

A PHASE III, MULTICENTRE, DOUBLE BLIND, PROSPECTIVE, RANDOMISED, CONTROLLED, MULTIPLE TREATMENT STUDY ASSESSING EFFICACY AND SAFETY OF DYSPORT USED IN THE TREATMENT OF UPPER LIMB SPASTICITY IN CHILDREN

STUDY PROTOCOL
Study number: Y-52-52120-153
DYSPORT
EudraCT number: 2010-021817-22
Final 5.0: 24 July 2017

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PROTOCOL SIGNATURES**Investigator Signature:**

I have read and agree to the protocol Y-52-52120-153, a phase III, multicentre, double blind, prospective, randomised, controlled, multiple treatment study assessing efficacy and safety of Dysport used in the treatment of upper limb spasticity in children. I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)¹, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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Note: For IND studies, a Form 1572 will also be completed.

¹ ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

SYNOPSIS

<p>Study Title:</p>	<p>A phase III, multicentre, double blind, prospective, randomised, controlled, multiple treatment study assessing efficacy and safety of Dysport used in the treatment of upper limb spasticity in children.</p> <p>STUDY NUMBER: Y-52-52120-153</p>
<p>Study Objectives:</p>	<p>The primary study objective is to assess the efficacy of two doses of Dysport (8 units (U)/kg and 16 U/kg) compared to Dysport 2 U/kg used in the treatment of upper limb spasticity in children with cerebral palsy (CP) following a single treatment.</p> <p>The secondary study objective is to assess the long term safety of multiple treatments of Dysport used in this study population.</p> <p>The tertiary study objectives CCI [REDACTED] quality of life (QoL)</p> <p>CCI [REDACTED]</p>
<p>Study Design:</p>	<p>This is a phase III, multicentre, double blind, prospective, randomised, controlled, multiple treatment study. Subjects will receive a maximum of four treatments over the course of a minimum of one year’s study participation.</p> <p>At study entry, subjects will be randomised into one of the following three treatment groups for Treatment 1:</p> <ul style="list-style-type: none"> • Group A: Dysport 16 U/kg in one upper extremity (the study limb). • Group B: Dysport 8 U/kg in the study limb. • Group C: Dysport 2 U/kg in the study limb. <p>Randomisation will be done with an Interactive Response System (IRS) and will be in a 1:1:1 ratio. The IRS will be used to allocate packs and envelope numbers (to be considered to reconstitute the treatment) and then study treatment reconstitution will be performed by an independent reconstitutor who will not be involved in any other study related activities in order to maintain the blinding.</p> <p>For Treatments 2, 3 and 4, subjects are planned to receive Dysport 8 U/kg or 16 U/kg according to the treatment allocation by the IRS and will remain double blind throughout the study. CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED] The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.</p> <p>The planned retreatment interval is 16 weeks and a maximum of four treatments will be administered.</p> <p>At study entry, a primary targeted muscle group (PTMG), either the elbow flexors or wrist flexors, will be nominated by the Investigator. The PTMG can be changed for subsequent treatments, from elbow to wrist flexors or wrist to elbow flexors, provided that the following criteria are fulfilled:</p>

	<ul style="list-style-type: none">• The Modified Ashworth Scale (MAS) score of the other muscle group not selected for the last treatment (new PTMG) must be higher than the last treatment PTMG, and• The new PTMG must have a modified MAS score of greater or equal to 1+. <p>For Treatments 2, 3 and 4, injection into the lower extremity/extremities and the non-study upper limb will be allowed at the same time as the study limb is injected (see Study Treatment Section).</p> <p>The overall duration of the study is anticipated to be approximately 4 years and 9 months and will include subject recruitment (approximately 3 years) and last subject follow up (approximately 1 year and 9 months). Individual subject participation will be approximately 1 year to 1 year and 9 months.</p> <p>Stratification will be performed according to age range (2 to 9 years and 10 to 17 years) and BTX naïve or non-naïve status assessed at baseline.</p> <p>Prestudy physiotherapy, occupational therapy, or use of splints and/or orthoses must have been initiated at least 30 days prior to the baseline visit and agreed to continue the therapy throughout the study and at the minimum, up to Week 16 following the first treatment administration. In addition, instructions for home exercises will be provided to the parents/guardians/caregivers and/or subjects to encourage use of the muscle groups injected in the study. School therapy will also be allowed during term time.</p> <p>After each treatment administration, the follow up visit schedule is as follows:</p> <ul style="list-style-type: none">• Week 2 (telephone call, safety follow up).• Week 4 (telephone call, safety follow up).• Week 6.• Week 12 (telephone call, safety follow up).• Week 16. <p>At Week 16, subjects will be assessed for their eligibility to receive the next treatment. Subjects who are eligible for retreatment will be given the next treatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks ± 2 weeks in additional visits until they are eligible for retreatment.</p> <p>Each subject will participate in the study for approximately 1 year to 1 year and 9 months, depending on the number of treatments administered and the treatment intervals. The duration of the follow up period will be dependent upon the treatment interval as follows:</p> <ul style="list-style-type: none">• All subjects whose first three treatment intervals fall between ≥ 16 and ≤ 22 weeks will receive four treatments and will exit the study as soon as a new injection is required and no later than 22 weeks after last injection (up to a maximum of 1 year and 9 months' study duration).
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	(21) Any uncontrolled clinically significant medical condition other than CP.																
Study Treatment:	<p>Dysport will be supplied as a white, lyophilised powder in a vial containing 500 U of BTX-A-haemagglutinin complex. Before administration, the powder will be reconstituted at the investigational site with preservative free 0.9% sodium chloride for injection. All subjects will receive Dysport administered intramuscularly. The total volume for injection will be administered into one upper extremity (the study limb), divided between injections into the PTMG (elbow flexors or wrist flexors) and a number of other muscles selected by the Investigator, as specified in the protocol.</p> <p>Planned Doses:</p> <p>Subjects will receive Dysport 2 U/kg, 8 U/kg or 16 U/kg in the study limb in Treatment 1 and are planned to receive Dysport 8 U/kg or 16 U/kg in subsequent treatments according to the treatment allocation by the IRS, illustrated below, and both Investigators and subjects will remain blinded throughout the study.</p> <table border="1" data-bbox="523 913 1377 1115"> <thead> <tr> <th>Group</th> <th>Number of Subjects</th> <th>Treatment 1^(a)</th> <th>Treatments 2, 3 and 4^(a)</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>70</td> <td>Dysport 16 U/kg</td> <td>Dysport 16 U/kg</td> </tr> <tr> <td>B</td> <td>70</td> <td>Dysport 8 U/kg</td> <td>Dysport 8 U/kg</td> </tr> <tr> <td>C^(b)</td> <td>70</td> <td>Dysport 2 U/kg</td> <td>Dysport 8 U/kg or Dysport 16 U/kg</td> </tr> </tbody> </table> <p>^(a) The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group. ^(b) In this group, dynamic dose dispensing will be done by IRS at Treatment 2 to maintain a balance between subjects receiving 8 U/kg and 16 U/kg.</p>	Group	Number of Subjects	Treatment 1 ^(a)	Treatments 2, 3 and 4 ^(a)	A	70	Dysport 16 U/kg	Dysport 16 U/kg	B	70	Dysport 8 U/kg	Dysport 8 U/kg	C ^(b)	70	Dysport 2 U/kg	Dysport 8 U/kg or Dysport 16 U/kg
Group	Number of Subjects	Treatment 1 ^(a)	Treatments 2, 3 and 4 ^(a)														
A	70	Dysport 16 U/kg	Dysport 16 U/kg														
B	70	Dysport 8 U/kg	Dysport 8 U/kg														
C ^(b)	70	Dysport 2 U/kg	Dysport 8 U/kg or Dysport 16 U/kg														

