	1	2	<1
Psychiatric disorders			
Depression	2	3	1

REVIEWER COMMENT:

The TEAEs shown in the Dysport label are from studies completed for the approval of the treatment of UL spasticity in adults. The dose for these studies

included the maximum dose allowed in the studies for pediatric LL spasticity, 1000 U. The TEAEs are similar between the two groups, with infections and infestations being the most common SOC. However, the percent of subjects who experienced the TEAEs is higher in the pediatric studies for LL spasticity. This is likely multifactorial including higher rate of infections in pediatric population in general, and higher rate in patients with cerebral palsy.

7.4.2 Laboratory Findings

Data for clinical laboratory parameters were only systematically collected for the DBPC study 141 and the OLE study 147. No pooled analysis of the data was performed.

Clinical Hematology

Clinical Hematology values outside the normal range in pivotal study 141 at Week 4 and at the end of the study (EOS) are presented by dose in Table 52.

Table 52 Study 141: Subjects with Hematology Parameters outside the Normal Range, by Treatment Group (Dose per Leg) - Safety Population

Parameter	Placebo (N=79)		Dysport 10 U/kg/leg (N=80)		Dysport 15 U/kg/leg (N=80)		Total Dysport (N=160)	
	Week 4	EOS	Week 4	EOS	Week 4	EOS	Week 4	EOS
Values Below LLN; n (%)								
Red blood cell count	2 (2.5)	1 (1.3)	0	0	0	0	0	0
Hemoglobin	1 (1.3)	0	0	1 (1.3)	0	0	0	1 (0.6)
Mean cell hemoglobin	1 (1.3)	3 (3.8)	1 (1.3)	2 (2.5)	0	0	1 (0.6)	2 (1.3)
Mean cell hemoglobin concentration	12 (15.2)	8 (10.1)	7 (8.8)	7 (8.8)	4 (5.0)	7 (8.8)	11 (6.9)	14 (8.8)
Mean cell volume	1 (1.3)	1 (1.3)	0	1 (1.3)	0	0	0	1 (0.6)
Hematocrit	1 (1.3)	0	0	1 (1.3)	0	0	0	1 (0.6)
White blood cell count	4 (5.1)	4 (5.1)	5 (6.3)	3 (3.8)	4 (5.0)	6 (7.5)	9 (5.6)	9 (5.6)
Neutrophils	3 (3.8)	1 (1.3)	1 (1.3)	1 (1.3)	3 (3.8)	3 (3.8)	4 (2.5)	4 (2.5)
Lymphocytes	3 (3.8)	2 (2.5)	5 (6.3)	2 (2.5)	4 (5.0)	4 (5.0)	9 (5.6)	6 (3.8)
Monocytes	5 (6.3)	5 (6.3)	4 (5.0)	5 (6.3)	5 (6.3)	6 (7.5)	9 (5.6)	11 (6.9)
Eosinophils	0	0	0	0	0	0	0	0
Basophils	0	0	0	0	0	0	0	0
Platelets	6 (7.6)	3 (3.8)	5 (6.3)	2 (2.5)	3 (3.8)	0	8 (5.0)	2 (1.3)
Values Above ULN; n (%)								
Red blood cell count	19 (24.1)	13 (16.5)	16 (20.0)	16 (20.0)	11 (13.8)	14 (17.5)	27 (16.9)	30 (18.8)
Hemoglobin	41 (51.9)	30 (38.0)	48 (60.0)	40 (50.0)	40 (50.0)	34 (42.5)	88 (55.0)	74 (46.3)
Mean cell hemoglobin	25 (31.6)	17 (21.5)	25 (31.3)	25 (31.3)	24 (30.0)	23 (28.8)	49 (30.6)	48 (30.0)
Mean cell hemoglobin concentration	4 (5.1)	2 (2.5)	5 (6.3)	4 (5.0)	4 (5.0)	6 (7.5)	9 (5.6)	10 (6.3)
Mean cell volume	36 (45.6)	26 (32.9)	35 (43.8)	29 (36.3)	29 (36.3)	29 (36.3)	64 (40.0)	58 (36.3)
Hematocrit	45 (57.0)	38 (48.1)	53 (66.3)	46 (57.5)	48 (60.0)	40 (50.0)	101 (63.1)	86 (53.8)

White blood cell count	4 (5.1)	3 (3.8)	3 (3.8)	2 (2.5)	2 (2.5)	0	5 (3.1)	2 (1.3)
Neutrophils	2 (2.5)	2 (2.5)	3 (3.8)	1 (1.3)	1 (1.3)	0	4 (2.5)	1 (0.6)
Lymphocytes	0	0	0	1 (1.3)	0	0	0	1 (0.6)
Monocytes	0	0	1 (1.3)	1(1.3)	0	0	1 (0.6)	1 (0.6)
Eosinophils	2 (2.5)	2 (2.5)	3 (3.8)	1 (1.3)	0	2 (2.5)	3 (1.9)	3 (1.9)
Basophils	0	0	0	0	1 (1.3)	0	1 (0.6)	0
Platelets	8 (10.1)	8 (10.1)	15 (18.8)	9 (11.3)	12 (15.0)	8 (10.0)	27 (16.9)	17 (10.6)

EOS=end of study; LLN=lower limit of normal; N=number of subjects in group; n=number of subjects with observation; U=units; ULN=upper limit of normal.
Data Source: Study 141, Table 14.3.5.1.2 and Listing 16.2.8.2.
Note: The denominator is the number of subjects in the given column (N).

Source:Sponsor

REVIEWER COMMENT:

There is no consistent pattern of mean or outlying abnormal hematologic values associated with treatment cohort, including dose of Dysport.

Clinical Chemistry

Blood Glucose

Changes in mean glucose levels from Baseline to Week 4 and to EOS across all treatment groups are presented in Table 53. Mean changes were similar across treatment groups.

Table 53 Study 141: Mean Change from Baseline to Week 4 and End of Study Visit in Blood Glucose (mmol/L) by Treatment Group (Dose per Leg) - Safety Population

Visit Statistic	**Placebo (N=79)**	**Dysport 10 U/kg/leg (N=80)**	**Dysport 15 U/kg/leg (N=80)**	**Total Dysport (N=160)**
Week 4				
n	69	65	61	126
Mean change (range)	0.147 (-2.39, 1.89)	0.102 (-2.17, 3.99)	0.186 (-1.66, 2.38)	0.143 (-2.17, 3.99)
End of Study				
n	63	63	54	117
Mean change (range)	-0.054 (-1.83, 2.44)	-0.050 (-3.11, 2.39)	0.040 (-1.45, 1.78)	-0.009 (-3.11, 2.39)

N=number of subjects in group; n=number of subjects with observation, U=units
Data Source: Study 141, Table 14.3.5.2.1

Source:Sponsor

Alkaline phosphatase:

There was a decrease in total alkaline phosphatase in all treatment groups, placebo > Dysport 10 U/kg/leg > Dysport 15 U/kg/leg. However, the mean change in Bone Specific

Alkaline Phosphatase was highest in the Dysport 10 U/kg/leg at week 4, with similar decreases in placebo and Dysport 15 U/kg/leg (Table 54)