The dose for each subject will be calculated according to the subject's body weight, up to a maximum body weight of 40 kg (even if the subject weighs more than 40 kg and therefore a maximum total dose of 320 U in the 8 U/kg group and 640 U in the 16 U/kg group). The allocated dose will be reconstituted to a fixed volume of 1.6 mL for injection.

CCI [Redacted]
[Redacted]
[Redacted]



Dose/Volume:

For treatments 2, 3 and 4, the investigator may modify the nature and number of injected muscles. The volume by muscle may be decreased (to allow more muscles to be injected) or increased providing that:

- the volume per muscle never exceeds the maximum volume/dose indicated in table.

CCI [Redacted]

	<ul style="list-style-type: none">• the total injection volume in the study upper limb is always 1.6 mL. <p>For Treatments 2, 3 and 4, and according to subject response, if any given total dose is not tolerated, the Investigator will request a dose reduction of 50% in the IRS. CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>For Treatments 3 and 4, if any given total dose is not adequate for the treatment of the subject's upper limb spasticity, the Investigator can request a dose increase in the IRS.</p> <p>CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED] No dose increase is possible for those subjects who were given Dysport 16 U/kg as the subject was already given the highest dose allowed in the study. CCI [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
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	<p>CCI</p> 												
	<p>Concomitant Treatment of Lower Limb Spasticity and the Non-study Upper Limb:</p> <p>For Treatments 2, 3 and 4, injection into the lower extremity/extremities and the non-study upper limb will be allowed at the same time as the study limb is injected. Muscle(s) for injection will be selected according to the Investigator’s judgement. If there is no need to inject the lower limbs, and only the non-study upper limb is to be injected (on top of the study upper limb), the dose in the non-study upper limb should not exceed the dose detailed in table.</p> <table border="1" data-bbox="580 1115 1321 1211"> <thead> <tr> <th>Body Weight (kg)</th> <th>Maximum Dose</th> </tr> </thead> <tbody> <tr> <td>10 to 40</td> <td>5 U/kg, calculated up to 40 kg</td> </tr> <tr> <td>40 and over</td> <td>200 U</td> </tr> </tbody> </table> <p>For dose by muscle, please refer to table below</p> <p>If there is no need to inject the non-study upper limb and only one or two lower limb(s) are to be injected (on top of the study upper limb), the dose in the lower limb(s) should not exceed the dose detailed in table.</p> <table border="1" data-bbox="496 1440 1406 1536"> <thead> <tr> <th>Body Weight (kg)</th> <th>Maximum Dose</th> </tr> </thead> <tbody> <tr> <td>10 to 36</td> <td>10 U/kg, calculated up to 36 kg</td> </tr> <tr> <td>36 and over</td> <td>360 U</td> </tr> </tbody> </table> <p>Electrical stimulation (ES) and/or ultrasound will be used to localise the targeted injection sites. Complementary techniques, such as electromyography will be allowed in addition to ES and/or ultrasound.</p> <p>CCI</p> 	Body Weight (kg)	Maximum Dose	10 to 40	5 U/kg, calculated up to 40 kg	40 and over	200 U	Body Weight (kg)	Maximum Dose	10 to 36	10 U/kg, calculated up to 36 kg	36 and over	360 U
Body Weight (kg)	Maximum Dose												
10 to 40	5 U/kg, calculated up to 40 kg												
40 and over	200 U												
Body Weight (kg)	Maximum Dose												
10 to 36	10 U/kg, calculated up to 36 kg												
36 and over	360 U												

	<p>CCI [Redacted]</p> <p>CCI [Redacted]</p> <p>CCI [Redacted]</p> <p>CCI [Redacted]</p>
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	<ul style="list-style-type: none"> • CCI [REDACTED] <p>CCI [REDACTED]</p> <p>No more than 0.5 ml will be injected per injection site. For the injection, each participating centre should maintain their usual injection environment and procedures for their pain management strategies (e.g. use of general anaesthesia, topical anaesthesia, or oral, intranasal or rectal medication).</p>
<p>Study Evaluations:</p>	<p>Efficacy Evaluations:</p> <p>Every effort should be made in each centre to ensure that the evaluating Investigators are the same individuals for the duration of the study for a given subject. The assessor who conducts the global assessment of the treatment response must be different from the evaluator performing the CCI [REDACTED] and Muscle Tone (MAS CCI [REDACTED]) examination. None of the assessors will have knowledge of the scores obtained by the other assessor at the time of his/her assessment.</p> <p>The following efficacy variables will be evaluated:</p> <p>Primary Efficacy Evaluation:</p> <ul style="list-style-type: none"> • Modified Ashworth Scale in the PTMG group (elbow flexors or wrist flexors) at Treatment 1. <p>Secondary Efficacy Evaluations:</p> <ul style="list-style-type: none"> • Physician’s Global Assessment (PGA). • Goal Attainment Scale. <p>Tertiary Efficacy Evaluations:</p>

	<ul style="list-style-type: none"> Modified Ashworth Scale in the injected muscles (elbow, wrist and finger flexors) in the study limb other than the ones of the PTMG. Modified Ashworth Scale in the injected muscles (elbow, wrist and finger flexors) in the non-study upper limb. CCI [REDACTED] CCI [REDACTED] CCI [REDACTED] CCI [REDACTED] CCI [REDACTED] Paediatric Quality of Life (PedsQL™) child and parent inventory and CP module. <p>Safety Evaluations: A Data and Safety Monitoring Board (DSMB) composed of independent experts will review safety data including AEs and serious AEs. Safety will be assessed through collection of AEs, physical examination, body weight and height, vital signs (heart rate (HR) and blood pressure (BP)), clinical chemistry (including serum alkaline phosphatase (ALP) - total and bone isoenzyme, and glycosylated haemoglobin (HbA1c)), the presence of antibodies against BTX-A (BTX-A-Abs) and electrocardiograms (ECGs). Prior and concomitant medications will also be recorded.</p>
<p>Study Endpoints:</p>	<p>Efficacy Endpoints: Efficacy variables will be assessed at the following schedule:</p> <ul style="list-style-type: none"> CCI [REDACTED] Muscle Tone examination, GAS, and CCI at baseline (Treatment 1, Day 1) and at each post-treatment visit to the study centre. Physician’s Global Assessment at each post-treatment visit to the study centre. CCI [REDACTED] Paediatric Quality of Life at baseline (Treatment 1, Day 1), Treatment 1, Week 16 and at the end of study visit or early withdrawal. <p>Primary Efficacy Endpoint:</p> <ul style="list-style-type: none"> Mean change from Baseline to Treatment 1, Week 6 in MAS score in the Treatment 1 PTMG (elbow flexors or wrist flexors). <p>Secondary Efficacy Endpoints:</p> <ul style="list-style-type: none"> Mean PGA score at Treatment 1, Week 6. Mean GAS score at Treatment 1, Week 6.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
CCI	
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
BP	Blood Pressure
BTX	Botulinum Toxin
BTX-A	Botulinum Toxin type A
BTX-A-Abs	Antibodies Against BTX-A
BTX-A-HAC	BTX-A-Hemagglutinin Complex
CAs	Competent Authorities
CP	Cerebral Palsy
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTSU	Clinical Trial Supplies Unit
Da	Daltons (Unit of Atomic Mass)
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ES	Electrical Stimulation
e-signature	Electronic Signature
EU	European Union
FDA	Food and Drug Administration
CCI	
GAS	Goal Attainment Scale
GCP	Good Clinical Practice
GMFCS	Gross Motor Function Classification Scale
HbA1c	Glycosylated Haemoglobin
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRS	Interactive Response System
MACS	Manual Ability Classification System
MAS	Modified Ashworth Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat
PDD	Protocol Deviations Document
PedsQL™	Paediatric Quality of Life™
PGA	Physician's Global Assessment
POM	Proportional Odds Model
PP	Per Protocol
CCI	████████████████████
PTMG	Primary Targeted Muscle Group
QoL	Quality of Life
RIPA	Radioimmunoprecipitation Assay
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
CC	████████████████
U	Units
US	United States
C	██
CCI	██
CCI	██
C	██

2 INTRODUCTION

Dysport[®] is a neurotoxin complex derived from the bacterium *Clostridium botulinum*. It prevents the release of acetylcholine at neuromuscular junctions, which in turn results in weakness of the injected muscle. Over a period of months new nerve endings sprout which allows nerve function to return, thus treatment may need to be repeated as required. Dysport has been found to be of significant value in the treatment of a variety of ophthalmological and neurological disorders, particularly blepharospasm, hemifacial spasm, spasticity and cervical dystonia [1, 2, 3, 4, 5, 6, 7, 8].

2.1 Disease Review

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems leading to posture and gait impairment, and limb deformities [9]. The reported prevalence of CP is between 1.5 and 3 cases per 1000 live births [10, 11]. The bilateral form of CP (which includes diplegia, triplegia and quadriplegia) predominates, followed by unilateral (hemiplegia), which accounts for about one quarter to one third of all spastic cases [9, 11].

Cerebral palsy is an upper motor neuron disorder, which can present clinically with different combinations of positive and negative phenomena. The positive phenomena of the syndrome include among others spasticity, increased tendon reflexes, clonus and muscle co-contraction. The negative phenomena are muscle weakness, impaired motor control, loss of skilled movements and easy fatigability. In children, the positive phenomena of CP are a major cause of disability and considered more amenable to treatment [12].

Ninety percent (90%) of subjects with CP suffer from spastic hypertonia. Spasticity is a motor disorder, characterised by an increase in velocity dependant stretch reflexes, with exaggerated tendon reflexes, resulting from hyper-excitability of the stretch reflex, as one of the manifestations of the upper motor neuron syndrome [13]. The increased muscle tone in spasticity leads to muscle contractures, initially dynamic and later fixed, followed by shortening of ligaments, fascias and joint capsules, and eventually joint deformities and instabilities.

The Gross Motor Function Classification System (GMFCS) [14, 15, 16] classifies the severity of CP and establishes a prognosis of motor development in affected children by describing the child's ability in self-initiated movements, such as sitting and walking. Severity of motor impairment depends on the type of CP and children with hemiplegia often have less severe disease than children with di- or quadriplegia, with the majority of hemiplegic children being classified as GMFCS Level 1 and 2 [17]. However, in children with CP, manual ability and gross motor function do not always correlate, thus a different classification is required to assess the level of impairment of hand function. The Manual Ability Classification System (MACS) focuses on the upper limbs of children with CP and describes how well the children use their hands for handling objects in daily activities [18]. The severity of upper limb functional impairment as described by MACS varies, ranging from very minor (Level 1) to severe limitation of activities and complete dependence (Level 5). In contrast to children with diplegia, children with spastic hemiplegia have a lower degree of manual ability despite having less severely impaired gross motor function [19]. This could be explained by the fact that children with spastic hemiplegia who have one unaffected upper limb, develop various compensatory strategies for coping with their disability. Those children tend to use their unaffected upper limb for all activities, partially or fully neglecting the affected arm [20]. If left untreated, spasticity of the one affected upper limb and associated functional impairment do not allow the children to develop the fine motor skills required for bimanual activities.

In the upper limbs in particular, the increased muscle tone impairs the reach, grasp, manipulation and release, leading to restriction in everyday life and educational activities. The inability to fully use the affected arm(s) for bimanual activities prohibits the development of independent functioning in daily life. Although the children often have normal intellectual capacity to attend school, their impaired arm function prevents them from fully engaging in social, educational and leisure roles. Consequently, reduction of the increased muscle tone and spasticity is important for the improvement of the motor ability and functional skills of children with CP, and for prevention of fixed muscle contractures and deformities.

The choice of appropriate treatment for spasticity in children with CP depends on the topographic distribution of the disorder and any associated co-morbidities. In spastic hemiplegia and monoplegia with upper limb involvement, localised treatment of spasticity with botulinum toxin (BTX) with or without complementary techniques, such as regular physiotherapy, occupational therapy and various therapeutic modalities aimed at improving upper limb muscle strength, movement control and manual dexterity, is often used [21, 22]. The intramuscular injection of botulinum toxin type A (BTX-A) in targeted muscles reduces muscle spasticity which would translate into improved functional ability and pain relief. More specifically, the muscles of children to be injected will depend on the specific disease presentation for each subject, age, number of muscles affected, disability, presence or absence of fixed contractures and the treatment goals. As a result, there is increasing evidence for the use of BTX as an adjunct for treatment of upper limb spasticity in children with CP [23].

There are a number of systemic antispasticity drugs available, such as baclofen, tizanidine and diazepam, but the associated systemic side effects often limit their use in the paediatric population. In a limited number of cases intrathecal baclofen has been used for improving upper limb spasticity [12]. Orthopaedic surgery is generally reserved for children with already developed fixed contractures and deformities.