Table 54 Study 141: Mean Change from Baseline to Week 4 and End of Study Visit in Alkaline Phosphatase and Bone Specific Alkaline Phosphatase, by Treatment Group (Dose per Leg) – Safety Population

Visit Statistic	Placebo (N=79)	Dysport 10 U/kg/leg (N=80)	Dysport 15 U/kg/leg (N=80)	Total Dysport (N=160)
Alkaline Phosphatase (IU/L)				
Week 4				
n	70	66	60	126
Mean change (range)	-29.3 (-1928, 63)	-17.7 (-87, 130)	-15.1 (-86, 65)	-16.5 (-87, 130)
End of Study				
n	63	63	54	117
Mean change (range)	-35.0 (-1995, 67)	-5.7 (-99, 132)	9.8 (-103, 654)	1.5 (-103, 654)
Bone Specific Alkaline Phosphatase (IU/L)				
Week 4				
n	67	70	64	134
Mean change (range)	-12.01 (-890.5, 92.7)	-26.88 (-190.9, 42.6)	-11.58 (-135.1, 64.2)	-19.57 (-190.9, 64.2)
End of Study				
n	58	61	57	118
Mean change (range)	-23.27 (-911.5, 107.7)	-22.00 (-193.2, 148.6)	-6.45 (-170.7, 86.5)	-14.49 (-193.2, 148.6)

IU=international unit, N=number of subjects in group; n=number of subjects with observation, SD=standard deviation
Data Source: Study 141, Table 14.3.5.2.1 and Listing 16.2.8.3.

Source:Sponsor

REVIEWER COMMENT:

There is no consistent pattern of abnormal clinical chemistry values associated with treatment cohort, including dose of Dysport.

7.4.3 Vital Signs

Heart Rate

Changes in heart rate from baseline for Pooled Double Blind Placebo Controlled Studies are presented in Table 55

Table 55 Heart Rate by Lower Limb Dose in U/kg Injected Unilaterally or Bilaterally - Pooled Double Blind Placebo Controlled Studies - Safety Population

Heart Rate (bpm)	Placebo (N=164)	Subjects.Treated Unilaterally (1 Leg)		Subjects Treated Bilaterally (2 Legs)		Dysport All Doses (N=313)[a]
		Dysport 10 U/kg (N=43)	Dysport 15 U/kg (N=52)	Dysport 20 U/kg (N=64)	Dysport 30 U/kg (N=116)	
Baseline						
n	163	43	52	64	116	311
Missing	1	0	0	0	0	2

Mean (SD)	92.4 (15.57)	89.2 (15.99)	92.1 (15.94)	95.2 (13.43)	92.7 (13.64)	92.8 (14.09)
Median	92.0	92.0	92.0	96.0	90.0	92.0
Min ; Max	53 ; 130	60 ; 121	55 ; 128	60 ; 124	60 ; 124	55 ; 128
LVA Post-treatment						
n	163	43	52	63	115	310
Missing	1	0	0	1	2	3
Mean (SD)	92.1 (15.57)	87.2 (15.43)	90.5 (16.01)	91.4 (14.34)	93.3 (14.80)	91.7 (14.55)
Median	92.0	88.0	91.5	91.0	93.0	91.5
Min ; Max	55 ; 155	60 ; 121	60 ; 124	59 ; 120	60 ; 140	59 ; 140
Change from Baseline to LVA Post-treatment						
n	162	43	52	63	115	309
Missing	2	0	0	1	1	4
Mean (SD)	-0.3 (15.66)	-2.0 (14.00)	-1.6 (12.16)	-3.8 (11.37)	0.6 (14.67)	-1.1 (12.90)
Median	0.0	0.0	-1.0	-4.0	0.0	0.0
Min ; Max	-46 ; 62	-30 ; 26	-32 ; 24	-34 ; 21	-50 ; 36	-50 ; 36

bpm=beats per minute, LVA=last value available after the first dose of study treatment, max=maximum, min=minimum, N=number of subjects in group, n=number of subjects, SD=standard deviation, U=units
Data Source: Appendix 2a, Table VS.1.1
a Studies included: 141, 040, 701, 094

Source:Sponsor

Systolic Blood Pressure

Changes in systolic blood pressure from baseline for Pooled Double Blind Placebo Controlled Studies are presented in Table 56.

Table 56 Systolic Blood Pressure by Lower Limb Dose in U/kg Injected Unilaterally or Bilaterally - Pooled Double Blind Placebo Controlled Studies - Safety Population

Systolic Blood Pressure (mmHg)	Placebo (N=164)	Subjects Treated Unilaterally (1 Leg)		Subjects Treated Bilaterally (2 Legs)		Dysport All Doses (N=313)[a]
		Dysport 10 U/kg (N=43)	Dysport 15 U/kg (N=52)	Dysport 20 U/kg (N=64)	Dysport 30 U/kg (N=116)	
Baseline						
n	160	43	52	64	114	310
Missing	4	0	0	0	2	3
Mean (SD)	99.6 (13.90)	97.8 (13.37)	97.7 (11.79)	100.3 (13.28)	101.5 (12.69)	99.9 (12.41)
Median	100.0	95.0	91.5	100.0	100.0	100.0
Min ; Max	60 ; 135	75 ; 135	80 ; 130	70 ; 130	70 ; 144	70 ; 144
LVA Post-treatment						
n	161	43	52	63	112	306
Missing	3	0	0	1	4	7
Mean (SD)	100.0 (11 31)	98.9 (13.49)	97.1 (11.40)	103.3 (12.08)	100.3 (11.82)	100.0 (12.14)
Median	100.0	100.0	98.0	100.0	100.0	100.0
Min ; Max	70 ; 130	75 ; 124	75 ; 125	75 ; 136	70 ; 130	65 ; 136
Change from Baseline to LVA Post-treatment						
n	159	43	52	63	112	306

Missing	5	0	0	1	4	7
Mean (SD)	0.7 (14.42)	1.1 (12.25)	-0.6 (12.54)	3.3 (14.45)	-1.1 (12.68)	0.2 (12.90)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min ; Max	-50 ; 57	-21 ; 28	-33 ; 20	-43 ; 40	-60 ; 35	-60 ; 40

LVA=last value available after the first dose of study treatment, max=maximum; n=number of subjects, min=minimum, N=number of subjects in group, n= number of subjects with observation, SD=standard deviation, U=units
Data Source: Appendix 2a, Table VS.1.1
a Studies included: 141, 040, 701, 094

Source:Sponsor

Diastolic Blood Pressure

Changes in diastolic blood pressure from baseline for Pooled Double Blind Placebo Controlled Studies are presented in Table 57

Table 57 Diastolic Blood Pressure by Lower Limb Dose in U/kg Injected Unilaterally or Bilaterally - Pooled Double Blind Placebo Controlled Studies - Safety Population