2.2 Compound Review

Botulinum toxin type A is a potent neurotoxin isolated from the bacterium *Clostridium botulinum*, a gram positive, spore forming anaerobe. Botulinum toxin type A, a single chain protein with a molecular weight of approximately 150,000 Daltons (Da), is one of seven different serotypes (classed A through G) of BTX produced by this organism. Proteins endogenous to the bacterium cleave the single chain protein, resulting in a di-chain neurotoxin containing a light chain (molecular weight ~50,000 Da) and a heavy chain (molecular weight ~100,000 Da) that remain linked by an inter chain disulphide and noncovalent bonds.

Dysport 500 units (U) is a freeze-dried preparation of *Clostridium* BTX-A-hemagglutinin complex (BTX-A-HAC) formulated with lactose (bulking agent) and human serum albumin. A more detailed description of the product is provided in Section 9.1.1.

For the treatment of spasticity, Dysport is injected directly into target muscles where it acts selectively on peripheral cholinergic nerve endings, inhibiting acetylcholine release, effectively blocking signal transmission from nerve to muscle and inducing a temporary, partial chemodenervation of the injected muscle.

Typically, Dysport is reconstituted with 1.0 mL or 2.5 mL of preservative free 0.9% sodium chloride for injection to yield a solution containing 500 U or 200 U of Dysport per mL, respectively, depending on the indication.

Further details can be found in the Investigator's brochure [24].

2.3 Clinical Study Rationale

Previous studies have investigated the use of BTX for the treatment of upper limb spasticity in children with hemiplegia due to CP [25, 26, 27, 28, 29, 30]. The effect of a single injection of BTX, with or without additional treatments such as occupational therapy, on spasticity,

increased muscle tone, and on the level of functional ability has been compared to control groups. In the majority of these studies temporary improvements in spasticity and muscle tone were observed in the targeted muscles, providing clear evidence for the beneficial effect of BTX. However, the assessment of functional improvement following a single treatment has shown variable results in these studies. Functional improvement in upper limb is expected to manifest after a sufficiently long period of reduced muscle tone of the upper limb following multiple treatments, during which children would have the opportunity to have adequate occupational therapy, and to learn new motor skills, necessary for the achievement of their individual goals [31].

The use of BTX for the treatment of upper limb spasticity in children is well recognised [23, 32, 33]. The choice of control group in studies is usually occupational therapy, physiotherapy and/or no treatment (no placebo injection). However, for the purpose of a phase III study, these methods of control are not adequate enough to provide sufficient scientific robustness. Only one published placebo controlled study [26] has been identified in this indication. The use of placebo as a control group is considered ethically unacceptable since injection into the upper limb muscles to this paediatric population often requires anaesthesia or heavy sedation. Therefore, a low dose control group has been chosen for this study to maintain the study blinding. The dose chosen (2 U/kg) is in line with the lowest upper limb dose used in a previous Ipsen sponsored, retrospective study [34]).

Dysport is licensed in over 75 countries for various indications. It has been approved for the treatment of spasticity of the lower limbs in children (aged 2 to 17 years) with CP at doses up to 15 U/kg (with a maximum total dose of 1000 U). In some countries Dysport has also been approved for the treatment of adult upper limb spasticity at doses up to 1000 U.

CCI

[REDACTED]

PPD

[REDACTED]

The Sponsor has not conducted any prospective clinical study specifically for the evaluation of safety and efficacy in the treatment of upper limb spasticity in children with CP.

The present phase III, multicentre, double blind, prospective, randomised, controlled multiple treatment study has been designed to assess the efficacy of a single treatment of Dysport at the doses of 8 U/kg and 16 U/kg compared to Dysport 2 U/kg used in the treatment of upper limb spasticity in children with CP. A primary targeted muscle group (PTMG), either the elbow flexors or wrist flexors, will be nominated by the Investigator (see Section 9.1.3). Effects of muscle tone on the PTMG (using the Modified Ashworth Scale (MAS)) will be assessed as primary criterion. The Physician’s Global Assessment (PGA) of the treatment response and individual goal attainment are secondary criteria. Furthermore, the study has also been designed

to evaluate the long term safety and efficacy following multiple Dysport treatments over the course of a minimum of one year's study participation.

3 STUDY OBJECTIVES

3.1 Primary Study Objective

The primary study objective is to assess the efficacy of two doses of Dysport (8 U/kg and 16 U/kg) compared to Dysport 2 U/kg used in the treatment of upper limb spasticity in children with CP following a single treatment.

3.2 Secondary Study Objectives

The secondary study objective is to assess the long term safety of multiple treatments of Dysport used in this study population.

3.3 Tertiary Study Objectives

The tertiary study objectives CCI [REDACTED] quality of life (QoL) CCI [REDACTED]

3.4 Ancillary Study Objectives

There are no ancillary study objectives.

4 STUDY DESIGN

4.1 Overview

4.1.1 Population Characteristics

The study will include approximately 210 male and female subjects between 2 and 17 years of age, with a body weight ≥ 10 kg, with a diagnosis of CP and who have increased muscle tone/spasticity in at least one upper limb. Additionally, subjects must have a MAS score ≥ 2 in the upper limb PTMG of the study limb (the limb to be injected in the first treatment) at the baseline visit and be classified as GMFCS Level 1 to 4. CCI [REDACTED]

4.1.2 Design

This is a phase III, multicentre, double blind, prospective, randomised, controlled multiple treatment study. Subjects will receive a maximum of four treatments over the course of a minimum of one year's study participation.

4.1.3 Study Structure

At study entry, subjects will be randomised into one of the following three treatment groups for Treatment 1:

- Group A: Dysport 16 U/kg in one upper extremity (the study limb).
- Group B: Dysport 8 U/kg in the study limb.
- Group C: Dysport 2 U/kg in the study limb.

Randomisation will be done with an Interactive Response System (IRS) and will be in a 1:1:1 ratio. The IRS will be used to allocate packs and envelope numbers (to be considered to reconstitute the treatment) and then study treatment reconstitution will be performed by an independent reconstitutor who will not be involved in any other study related activities in order to maintain the blinding.

For Treatments 2, 3 and 4, subjects are planned to receive Dysport 8 U/kg or 16 U/kg according to the treatment allocation by the IRS and will remain double blind throughout the study.

CCI [REDACTED]

The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

The planned retreatment interval is 16 weeks and a maximum of four treatments will be administered.

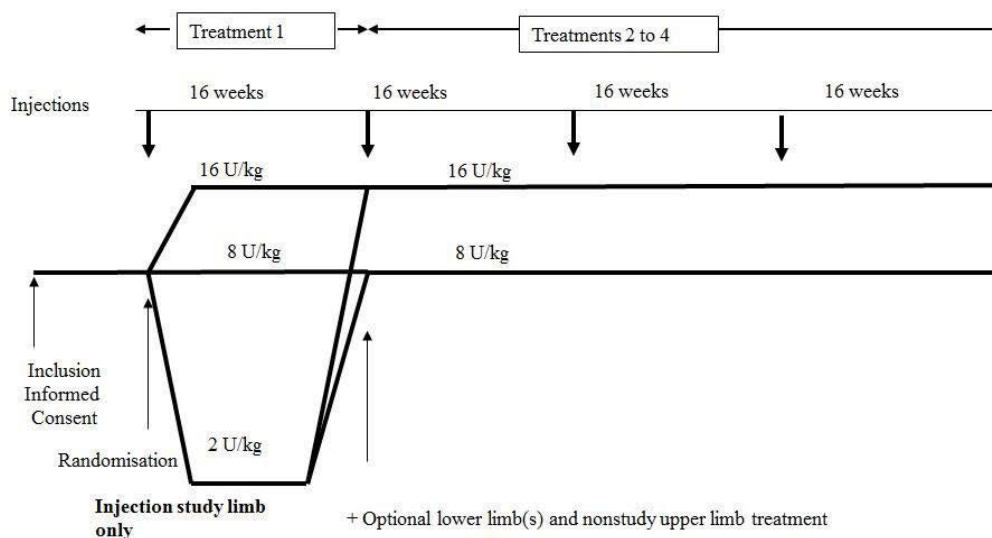
At study entry, a PTMG, either the elbow flexors or wrist flexors, will be nominated by the Investigator. The PTMG can be changed for subsequent treatments, from elbow to wrist flexors or wrist to elbow flexors, provided that the following criteria are fulfilled:

- The Modified Ashworth Scale (MAS) score of the other muscle group not selected for the last treatment (new PTMG) must be higher than the last treatment PTMG, and
- The new PTMG must have a modified MAS score of greater or equal to 1+.

For Treatments 2, 3 and 4, injection into the lower extremity/extremities and the non-study upper limb will be allowed at the same time as the study limb is injected (see Section 9.1.4).

The stages of the study and the planned doses for the study are provided in Figure 1.

Figure 1 Planned Study Structure



Stratification will be performed according to age range (2 to 9 years and 10 to 17 years) and BTX naïve or non-naïve status assessed at baseline.

CCI [REDACTED]

A maximum of four treatments will be administered in this study. After each treatment administration, the follow up visit schedule is as follows:

- Week 2 (telephone call, safety follow up).
- Week 4 (telephone call, safety follow up).
- Week 6.
- Week 12 (telephone call, safety follow up).
- Week 16.

At Week 16, subjects will be assessed for their eligibility to receive the next treatment. Subjects who are eligible for retreatment will be given the next treatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks \pm 2 weeks in additional visits until they are eligible for retreatment.

Each subject will participate in the study for 1 year to 1 year and 9 months depending on the number of treatments administered and the treatment intervals. The duration of the follow up period will be dependent upon the treatment interval as follows:

- All subjects whose first three treatment intervals fall between ≥ 16 and ≤ 22 weeks will receive four treatments and will exit the study as soon as a new injection is required and no later than 22 weeks after last injection (up to a maximum of 1 year and 9 months study duration).
- All other subjects will not be given any further study treatment after Week 52 and will exit the study after 16 weeks of follow up of the last treatment.

CCI



The efficacy and safety of Dysport will be continuously assessed throughout the study. An independent Data and Safety Monitoring Board (DSMB) will be put in place and will monitor the safety in this study. At any point during the study and after review of the available data, the DSMB may recommend that the study is stopped based on safety data. Further details are provided in Section 13.6.1.

4.1.4 *Stopping Rules and Discontinuation Criteria*

The DSMB can recommend that the study (or any individual subject participation) is stopped at any time based on safety data (see Section 13.6.1).

In addition, subjects will be discontinued if:

CCI



For other reasons for withdrawal or discontinuation, see Sections 4.1.5 and 6.4.

4.1.5 *Early Study Termination*

The Sponsor may terminate this study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this and/or other studies point to a potential health hazard for study subjects.
- Insufficient subject enrolment.
- Any information becoming available during the study that substantially changes the expected benefit risk profile of the study treatments.

- Recommendation by the DSMB.

4.2 Endpoints

4.2.1 Efficacy Endpoints

Efficacy variables will be assessed at the following schedule:

- Modified Ashworth Scale, GAS, CCI [REDACTED] at baseline (Treatment 1, Day 1) and at each post-treatment visit to the study centre.
- Physician’s Global Assessment at each post-treatment visit to the study centre.
- CCI [REDACTED]
- Paediatric Quality of Life (PedsQL™) at baseline (Treatment 1, Day 1), Treatment 1, Week 16 and at the end of study visit or early withdrawal.

4.2.1.1 Primary Efficacy Endpoint

- Mean change from Baseline to Treatment 1, Week 6 in MAS score in the Treatment 1 PTMG (elbow flexors or wrist flexors).

4.2.1.2 Secondary Efficacy Endpoints

- Mean PGA score at Treatment 1, Week 6.
- Mean GAS score at Treatment 1, Week 6.

4.2.1.3 Tertiary Efficacy Endpoints

- Mean change from Baseline to all post-treatment visits of treatment 1 (except Week 6) in MAS score in the Treatment 1 PTMG.
- CCI [REDACTED]
- Mean change from Baseline to all post-treatment visits in MAS score in each injected muscle group (elbow, wrist and finger flexors) of the study limb.
- CCI [REDACTED]
- CCI [REDACTED]
- Mean PGA score at all post-treatment visits (except Treatment 1, Week 6).
- [REDACTED] CCI [REDACTED]
- Mean GAS score at all post-treatment visits (except Treatment 1, Week 6).
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Mean change from Baseline to both post-treatment PedsQL scores.

4.2.2 Safety Endpoints

The safety endpoints of this study are:

- Treatment emergent adverse events (TEAEs).
- Vital signs (systolic and diastolic blood pressure (BP) and heart rate (HR)): absolute values and change from Baseline at each visit to the study centre.
- Body weight and height: absolute values and change from baseline at Week 16 of each treatment and at the end of study visit or early withdrawal.
- Clinical chemistry (including serum ALP - total and bone isoenzyme, and HbA1c): absolute values and change from Baseline at Treatment 1, Week 16 (serum ALP - total and bone isoenzyme, and HbA1c only) and at the end of study visit or early withdrawal.
- Presence of antibodies against BTX-A (BTX-A-Abs) at baseline and at the end of study visit or early withdrawal.
- A 12-lead electrocardiogram (ECG): absolute values and change from Baseline in ECG parameters and morphology at Treatment 1, Week 6 and at the end of study visit or early withdrawal.

4.3 Justification of Design

The present study will be conducted as a phase III, multicentre, double blind, prospective, randomised, controlled, multiple treatment study comparing efficacy and safety of Dysport at the doses of 8 U/kg and 16 U/kg to Dysport 2 U/kg used in the treatment of upper limb spasticity in children with CP.