Diastolic Blood Pressure (bpm)	Placebo (N=164)	Subjects Treated Unilaterally (1 Leg)		Subjects Treated Bilaterally (2 Legs)		Dysport All Doses (N=313)[a]
		Dysport 10 U/kg (N=43)	Dysport 15 U/kg (N=52)	Dysport 20 U/kg (N=64)	Dysport 30 U/kg (N=116)	
Baseline						
n	160	43	52	64	114	310
Missing	4	0	0	0	2	3
Mean (SD)	62.2 (9.54)	64.0 (9.62)	61.6 (8.43)	61.0 (9.53)	64.1 (9.37)	63.1 (9.25)
Median	60.0	60.0	60.0	60.0	60.0	60.0
Min ; Max	40 ; 95	50 ; 85	47 ; 80	40 ; 89	40 ; 91	40 ; 91
LVA Post-treatment						
n	161	43	52	63	112	306
Missing	3	0	0	1	4	7
Mean (SD)	64.1 (9.30)	62.2 (7.47)	62.3 (7.97)	62.6 (9.10)	63.9 (9.95)	63.0 (9.24)
Median	61.0	60.0	60.0	60.0	60.0	60.0
Min ; Max	38 ; 97	50 ; 79	40 ; 80	40 ; 89	43 ; 120	35 ; 120
Change from Baseline to LVA Post-treatment						
n	159	43	52	63	112	306
Missing	5	0	0	1	4	7
Mean (SD)	1.9 (10.86)	-1.7 (8.86)	0.7 (10.42)	1.6 (10.87)	-0.2 (10.61)	-0.1 (10.78)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min ; Max	-35 ; 40	-23 ; 23	-25 ; 30	-27 ; 30	-30 ; 50	-35 ; 50

Bpm=beats per minute, LVA=last value available after the first dose of study treatment, max=maximum , min=minimum, N=number of subjects in group, n=number of subjects with observation, SD=standard deviation, U=units
Data Source: Appendix 2a, Table VS.1.1
a Studies included: 141, 040, 701, 094

Source:Sponsor

REVIEWER COMMENT:

There were no significant changes noted in vital signs.

7.4.4 Electrocardiograms (ECGs)

ECG was recorded throughout Studies 141 (double blind) and 147 (open label extension.

No subjects had a QTcB interval that was >480msec or QTcF >450 msec. There were no increases from Baseline >60 msec in either QTcB or QTcF.

Two subjects had an ECG abnormality that was considered to be clinical significant, both in Study 141:

- Subject 61600100018, a 6-year-old female in the Dysport 10 U/kg treatment group, had a sinus tachycardia >150 bpm recorded at Week 16. Her HR recorded during the vital signs measurements was 96 bpm at this visit.

- Subject 61600100023, a 2-year-old female in the Dysport 15 U/kg treatment group, had a technically poor tracing at Week 12 which showed a sinus tachycardia that was potentially significant. Her HR recorded during the vital signs measurements was 85 bpm at this visit.

REVIEWER COMMENT:

Two subjects experienced tachycardia; however, there was no clinical sequelae. There were no other significant changes noted in ECG parameters.

7.4.6 Immunogenicity

The presence of binding and neutralizing antibodies to BTX was evaluated in Studies 141 and 147. A sequential testing approach was employed whereby samples were first evaluated for the presence of binding antibodies. If a positive result for binding antibodies was obtained then a sample was tested for neutralizing antibodies.

In Study 702, only neutralizing antibodies were evaluated.

Table 58 Summary of the Number of Subjects with Positive Antibodies at Baseline or Who Developed Positive Antibodies Following Dysport Treatment in the Combined Studies 141 Plus 147 and in Study 702

	Combined Studies 141 and 147 N=226[a,b]	Study 702 Dysport 4-Monthly N=102[a,c]	Study 702 Dysport Yearly N=101[a,c]	Study 702 Dysport Overall N=203
Number of subjects with positive binding antibodies at Baseline	5	NA	NA	NA
Number of subjects who developed binding antibodies following Dysport treatment	9	NA	NA	NA
Number of subjects with positive neutralising antibodies at Baseline	2	1	1	2
Number of subjects who developed neutralising antibodies following Dysport treatment	4	4	1	5

N=number of subjects in group, NA=not assessed
a N=number of subjects having received Dysport with at least one evaluable antibodies assessment Baseline or post-treatment. b Source: Study 147, Listing 16.2.9.4.1
c Source: Study 702, Listing 16.2.7 3

Source:Sponsor

A total of 319 samples from 193 subjects were analyzed during the study for antibodies. The number of subjects positive for binding and/or neutralizing antibodies is summarized in Table 59.

Table 59 Presence of Binding or Neutralizing Antibodies to Botulinum Toxin Type A at Baseline and/or at the End of Study Visit in the Double Blind Study and During the Open Label Study, by Total Dose Received in the Lower Limb(s) - Safety Population

Visit Presence	Placebo		Lower Limb Dysport Total Dose								Dysport All Doses	
			10 U/kg[a]		15 U/kg[b]		20 U/kg[c]		30 U/kg[d]			
	BAb	NAb	BAb	NAb	BAb	NAb	BAb	NAb	BAb	NAb	BAb	NAb
Double Blind Study	N=71		N=39		N=48		N=35		N=23		N=145	
Baseline, n (%)												
Yes	3 (4.2)	1 (1.4)	0	0	1 (2.1)	0	0	0	1 (4.3)	1 (4.3)	2 (1.4)	1 (0.7)
No[e]	66 (93.0)	1 (1.4)	35 (89.7)	0	43 (89.6)	0	34 (97.1)	0	20 (87.0)	0	132 (91.0)	0
Missing[f]	2 (2.8)	1 (1.4)	4 (10.3)	0	4 (8.3)	1 (2.1)	1 (2.9)	0	2 (8.7)	0	11 (7.6)	1 (0.7)
End of Study, n (%)												
Yes	3 (4.2)	2 (2.8)	0	0	2 (4.2)	1 (2.1)	0	0	1 (4.3)	1 (4.3)	3 (2.1)	2 (1.4)
No[e]	58 (81.7)	1 (1.4)	31 (79.5)	0	34 (70.8)	1 (2.1)	29 (82.9)	0	16 (69.6)	0	110 (75.9)	1 (0.7)
Missing[f]	10 (14.1)	0	8 (20.5)	0	12 (25.0)	0	6 (17.1)	0	6 (26.1)	0	32 (22.1)	0
Open Label Study												
Treatment Cycle 1, Day 1, n (%)	N/A		N=117		N/A		N=84		N/A		N=201	
Yes	N/A	N/A	4 (3.4)	3 (2.6)	N/A	N/A	2 (2.4)	1 (1.2)	N/A	N/A	6 (3.0)	4 (2.0)
No[e]	N/A	N/A	88 (75.2)	1 (0.9)	N/A	N/A	63 (75.0)	1 (1.2)	N/A	N/A	151 (75.1)	2 (1.0)

Missing[f]	N/A	N/A	25 (21.4)	-	N/A	N/A	19 (22.6)	-	N/A	N/A	44 (21.9)	-
Treatment Cycle 2, Week 4, n (%)	**N/A**		**N=59**		**N=39**		**N=31**		**N=39**		**N=168**	
Yes	N/A	N/A	1 (1.7)	1 (1.7)	3 (7.7)	2 (5.1)	0	0	2 (5.1)	2 (5.1)	6 (3.6)	5 (3.0)
No[e]	N/A	N/A	49 (83.1)	0	31 (79.5)	0	24 (77.4)	0	32 (82.1)	0	136 (81.0)	0
Missing[f]	N/A	N/A	9 (15.3)	0	5 (12.8)	1 (2.6)	7 (22.6)	0	5 (12.8)	0	26 (15.5)	1 (0.6)
End of Study/early withdrawal, n (%)	**N/A**		**N=119**		**N=48**		**N=87**		**N=44**		**N=204**	
Yes	N/A	N/A	1 (0.8)	1 (0.8)	3 (6.3)	1 (2.1)	3 (3.4)	1 (1.1)	5 (11.4)	3 (6.8)	12 (5.9)	6 (2.9)
No[e]	N/A	N/A	54 (45.4)	0	37 (77.1)	1 (2.1)	31 (35.6)	1 (1.1)	34 (77.3)	1 (2.3)	156 (76.5)	3 (1.5)
Missing[f]	N/A	N/A	64 (53.8)	0	8 (16.7)	1 (2.1)	53 (60.9)	1 (1.1)	5 (11.4)	1 (2.3)	36 (17.6)	3 (1.5)