Reduction of the increased muscle tone and spasticity is important for the improvement of the motor ability and functional skills of children with CP, and for prevention of fixed muscle contractures and deformities and to delay the need for surgery. Therefore, the assessment of reduction of increased muscle tone of the upper limb has been specified as a primary efficacy endpoint of interest for this study. This assessment of muscle tone will be performed using MAS, which is the sole validated scale to date, widely used to measure muscle tone [35, 36]. The other assessment scales used in this study have been chosen to demonstrate physician's global impression of the treatment effect (PGA), functional outcomes (GAS and CCI), CCI, QoL, and CCI. The optimal time to demonstrate the primary and secondary measures is thought to be 6 weeks following injection and therefore Week 6 of Treatment 1 has been selected for the primary endpoint.

The clinical presentation of spasticity differs from one subject to another. The Investigator should consider the clinical condition, the specific upper limb spasticity pattern (i.e. elbow flexion, forearm pronation, wrist and finger flexion, and thumb adduction and flexion) and any

associated functional impairment when providing treatment [37]. The design of this study allows the Investigator to select the study limb and the PTMG (elbow flexors or wrist flexors) and a number of other muscles, as specified in the dosing paradigm (see Section 9.1.2).

The three Dysport doses chosen for this study are 2 U/kg, 8 U/kg and 16 U/kg. The two higher doses of Dysport (8 U/kg and 16 U/kg) will be compared to the lowest dose group (Dysport 2 U/kg). The choice of each individual muscle dose is based on in house efficacy and safety data with Dysport (CCI [34]), other published data on BTX-A products in this indication, and on recommendations from leading clinical experts. CCI

The study is designed to allow injections into multiple muscle groups in the study limb and since the elbow and the wrist flexors were the most commonly injected upper limb muscles in CCI, the total dose in each treatment group is set to allow concurrent treatment of these two muscle groups. Furthermore, the chosen doses are well within the maximum total dose of 30 U/kg of Dysport (with a maximum total dose of 1000 U) per treatment session for use in lower limb spasticity in children, recommended in the international consensus paper in 2010 [29].

A fixed dosing volume was chosen for the study to eliminate the confounding effect of dilution. The injection volume of 1.6 mL will be sufficient to inject multiple muscles of the upper limb, as required according to clinical need. Proximal and distal muscle groups of the upper limb have different sizes of the muscle bulk and may require different doses and volumes of injection [33]. For Treatments 2, 3 and 4, Investigators will be allowed to adjust the dose, according to treatment response, at the level of individual muscles by changing the injection volume, or total dose by requesting a dose change in the IRS without having to break the blind. Furthermore, for Treatments 2, 3 and 4, injection into the lower extremity/extremities and the non-study upper limb will be allowed at the same time as the study limb is injected. In order to stay within the total body dose of 30 U/kg, maximum 1000 U, CCI

The planned retreatment interval in this study is 16 weeks, as previously conducted paediatric lower limb studies suggest that the effect of Dysport can still be observed 16 weeks after treatment [38,39]. In another study, the treatment interval was 4 months [40].

4.3.1 *Study Population for Analysis*

The primary analysis will be performed on the mITT population (see Section 11.2).

4.3.2 *Study Duration*

The overall duration of the study is anticipated to be approximately 4 years and 9 months and will include subject recruitment (approximately 3 years) and last subject follow up (approximately 1 year and 9 months). The study will be considered to have started when the first subject has provided signed informed consent. The study will be considered to have finished after the last subject has completed the end of study visit.

Individual subject participation will be approximately 1 year to 1 year and 9 months, depending on the number of treatments administered and the treatment intervals. The 1 year and 9 month follow up period will enable subjects whose first three treatment intervals fall between >16 and

≤22 weeks to receive four treatments, therefore providing efficacy data for a minimum of 1 year.

5 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS AND INFORMED CONSENT

5.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines [41].

For electronic data capture (EDC) studies the following regulations must be adhered to: Food and Drug Administration (FDA), 21 CFR Part 11: Electronic Records, Electronic Signatures (e-signature); and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials [42, 43]. In addition, this study will adhere to all local regulatory requirements. Before initiating a study, the Investigator/institution must have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form (ICF), any consent form updates, paediatric assent form and any updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

5.2 Informed Consent

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject and subject's legally acceptable representative and impartial witness, as applicable. Written informed consent must be obtained from the child's parent(s)/guardian(s) (either one or both parent(s)/guardian(s) according to local legislation) and a signed assent from the child when and where applicable, prior to the subject entering the study (before initiation of any study related procedure and administration of study treatment). Sufficient time will be allowed to discuss any questions raised by the subject/subject's representative. If applicable, when a subject becomes an adult during study participation, they may be required to sign an adult consent form according to local legislation.

The Sponsor will provide a sample ICF. The final version controlled form must be agreed to by the Sponsor, and the IEC/IRB and must contain all elements included in the sample form, in a language readily understood by the child's parent(s)/guardian(s). Each subject's original ICF (and assent form where appropriate), signed and dated by the parent(s)/guardian(s) (and subject where appropriate) and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled child's parent(s)/guardian(s) with a copy of the signed ICF.

The ICF may need to be revised during the course of the study should important new information become available that may be relevant to the safety of the subjects or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the Investigator's responsibility to ensure that all parent(s)/guardian(s) of subjects subsequently

entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Parent(s)/guardian(s) of subjects who have completed the study should be informed of any new information that may impact on the subjects' welfare/wellbeing.

The Investigator should, with the consent of the child's parent(s)/guardian(s), inform the subject's primary physician about their participation in the clinical study.

6 STUDY POPULATION

6.1 Screening Log and Number of Subjects

Each Investigator will maintain a record of all subjects who were considered potentially eligible for entry into the study but who were not enrolled. For each subject, the primary reason for exclusion will be recorded.

Each Investigator will also maintain a record of all subjects enrolled into the study (i.e. whose parent(s)/guardian(s) signed the ICF). In the event that the subject was not receiving study treatment, the primary reason will be recorded.

It is planned to recruit approximately 210 subjects in this multinational study. Section 11.3 provides a discussion of sample size.

6.2 Inclusion Criteria

Subjects must satisfy all of the following inclusion criteria to be eligible for the study:

- (1) Signed informed consent obtained from the child's parent(s)/guardian(s) and, if applicable, a signed assent from the child.
- (2) Be from 2 to 17 years of age, inclusive.
- (3) Body weight of 10 kg or more at the baseline visit.
- (4) Have a diagnosis of CP, as defined by Rosenbaum [9].
- (5) Have increased muscle tone/spasticity in at least one upper limb.
- (6) Have a MAS score ≥ 2 in the upper limb PTMG (elbow flexors or wrist flexors) of the study limb (the limb to be injected in the first treatment) at the baseline visit.
- (7) Be classified as GMFCS Level 1 to 4.
- (8) CCI [REDACTED]

6.3 Exclusion Criteria

Subjects are to be excluded if any of the following applies:

- (1) Fixed myocontracture in the PTMG (elbow flexors or wrist flexors) of the study limb CCI [REDACTED]

- (7) CCI [REDACTED]
[REDACTED]
- (9) Previous injection of alcohol and/or phenol within 1 year prior to the baseline visit affecting the study limb wrist flexors and/or elbow flexors selected for injection in Treatment 1.
- (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.
- CCI [REDACTED]
[REDACTED]
[REDACTED]
- (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.
- CCI [REDACTED]
- (17) Previous rhizotomy less than 6 months prior to the baseline visit or rhizotomy planned/anticipated during the course of the study.
- (18) Subjects treated or likely to be treated with intrathecal baclofen within 30 days prior to the baseline visit or during the course of the study.
- CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- (22) Any known 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.
- (23) Any uncontrolled clinically significant medical condition other than CP.

6.4 Subject Withdrawal Criteria

Under no circumstances will subjects be randomised into this study more than once. If one or more of the following occurs, the subject will be withdrawn from the study:

- (1) Withdrawal of informed consent.
- (2) Requirement for administration of concomitant medications and/or treatments that are not allowed under the study protocol.
- (3) Occurrence of an AE or other nonmedical event, that in the opinion of the Investigator, would not be in the subject's best interest were they to continue in the study.
- (4) Pregnancy.
- (5) Investigator's and/or Sponsor's decision to withdraw the subject if it is considered to be in the subject's best interest.
- (6) Continuous failure to comply with the provisions of the study protocol which is likely to have an adverse impact on the safety or wellbeing of the subject or subjects, or to jeopardise the scientific value of the study.
- (7) Any subjects who met any of the stopping rules in Section 4.1.4.

6.5 Discontinuation/Withdrawal Procedures

If a subject withdraws from the study (i.e. ceases participation in the study prior to completion of the assessments planned in the protocol), the primary reason should be recorded in the electronic case report form (eCRF). Withdrawal due to AEs should be distinguished from withdrawal due to insufficient response.

The Investigator will provide or arrange for appropriate follow up (if required) for subjects withdrawing from the study, and will document the course of the subject's condition. Where the subject has withdrawn due to an AE the Investigator should follow the procedures documented in Section 10 in order to assess the safety of the study treatment.

7 METHODOLOGY

7.1 Study Schedule

The schedule of observations and assessments is presented in Appendix 1; Treatment 1 is presented in Table 8, Treatments 2, 3 and 4 are presented in Table 11, and the additional visits and the end of study/early withdrawal visit are presented in Table 12.

7.2 Study Visits

Details of the timing of each visit, together with the tests and procedures to be performed are summarised in Appendix 2. Every effort should be made to ensure that visits take place at the visit timepoint, or within the visit window where applicable.

7.2.1 Screening (Day -7 to Day 1, Visit 1)

Written informed consent must be signed by the parent(s)/guardian(s) of all subjects, and assent obtained from the child, when and where applicable, prior to entry into this study.

This visit may occur on the same day as the baseline visit (Visit 2 (see Section 7.2.2)) at the discretion of the Investigator. Subjects have to undergo the following assessments in order to be randomised into the study:

- Eligibility checks (inclusion/exclusion criteria).
- Demographics (date of birth/age, sex, ethnicity and race)².
- Medical/surgical history, including ongoing medical history.
- Cerebral palsy history and status.
- Botulinum toxin treatment history.
- Prior and concomitant medications. Prior medications will be all medications administered within 30 days before the screening visit and stopped either before or at study entry.
- Prior and concomitant nondrug therapies. Prior nondrug therapies will be all nondrug therapies administered within 30 days before the screening visit and stopped either before or at study entry.
- Physiotherapy and occupational therapy (frequency and intensity). Prior physiotherapy and occupational therapy will be all therapy within 90 days before the screening visit and stopped either before or at study entry.
- Use of splints and/or orthoses.
- Gross Motor Function Classification System level [44].
- Physical and neurological examinations.
- Vital signs (BP and HR) and body weight.
- A 12-lead ECG.
- Collection of AEs.

² Demographics data will be collected according to individual country requirements.

7.2.2 Baseline (Treatment 1, Day 1, Visit 2)

The screening visit (Visit 1) and the baseline visit (Visit 2) may occur on the same day at the discretion of the Investigator.

All baseline assessments should be performed at this visit prior to randomisation and administration of study treatment. If the subject is scheduled to receive study treatment during a morning operating theatre session, performance of baseline assessment within 24 hours prior to study treatment administration will be acceptable.

- Eligibility checks (inclusion/exclusion criteria).
- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy, occupational therapy (frequency and intensity).
- Home exercise instructions
- Use of splints and/or orthoses.
- Vital signs (BP and HR) and body weight and height.
- Blood sampling for BTX-A-Ab testing.
- Blood sampling for clinical chemistry (including serum ALP - total and bone isoenzyme, and HbA1c).
- Tanner Grading Scale for all female subjects.
- Urine pregnancy test for all female subjects of childbearing potential and for those subjects reaching Tanner Grading Scale for breast development Stage II or more will be performed at the investigational site. If urine cannot be collected, then alternatively, the urine can be taken at home 1 day prior to the visit (only if the ICF has been signed prior to urine collection). If the urine pregnancy test is found to be positive, it will be followed up with a serum pregnancy test conducted at the central laboratory.
- Hypertonia Assessment Tool will be used for all subjects entering the study (exploratory scale) [46].
- Manual Ability Classification System (MACS) for subjects older than 4 years of age (4 years included) and mini-MACS for subjects between 2 and 4 years of age (4 years excluded) [18, 19].
- CCI [REDACTED]
- Goal Attainment Scale. Individual treatment goals are set at this visit.
- CCI [REDACTED]
- CCI [REDACTED]
- The PedsQL.
- Collection of AEs.
- Randomisation. If the subject is being anaesthetised prior to treatment injection, randomisation must occur before the anaesthetic is given.
- Study treatment administration in the study limb.

7.2.3 Treatment 1 – Follow Up Visits

7.2.3.1 Week 2 ±1 week Visit 3 - Telephone Contact

The following assessments will be collected by telephone at Week 2 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).

- Use of splints and/or orthoses.
- Collection of AEs.

7.2.3.2 Week 4 \pm 1 week Visit 4 - Telephone Contact

The following assessments will be collected by telephone at Week 4 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Collection of AEs.

7.2.3.3 Week 6 \pm 4 days, Visit 5

The following assessments will be performed at Week 6 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Vital signs (BP and HR).
- A 12-lead ECG.
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
This can be scheduled separately provided it is performed within the visit window.
- CCI [REDACTED]
- Collection of AEs.

7.2.3.4 Week 12 \pm 1 week, Visit 6 - Telephone Contact

The following assessments will be collected by telephone at Week 12 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Collection of AEs.

7.2.3.5 Week 16 \pm 2 weeks, Visit 7

The following assessments will be performed at Week 16 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Vital signs (BP and HR) and body weight and height.