Abbreviations: BAb=binding antibodies; N=number of subjects in group; n=number of subjects with data; N/A=not applicable; NAb=neutralising antibodies; U=Units.
(a) The actual administered doses in the lower limb were >7.5 to ≤12.5 U/kg in the open label study.
(b) The actual administered doses in the lower limb were >12 5 to ≤17.5 U/kg in the open label study.
(c) The actual administered doses in the lower limb were >15 to ≤25 U/kg in the open label study.
(d) The actual administered doses in the lower limb were >25 to ≤35 U/kg in the open label study.
(e) Only positive binding antibody results were analysed for neutralising antibodies (i.e. subjects who had negative binding antibody results were not included in this table because they had no assessment of neutralising antibodies).
(f) Subjects with missing binding antibody results were excluded from the neutralising antibody assessments.
Data Source: Table 14.3.6.3.1, Table 14.3.6.3.2, Table 14.3.6.3.3 and Table 14 3.6.3.4.
Note: The denominator is the number of subjects in the given column (N). Subjects with dosage outside of the ranges specified (i.e. Treatment Cycle 1: ≤7.5 or >12.5 U/kg (one leg), ≤15 or >25 U/kg (two legs), Treatment Cycles 2 to 4: ≤7 5 or >17.5 U/kg (one leg), ≤15 or >35 U/kg (two legs)) were excluded from the table, including the Dysport All Doses column (see Listing 16.2.5.6). Individual data are provided for these subjects in Listing 16.2.

Source:Sponsor

REVIEWER COMMENT:
Among the 193 subjects who had samples analyzed, 5 (2.6%) subjects were positive at baseline of the double blind study (Study 141) for the presence of binding antibodies, and 2 (1.0%) were also found positive for the presence of neutralizing antibodies. Nine subjects showed evidence of seroconversion for binding antibodies, one during the double blind study and 8 during the open label study, corresponding to 4.7% (9/193). Four subjects showed evidence of seroconversion during the double blind and open label phases of the study, corresponding to 2.1% (4/193) (TABLE 60).

Table 60 Subjects Positive for Binding and/or Neutralising Antibodies During the Double Blind and/or Open Label Studies - Safety Population

Subject No.	BTX Status at Baseline	Treatment Cycle (Treatment)	Visit	BAb Result	NAb Result
Subjects with positive BAb and NAb at baseline					
61600200014	Non-naïve	Double Blind (placebo)	Baseline	Positive	Positive
		Double Blind (placebo)	Week 12	Positive	Positive
		Treatment Cycle 2	Week 4	Positive	Positive
		Treatment Cycle 2	Early withdrawal	Positive	Positive
79200700006	Non-naïve	Double Blind (Dysport)	Baseline	Positive	Positive

		Double Blind (Dysport)	Week 12	Positive	Positive
		Treatment Cycle 1	End of study	Positive	Positive
Subjects with positive BAb and missing NAb at baseline					
48400100003	Non-naïve	Double Blind (Dysport)	Baseline	Positive	Missing
		Double Blind (Dysport)	Week 12	Positive	Positive
		Treatment Cycle 2	End of study	Positive	Positive
84000400005	Non-naïve	Double Blind (placebo)	Baseline	Positive	Missing
		Double Blind (placebo)	Week 12	Positive	Positive
		Treatment Cycle 2	Week 4	Positive	Positive
		Treatment Cycle 2	Early withdrawal	Positive	Missing
Subjects with positive BAb and negative NAb at baseline					
61600200018	Non-naïve	Double Blind (placebo)	Baseline	Positive	Negative
		Double Blind (placebo)	Week 12	Positive	Negative
		Treatment Cycle 2	Week 4	Positive	Positive
		Treatment Cycle 4	End of study	Positive	Positive
Subjects with negative BAb at baseline, positive BAb in the study and negative NAb in the study					
61600100007	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 16	Negative	
		Treatment Cycle 2	Week 4	Negative	
		Treatment Cycle 3	End of study	Positive	Negative
61600200012	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Negative	
		Double Blind (Dysport)	Week 16	Negative	
		Double Blind (Dysport)	Week 22	Negative	
		Treatment Cycle 2	Week 4	Negative	
		Treatment Cycle 2	End of study	Positive	Negative
79200700002	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Positive	Negative
		Treatment Cycle 2	Week 4	Negative	
		Treatment Cycle 3	End of study	Negative	
79200900007	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Treatment Cycle 2	Week 4	Positive	Missing
		Treatment Cycle 2	End of study	Positive	Negative
Subjects with negative BAb at baseline, positive BAb in the study and missing NAb in the study					
48400100008	Non-naïve	Double Blind (placebo)	Baseline	Negative	
		Double Blind (placebo)	Week 16	Negative	
		Treatment Cycle 2	Week 4	Negative	
		Treatment Cycle 3	End of study	Positive	Missing
84000400007	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Negative	
		Treatment Cycle 2	Week 4	Positive	Missing
		Treatment Cycle 2	Early withdrawal	Positive	Missing
Subjects with negative BAb at baseline, positive BAb in the study and positive NAb in the study					
61600200021	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Negative	
		Treatment Cycle 2	Week 4	Negative	
		Treatment Cycle 3	End of study	Positive	Positive
79200300004	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Negative	
		Treatment Cycle 3	End of study	Positive	Positive
79200700011	Non-naïve	Double Blind (Dysport)	Baseline	Negative	
		Double Blind (Dysport)	Week 12	Negative	
		Treatment Cycle 2	Week 4	Positive	Positive
		Treatment Cycle 2	End of study	Negative	

Abbreviations: BAb=binding antibodies; NAb=neutralising antibodies.
Data Source: Listing 16 2 5.4 and Listing 16.2.9.4.1.

REVIEWER COMMENT:

Four subjects who had positive binding or neutralizing antibodies at baseline had loss of efficacy during the open label extension study. Four subjects who had evidence of seroconversion for binding antibodies during the study had loss of

efficacy. None of the subjects who had evidence of seroconversion for neutralizing antibodies during the study had loss of efficacy.

7.5 Other Safety Explorations

7.5.1 Time Dependency for Adverse Events

Adverse events by Treatment Cycle for Pooled Open Label studies are presented by treatment cycle in Table 61

Table 61 Treatment Emergent Adverse Events Observed in at Least 2% of Subjects in Any Treatment Cycle (and >1 Subject) by Dysport Cycle Number, System Organ Class and Preferred Term – Open Label Studies – Safety Population

System Organ Class Preferred Term, n (%)	Dysport, All Doses[a]						
	Treatment Cycle 1 N=476	Treatment Cycle 2 N=392	Treatment Cycle 3 N=273	Treatment Cycle 4 N=105	Treatment Cycle 5 N=88	Treatment Cycle 6 N=85	Treatment Cycle 7 N=84
Infections and Infestations	**206 (43.3%)**	**147 (37.5%)**	**79 (28.9%)**	**38 (36.2%)**	**25 (28.4%)**	**34 (40.0%)**	**21 (25.0%)**
Bronchitis	36 (7.6%)	28 (7.1%)	19 (7.0%)	9 (8.6%)	3 (3.4%)	9 (10.6%)	6 (7.1%)
Nasopharyngitis	50 (10.5%)	28 (7.1%)	6 (2.2%)	6 (5.7%)	1 (1.1%)	1 (1.2%)	1 (1.2%)
Pharyngitis	35 (7.4%)	29 (7.4%)	17 (6.2%)	5 (4.8%)	5 (5.7%)	10 (11.8%)	5 (6.0%)
Upper respiratory tract infection	25 (5.3%)	16 (4.1%)	7 (2.6%)	2 (1.9%)	4 (4.5%)	0	1 (1.2%)
Viral infection	11 (2.3%)	13 (3.3%)	4 (1.5%)	4 (3.8%)	0	5 (5.9%)	4 (4.8%)
Influenza	24 (5.0%)	5 (1.3%)	4 (1.5%)	0	2 (2.3%)	0	1 (1.2%)
Rhinitis	14 (2.9%)	10 (2.6%)	7 (2.6%)	3 (2.9%)	1 (1.1%)	1 (1.2%)	1 (1.2%)
Tonsillitis	9 (1.9%)	13 (3.3%)	6 (2.2%)	2 (1.9%)	3 (3.4%)	0	0
Varicella	15 (3.2%)	9 (2.3%)	3 (1.1%)	4 (3.8%)	0	0	0
Respiratory tract infection	5 (1.1%)	14 (3.6%)	7 (2.6%)	4 (3.8%)	1 (1.1%)	3 (3.5%)	2 (2.4%)
Otitis media	12 (2.5%)	5 (1.3%)	0	2 (1.9%)	3 (3.4%)	0	0
Acute tonsillitis	5 (1.1%)	4 (1.0%)	2 (0.7%)	0	2 (2.3%)	2 (2.4%)	1 (1.2%)
Pneumonia	5 (1.1%)	5 (1.3%)	2 (0.7%)	1 (1.0%)	0	2 (2.4%)	0
Ear infection	4 (0.8%)	5 (1.3%)	1 (0.4%)	1 (1.0%)	1 (1.1%)	2 (2.4%)	0
General Disorders and Administration Site Conditions	53 (11.1%)	29 (7.4%)	17 (6.2%)	3 (2.9%)	0	2 (2.4%)	1 (1.2%)
Pyrexia	26 (5.5%)	17 (4.3%)	9 (3.3%)	1 (1.0%)	0	0	1 (1.2%)
Musculoskeletal and Connective Tissue Disorders	38 (8.0%)	26 (6.6%)	23 (8.4%)	7 (6.7%)	6 (6.8%)	7 (8.2%)	8 (9.5%)
Pain in extremity	16 (3.4%)	11 (2.8%)	13 (4.8%)	4 (3.8%)	4 (4.5%)	4 (4.7%)	3 (3.6%)
Muscular weakness	14 (2.9%)	11 (2.8%)	6 (2.2%)	3 (2.9%)	2 (2.3%)	3 (3.5%)	6 (7.1%)
Gastrointestinal Disorders	32 (6.7%)	27 (6.9%)	1 (0.4%)	2 (1.9%)	0	2 (2.4%)	2 (2.4%)
Diarrhoea	12 (2.5%)	9 (2.3%)	1 (0.4%)	1 (1.0%)	0	1 (1.2%)	1 (1.2%)
Vomiting	6 (1.3%)	8 (2.0%)	0	0	0	0	1 (1.2%)
Respiratory, Thoracic and Mediastinal Disorders	32 (6.7%)	13 (3.3%)	13 (4.8%)	4 (3.8%)	2 (2.3%)	4 (4.7%)	2 (2.4%)

Cough	17 (3.6%)	8 (2.0%)	8 (2.9%)	3 (2.9%)	2 (2.3%)	3 (3.5%)	2 (2.4%)
Nervous System Disorders	28 (5.9%)	25 (6.4%)	10 (3.7%)	3 (2.9%)	1 (1.1%)	3 (3.5%)	2 (2.4%)
Epilepsy	10 (2.1%)	8 (2.0%)	3 (1.1%)	0	0	0	0
Convulsion	3 (0.6%)	6 (1.5%)	3 (1.1%)	1 (1.0%)	1 (1.1%)	1 (1.2%)	2 (2.4%)
Skin and Subcutaneous Tissue Disorders	12 (2.5%)	7 (1.8%)	3 (1.1%)	0	2 (2.3%)	1 (1.2%)	0
Rash	3 (0.6%)	4 (1.0%)	1 (0.4%)	0	2 (2.3%)	1 (1.2%)	0
Immune System Disorders	3 (0.6%)	3 (0.8%)	1 (0.4%)	0	3 (3.4%)	1 (1.2%)	1 (1.2%)
Hypersensitivity	2 (0.4%)	1 (0.3%)	1 (0.4%)	0	3 (3.4%)	1 (1.2%)	0
Congenital, Familial and Genetic Disorders	1 (0.2%)	1 (0.3%)	0	0	0	3 (3.5%)	0
Peroneal muscular atrophy	0	0	0	0	0	2 (2.4%)	0

N=number of subjects in group, n=number of subjects with observation, TEAE=treatment emergent adverse event
Data Source: Appendix 2a Table AE.2.1.2.7.3 and Table AE.2.1.2.7.4 a
Studies included: 147, 702, 052, 711 and 062

Source:Sponsor

REVIEWER COMMENT:
There is a significant decrease (drop off) in the number of subjects treated with repeat injections after Cycle 3 (476 were treated in the first cycle and 105 subjects were treated for a fourth cycle.) Only one study, Study 702 allowed subjects more than 4 cycles of treatment (7 cycles.). The adverse events were similar across cycles, with a decrease in the number (percent) as subjects discontinued treatment.

7.5.3 Drug-Demographic Interactions

Age

An overview of the TEAEs by age group during double blind and open label studies is summarized in Table 62

Table 62 Overview of Treatment Emergent Adverse Events by Age Group – Double Blind Placebo Controlled and Open Label Studies – Overall Safety Population

	Double Blind Placebo Controlled Studies						Open Label Studies[b] Dysport, All Doses		
	<2		2 to 9 years		≥10				
	Placebo N=0	Dysport, All Doses[a] N=1	Placebo N=151	Dysport, All Doses[a] N=282	Placebo N=13	Dysport, All Doses[a] N=30	<2 years N=3	2 to 9 years N=442	≥10 years N=31
Any TEAE	0	1 (100%)	72 (47.7%)	169 (59.9%)	6 (46.2%)	12 (40.0%)	2 (66.7%)	320 (72.4%)	22 (71.0%)

Any treatment-related TEAE	0	0	10 (6.6%)	39 (13.8%)	2 (15.4%)	2 (6.7%)	1 (33.3%)	97 (21.9%)	2 (6.5%)
Any severe TEAE	0	1 (100%)	6 (4.0%)	9 (3.2%)	0	0	0	19 (4.3%)	1 (3.2%)
Any treatment-related severe TEAE	0	0	0	2 (0.7%)	0	0	0	1 (0.2%)	0
Any treatment emergent SAE	0	1 (100%)	6 (4.0%)	8 (2.8%)	0	1 (3.3%)	0	38 (8.6%)	0
Any treatment-related treatment emergent SAE	0	0	0	0	0	1 (3.3%)	0	2 (0.5%)	0
Any TEAE leading to withdrawal	0	0	1 (0.7%)	0	0	1 (3.3%)	0	3 (0.7%)	0
Any treatment emergent SAE leading to withdrawal	0	0	0	0	0	1 (3.3%)	0	0	0
Any fatal AE	0	0	0	0	0	0	0	0	0

AE=adverse event, n=number of subjects with observation, N=number of subjects in group having received study treatment (dose) in a specific group regardless of Treatment Cycle, SAE=serious adverse event, TEAE=treatment emergent adverse event
Data Source: Appendix 2a, Tables SUB-AE.2.1.1.1-3, and SUB-AE.2.1.3.1-3
a Studies included: 141, 040, 701 and 094
b Studies included: 147, 702, 052, 711 and 062

Source:Sponsor

REVIEWER COMMENT;

In both double blind placebo controlled and open label studies the highest rate of TEAEs was in the 2-9 year olds treated with Dysport. There were 8 (2.8%) SAEs in the double blind studies and 38 (8.6%) SAEs in the open label studies, in the 2-9 year olds. Of note, the majority of subjects in both double blind and open label studies were between the ages of 2 to 9 years old.

Gender

An overview of TEAEs by gender is presented in Table 63.

Table 63 Overview of Treatment Emergent Adverse Events by Gender – Double Blind Placebo Controlled and Pooled Open Label Studies – Overall Safety Population

	Double Blind Placebo Controlled Studies				Open Label Studies[b] Dysport, All Doses	
	Male		Female			
	Placebo N=92	Dysport, All Doses[a] N=183	Placebo N=72	Dysport, All Doses[a] N=131	Male N=285	Female N=191
Any TEAE	47 (51.1%)	107 (58.8%)	31 (43.1%)	75 (57.3%)	212 (74.4%)	132 (69.1%)
Any treatment related TEAE	7 (7.6%)	26 (14.3%)	5 (6.9%)	15 (11.5%)	69 (24.2%)	31 (16.2%)
Any severe TEAE	1 (1.1%)	7 (3.8%)	5 (6.9%)	3 (2.3%)	9 (3.2%)	11 (5.8%)
Any treatment related severe TEAE	0	1 (0.5%)	0	1 (0.8%)	0	1 (0.5%)
Any treatment emergent SAE	2 (2.2%)	8 (4.4%)	4 (5.6%)	2 (1.5%)	23 (8.1%)	15 (7.9%)
Any treatment related SAE	0	1 (0.5%)	0	0	1 (0.4%)	1 (0.5%)
Any TEAE leading to withdrawal	0	1 (0.5%)	1 (1.4%)	0	1 (0.4%)	2 (1.0%)
Any treatment emergent SAE leading to withdrawal	0	1 (0.5%)	0	0	0	0
Any Fatal AE	0	0	0	0	0	0

AE=adverse event, N=number of subjects in group, n=number of subjects with observation, SAE=serious adverse event, TEAE=treatment emergent adverse event
Data Source: Appendix 2a, Tables SUB-AE-2.1.1.1-2 and SUB-AE.2.1.3.1-2
a Studies included: 141, 040, 701 and 094
b Studies included: 147, 702, 052, 711 and 062

Source:Sponsor

REVIEWER COMMENT:

There was similar rate of overall TEAEs in males and females in both double blind and open label studies. There was a slightly higher rate SAEs of males versus females treated with Dysport (4.4% versus 1.5%) in the double blind studies. However, more females than males treated with placebo experienced SAEs (2.2% versus 5.6 %.) The rates were similar during the open label studies.

7.5.4 Drug-Disease Interactions

Epilepsy

Epilepsy was reported in five subjects; four of the five subjects had a history of epilepsy. All five cases were in the Dysport treatment groups:

- **Subject 48400500009**, a 7-year-old male, received Dysport 10 U/kg administered into his left leg on Day 1 (14 August 2012) of the study. This subject **had a history of epilepsy** since July 2006 which was treated with oral oxcarbazepine 300 mg twice daily (BID). On Day 78, he had mild

aggravation of epilepsy reported as an AE which was treated with oral oxcarbazepine 7.5 mL BID and topiramate 50 mg BID. The event lasted for more than 43 days and was ongoing at the end of the study. Prior to the event of epilepsy this subject had a respiratory tract infection on Day 53 which resolved on Day 58. This AE was treated with oral ambroxol 5 mL three times daily (TID) from Day 53 to Day 57 and oral amoxicillin 5 mL TID from Day 56 to Day 62.

- **Subject 61600400004**, a 3-year-old female, received Dysport 10 U/kg administered into her right leg on Day 1 (30 August 2012) of the study. This subject had **no history of epilepsy**. On Day 19, she had mild epilepsy reported as an AE which was treated with oral ergenyl chrono 250 mg once daily (QD). The event lasted for more than 184 days and was ongoing at the end of the study. On Day 149, she had another event of mild epilepsy reported. This event resolved the same day. No other AEs were reported for this subject.

- **Subject 61600200002**, a 4-year-old male, received Dysport 15 U/kg administered into both legs on Day 1 (30 August 2012) of the study. This subject **had a history of epilepsy** since February 2009 which was treated with oral oxcarbazepine 4 mL BID. On Day 52, he had mild epilepsy reported as an AE which was treated with rectal diazepam 10 mg. This event resolved the same day. Prior to the event of epilepsy this subject reported pain in extremity from Day 2 to Day 8, pyrexia from Day 29 to Day 30 and a cough from Day 29 to Day 34. The cough was treated with oral acetylcysteine 200 mg BID from Day 29 to Day 34 and the pyrexia was treated with oral ibuprofen 400 mg TID from Day 29 to Day 30.

- **Subject 61600200007**, a 5-year-old male, received Dysport 15 U/kg administered into both legs on Day 1 (04 October 2012) of the study. This subject had **a history of epilepsy** since July 2010 and under treatment with oral carbamazepine 0.75 tablets BID which was stopped on 15 October 2012. On Day 4, he had mild epilepsy reported as an AE. This event resolved the same day. On Day 9, he had another event of mild epilepsy reported. No AEs were reported for this subject prior to the event of epilepsy. Subsequent to the episodes of epilepsy, on 16 October 2012 he was started with oral carbamazepine 225 mg BID and oral ergenyl chrono 250 mg once every night, both the medications were ongoing at the end of the study.

- **Subject 79200700003**, a 12-year-old female, received Dysport 15 U/kg administered into her left leg on Day 1 (16 April 2013) of the study. This subject had **a history of epilepsy** since 2005 which was treated with oral carbamazepine 200 mg BID and oral levetiracetam 250 mg BID. On an unknown date in June 2013, she had mild increased frequency of epileptic seizure reported as an AE which was treated with oral levetiracetam 375 mg

BID. This event lasted for more than 16 days and was ongoing at the end of the study. Prior to the event of epilepsy this subject reported hypothyroidism on Day 30 which was treated with oral levothyroxine sodium 50 µg QD from Day 32 to Day 71. She also had vitamin D deficiency reported on Day 72 (26 June 2013), which was treated with a single dose of oral cholecalciferol 30000 IU and oral calcium with vitamin D one tablet BID from 26 June 2013 to 09 July 2013. Both of these events were still ongoing at the end of the study.

REVIEWER COMMENT:

Epilepsy is a commonly associated with pediatric patients with cerebral palsy. In of the 5 cases reported, the epilepsy was pre-existing. In the one case of new onset, the patient was 3 years old and it is difficult to attribute the cause to Dysport versus underlying disease.

SUMMARY OF SAFETY

There were no deaths during the double blind placebo controlled studies.

The TEAEs included in the Dysport label from studies completed for the approval of the treatment of UL spasticity in adults, which includes the maximum dose allowed in the studies for pediatric LL spasticity of 1000 U, are similar between the two groups, with infections and infestations being the most common SOC. However, the percent of subjects who experienced the TEAEs is higher in the pediatric studies for LL spasticity. This is likely multifactorial including higher rate of infections in pediatric population in general, and higher rate in patients with cerebral palsy.
Overall, there was a higher rate of SAEs and TEAEs related to PDSOT in subjects who received Dysport 30 U/kg. This was most notable in Study 094, where subjects received Dysport in proximal as well as distal muscles.

There were no clinically significant laboratory, vital sign, or ECG findings during the study.

8 Postmarket Experience

An analysis of the post marketing safety data in pediatric subjects contained within the sponsor's safety database, ARISg, was conducted between first approval in 1990 and the cutoff date December 31, 2014. All serious events indicative of adverse events of special interest, AESIs (remote spread of toxin, hypersensitivity reaction) were evaluated in pediatric subjects treated with Dysport, Dyslor or botulinum toxin A NOS for any therapeutic indication, excluding aesthetic are included. The serious AESIs are

presented for spontaneous and solicited events and the indications of 'PLL only' and Concomitant PLL plus Other Therapeutic Indications.

Treatment of PLL Spasticity Only
Spontaneous treatment emergent serious adverse events reported in ≥1% of subjects are summarized in Table 64.

Table 64 Spontaneous Treatment Emergent Serious Adverse Events Reported in ≥1% of Subjects - Post marketing and Supporting Data – Indication PLL Spasticity Only

System Organ Class Preferred Term	Number of Events (N=121)[a]
Nervous System Disorders	**25**
Hypotonia	5
Neuromuscular toxicity	3
Generalized tonic-clonic seizure	2
Speech disorder	2
VIIth nerve paralysis	2
General Disorders and Administration Site Conditions	**24**
Asthenia	10
Pyrexia	4
Fatigue	3
Gait disturbance	3
Musculoskeletal and Connective Tissue Disorders	**17**
Muscular weakness	12
Musculoskeletal discomfort	2
Gastrointestinal Disorders	**10**
Dysphagia	5
Constipation	2
Respiratory, Thoracic and Mediastinal Disorders	**10**
Dyspnea	3
Eye Disorders	**9**
Eyelid ptosis	6
Injury, Poisoning and Procedural Complications	**7**
Overdose	3
Fall	2
Joint dislocation	2
Renal and Urinary Disorders	**7**
Urinary incontinence	7

N=total number of unique events, defined as unique combinations (case number, system organ class, preferred term, verbatim term and event onset date), n=number of events, PLL=pediatric lower limb
Data Source: Appendix 2b, Table AE.6.1.1
a Total number of unique events, defined as unique combinations (case number, system organ class, preferred term, verbatim term and event onset date)

Source:Sponsor

Remote Spread of Toxin

A total of 25 spontaneous events in 17 subjects were considered to be indicative of remote effects of Dysport in the indication "PLL spasticity only" and 3 spontaneous

events in 2 subjects with concomitant PLL + Other Therapeutic Indications. These events are summarized in Table 65.

Table 65 Spontaneous Serious Adverse Events of Special Interest - Remote Spread of Effect of Toxin - Post marketing and Supportive Data

System Organ Class Preferred Term	PLL Only (N=25)	Concomitant PLL + Other Therapeutic Indications (N=3)
Gastrointestinal Disorders	**7**	**2**
Dysphagia	5	2
Constipation	2	0
Musculoskeletal and Connective Tissue Disorders	**7**	**0**
Muscular weakness	7	0
Eye Disorders	**6**	**0**
Eyelid ptosis	6	0
Nervous System Disorders	**4**	**0**
Speech disorder	2	0
VIIth nerve paralysis	2	0
Respiratory, Thoracic and Mediastinal Disorders	**1**	**1**
Respiratory failure	1	1

N=number of events, PLL=pediatric lower limb
Data Source: Appendix 2a, Table AESI.3.1.1

Source:Sponsor

A summary of the subjects treated for "PLL spasticity only" and Concomitant PLL who experienced adverse events indicative of remote spread of toxin are outlined in Table 67.

Table 67 Listing of Serious Adverse Events Indicative of Remote Spread of Dysport Effects in the Postmarketing and Supportive Data

Indication: PLL Spasticity Only

Case Number	Gender/ Age/Race	System Organ Class/ Preferred Term/Verbatim Term	Dose/Date of Administration	Reason for Seriousness	Onset Date / End Date / Duration (days)
10E20080293	F/8/Unknown	Gastrointestinal Disorders/Constipation/ Constipation	1000 units as the total dose - 3 sites in both triceps surae; 48 (U/kg)/	Disability	Nov2007/-/
20120030257	M/3/Unknown	Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Generalized muscle weakness	1000 units single application (4 Gemelli, 2 Soleus 4 Ischiofibula);	Hospitalization	(b) (6)
20219990436	M/5/Caucasian	Eye Disorders/Eyelid ptosis/Ptosis	30 U/kg, mm gastrocnem+ischiocrur.;	Disability	10Nov1999/-/
10E19990048	M/4/ -	Eye Disorders/Eyelid ptosis/Ptosis	500 units/02May1996	Not Applicable	-
10E20020172	F/6/Unknown	Eye Disorders/Eyelid ptosis/ Slight bilateral ptosis	1200 units (600 units in each lower limb); 67	Not Applicable	-

		Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Neck hypotonia	1200 units (600 units in each lower limb); 67 (U/kg)/04Mar2002	Not Applicable	-
2008-1713	M/2/Asian	Eye Disorders/Eyelid ptosis/ Ptosis of both eyes	15 units/kg/ muscle/ Jul2004	Disability	Jul2004/-/
		Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Generalized weakness	15 units/kg/muscle/ Jul2004	Disability	Jul2004/-/
2010-3857	F/4/Not Reported	Eye Disorders/Eyelid ptosis/ Eyelids drooping	-/27Oct2010	Hospitalization	(b) (6)
		Gastrointestinal Disorders/Dysphagia/ Trouble swallowing	-/27Oct2010	Hospitalization	
20120030192	F/6/Unknown	Eye Disorders/Eyelid ptosis/Bilateral ptosis	600 Units last cycle (46 units/kg); 46 (U/kg)/ Nov2002	Not Applicable	11Apr2003/-/
		Gastrointestinal Disorders/Dysphagia/ Dysphagia	600 Units last cycle (46 units/kg); 46 (U/kg)/Nov2002	Not Applicable	11Apr2003/-/
		Nervous System Disorders/ VIIth nerve paralysis/Inexpressive face	600 Units last cycle (46 units/kg); 46 (U/kg)/ Nov2002	Not Applicable	11Apr2003/-/
		Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/Respiratory insufficiency	600 Units last cycle (46 units /kg); 46 (U/kg)/ Nov2002	Not Applicable	-
2013-0300	F/4/Not Reported	Nervous System Disorders/ VIIth nerve paralysis/Paralysis of seventh cranial nerve	200 units; 14 (U/kg)/11Dec2012	Medically significant	14Dec2012/-/
2013-1602	F/4/Not Reported	Gastrointestinal Disorders/Dysphagia/ Deglutition disorder	200 units; 15 (U/kg)/24Jan2013	Disability	Feb2013/ Mar2013/

Case Number	Gender/ Age/Race	System Organ Class/ Preferred Term/Verbatim Term	Dose/Date of Administration	Reason for Seriousness	Onset Date / End Date / Duration (days)
		Gastrointestinal Disorders/Constipation/ Slow intestinal transit	200 units; 15 (U/kg)/24Jan2013	Disability	Feb2013/ Mar2013/
2013-4755	F/9/Caucasian	Gastrointestinal Disorders/Dysphagia/ Difficulties eating and drinking	1500 Units; 88 (U/kg)/11Mar2013	Not Applicable	-
20219990025	F/17/	Nervous System Disorders/Speech disorder/ Speech impairment	1500 Units/18Mar1999	Not Applicable	
20219990313	M/6/Caucasian	Musculoskeletal and connective tissue disorders/Muscular weakness/Muscular weakness	30 units /kg/	Disability	May1999/-/
		Nervous System Disorders/Speech disorder/Worsened speech	30 units /kg/	Not Applicable	-
20220000039	M/3/Unknown	Gastrointestinal Disorders/ Dysphagia/Dysphagia	1000 units; 77 (U/kg)/20Dec1999	Hospitalization	(b) (6)
21220040269	F/6.5/Caucasian	Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Generalized muscular hypotonia	900 units; 82 (U/kg)/15Apr2004	Hospitalization	(b) (6)
23319960013	F/6/	Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Muscle weakness, generalized	1000 Units/20Aug1996	Hospitalization / Disability	(b) (6)
23320040382	F/2/Caucasian	Musculoskeletal and Connective Tissue Disorders/Muscular weakness/ Generalized weakness	1000 units/13May2004	Disability/ Overdose	(b) (6)

Indication: Concomitant PLL + Other Therapeutic Indications

2013-1248	F/17/Caucasian	Gastrointestinal Disorders/Dysphagia/ Dysphagia	1500 units; 29 (U/kg)/ 05Mar2013	Medically significant	Mar2013/-/
20220000249	M/15/Unknown	Respiratory, Thoracic and Mediastinal Disorders/Respiratory failure/ Obstructive respiratory insufficiency	1000U total (4x200U + 2x100U); 50 (U/kg)/28Mar2000	Life threatening /Hospitalization /Required intervention / Overdose	(b) (6)
		Gastrointestinal Disorders/Dysphagia/ Dysphagia	1000U total (4x200U + 2x100U); 50 (U/kg)/28Mar2000	Hospitalization	(b) (6)

F=female, gastrocnem.=gastrocnemius, ID=identification, ischiocrur.=ischiocrural, M=male, PLL=paediatric lower limb, U=units
Data Source: Appendix 3a, Listing AESI.5.1

Adapted from Sponsor Table

REVIEWER COMMENT:

Seven of the 17 subjects with PLL spasticity only who experienced SAEs indicative of Remote Spread of Toxin and 1 of the 2 subjects with concomitant PLL spasticity had received Dysport greater than 30 U/kg and/or > 1000 U total. In 4 of the subjects with PLL spasticity only, the dose U/kg and/or maximum dose injected are unknown.

According to the sponsor, a review of the safety data (from signal detection activities, the literature –including clinically significant new publications, the latest Periodic Safety Update Report to December 31, 2014, important follow up data and any action taken by the marketing authorization holder, data monitoring committee, or competent authority (Worldwide) for safety reasons) has not revealed any potentially important safety, efficacy and effectiveness findings from the cutoff date of December 31, 2014 to June 30, 2015.

SUMMARY OF POST MARKETING SAFETY

The post marketing safety information presented is consistent with the findings in the double blind placebo controlled and open label studies conducted in support of Dysport for LL spasticity in pediatric patients. The most commonly reported spontaneous adverse events are consistent with remote spread of toxin.

9 Appendices

Currently, labeling is being negotiated with the sponsor. The most recent draft of the label with recommendations from the Division is presented in Section 9.2.

9.2 Labeling Recommendations

The sponsor submitted labeling with the proposed indication for Dysport for the treatment of spasticity in the pediatric population (b) (4) The mechanism of action of botulinum toxin in the treatment of spasticity is (b) (4) it acts peripherally at the end organ, the neuromuscular junction (b) (4) (b) (4) (b) (4) .

In a letter dated December 11, 2015, the sponsor was asked to provide a scientific justification for (b) (4) propose labeling (b) (4) for the treatment of lower limb spasticity in all pediatric patients.

After consulting with the Office of Orphan Products Development regarding orphan exclusivity (b) (6) for all pediatric patients (March 15, 2016), the sponsor agreed to revise labeling for the pediatric population (June 2, 2016) stating:

(b) (6)

Labeling information pertaining to the treatment of UL spasticity includes the following:

2.5 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.

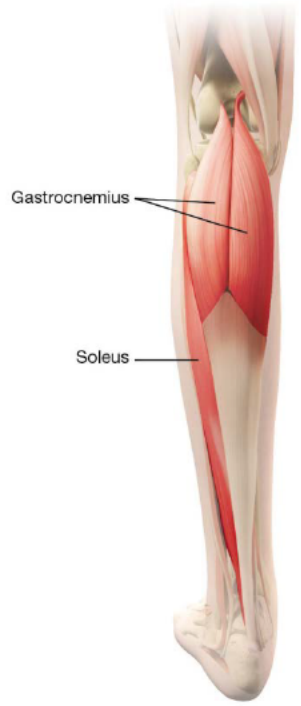
Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum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

Figure 3: Muscles for Injection for Lower Limb Spasticity



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 (b)(4) weeks after the previous injection. A majority of patients in the clinical study were retreated between 16-22 weeks.; 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.

6.1 Clinical Trials Experience

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					
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	2	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

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). The secondary efficacy endpoint was the Mean Goal Attainment Scaling (GAS) score at Week 4.

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 *

*p<0.05, = Least Square

In the assessment of GAS score the treatment goals were achieved in the Dysport treatment groups and not achieved in the placebo groups at Week 4.

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/s/

SUSANNE R GOLDSTEIN
07/19/2016

GERALD D PODSKALNY
07/25/2016