- Blood sampling for clinical chemistry (serum ALP - total and bone isoenzyme and HbA1c only).
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
- The PedsQL.
- Collection of AEs.
- Eligibility for retreatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks \pm 2 weeks in additional visits until they are eligible for retreatment (see Section 7.2.6).

7.2.4 *Treatments 2, 3 and 4, Day 1, Visits 8, 14 and 20*

This visit should occur on the same day as the last visit of the previous treatment.

The following assessments will be performed at this visit:

- Tanner Grading Scale for all female subjects.
- Urine pregnancy test for all female subjects of childbearing potential and for those subjects reaching Tanner Grading Scale for breast development Stage II or more will be performed at the investigational site. If urine cannot be collected, then alternatively, the urine can be taken at home 1 day prior to the visit. If the urine pregnancy test is found to be positive, it will be followed up with a serum pregnancy test conducted at the central laboratory.
- Goal Attainment Scale. Individual treatment goals are set at this visit.
- Study treatment administration in the study limb. Investigators will be allowed to adjust the dose according to treatment response, at the level of individual muscles by changing the injection volume or total dose, by requesting a dose change in the IRS without having to break the blind (see Section 9.1.3).
- Concomitant treatment of lower limb and/or the non-study upper limb (for subjects who require such treatment) (see Section 9.1.4).
- If Day 1 of Treatment 2, 3 or 4 occurs on the same day as the last visit of the previous treatment the following assessments will, if conducted, be referenced from that visit. If not conducted at that visit, the following assessments will need to be performed prior to study treatment administration and recorded in the eCRF:
 - Concomitant medications.
 - Concomitant nondrug therapies.
 - Physiotherapy and occupational therapy (frequency and intensity).
 - Home exercises (frequency).
 - Use of splints and/or orthoses.
 - Vital signs (BP and HR) and body weight.
 - Physician's Global Assessment Scale.
 - CCI [REDACTED]
 - CCI [REDACTED]
 - Collection of AEs.

7.2.5 *Treatments 2, 3 and 4 – Follow Up Visits*

7.2.5.1 *Week 2 ±1 week, Visits 9, 15 and 21 - Telephone Contact*

The following assessments will be collected by telephone at Week 2 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Collection of AEs.

7.2.5.2 *Week 4 ±1 week, Visits 10, 16 and 22 - Telephone Contact*

The following assessments will be collected by telephone at Week 4 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Collection of AEs.

7.2.5.3 *Week 6 ±4 days, Visits 11, 17 and 23*

The following assessments will be performed at Week 6 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Vital signs (BP and HR).
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
- Collection of AEs.

7.2.5.4 *Week 12 ±1 week, Visits 12, 18 and 24 - Telephone Contact*

The following assessments will be collected by telephone at Week 12 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Collection of AEs.

7.2.5.5 *Week 16 ±2 weeks, Visits 13, 19 and 25*

The following assessments will be performed at Week 16 post-treatment for all subjects:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Vital signs (BP and HR) and body weight and height.
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
- Collection of AEs.
- Eligibility for retreatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks ±2 weeks in additional visits until they are eligible for retreatment (see Section 7.2.6).

7.2.6 *Additional Visits*

Any subjects not eligible for retreatment, at Week 16 of any treatment, will be evaluated every 6 weeks ±2 weeks in additional visits until they are eligible for retreatment. All subjects whose first three treatment intervals fall between ≥ 16 and ≤ 22 weeks will receive four treatments and will exit the study as soon as a new injection is required and no later than 22 weeks after last injection (up to a maximum of 1 year and 9 months study duration). All other subjects will not be given any further study treatment after Week 52 and will exit the study after 16 weeks of follow up of the last treatment.

The following assessments will be performed at each additional visit:

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).
- Use of splints and/or orthoses.
- Vital signs (BP and HR).
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
- Collection of AEs.
- Eligibility for retreatment. Any subjects not eligible for retreatment will be evaluated every 6 weeks ±2 weeks in additional visits until they are eligible for retreatment.

7.2.7 *End of Study or Early Withdrawal Follow up Visit*

At the end of study visit or early withdrawal the following assessments will be performed (±2 weeks):

- Concomitant medications.
- Concomitant nondrug therapies.
- Physiotherapy and occupational therapy (frequency and intensity).
- Home exercises (frequency).

- Use of splints and/or orthoses.
- Physical examination.
- Vital signs (BP and HR) and body weight and height.
- A 12-lead ECG.
- Blood sampling for BTX-A-Ab testing.
- Blood sampling for clinical chemistry (including serum ALP - total and bone isoenzyme, and HbA1c).
- Physician's Global Assessment Scale.
- Goal Attainment Scale.
- CCI [REDACTED]
- CCI [REDACTED]
This can be scheduled separately provided it is performed within 2 weeks before study exit.
- CCI [REDACTED]
- The PedsQL.
- Collection of AEs.

8 STUDY EVALUATIONS

For the timing of assessments during the study, refer to the study schedules in Appendix 1.

The following examinations will be performed at screening or baseline only.

Evaluation of Cerebral Palsy

At baseline, the subjects CP will be evaluated by:

- A diagnosis of CP as defined by Rosenbaum [9].
- The presence of spastic hemiparesis, paraparesis, diparesis, or tetraparesis.
- Presence and intensity of severe athetoid or dystonic movements in the targeted upper limb.
- Evaluation of hypertonia to capture baseline dystonic/spastic characteristic using the Hypertonia Assessment Tool [45, 46].
- Planned or completed surgery of the upper limbs.
- History of injection of alcohol and/or phenol.

Neurological Examination

A neurological examination will be performed by the Investigator at screening. The neurological examination will include:

- Strength.
- Deep tendon reflexes (biceps and triceps only).

Gross Motor Function Classification System

The GMFCS is a five-level classification that differentiates children with CP based on the child's current gross motor abilities, limitations in gross motor function, and need for assistive technology and wheeled mobility [44]. Further details will be provided in the study manual.

Manual Ability Classification System

The MACS is a five-level classification that assesses how children with CP use their upper limb for handling objects in their daily life [18, 19]. Further details are provided in Appendix 7. Mini-MACS is the same scale adapted to children between 2 and 4 years of age (4 years excluded). For subjects already recruited in the study at the time of protocol amendment approval, the MACS (or mini-MACS) will be assessed retrospectively, based on source data obtained over 2 months prior to randomization into the study. The investigator will document the assessment at the date it is assessed both in the subjects file and in the eCRF (appendix

pages). In case it is not possible to assess MACS (or mini-MACS) the data will be noted as not applicable in the eCRF.

8.1 Efficacy Endpoints and Evaluations

Every effort should be made in each centre to ensure that the evaluating Investigators are the same individuals for the duration of the study for a given subject. The assessor who conducts the global assessment of the treatment response must be different from the evaluator performing the CCI and Muscle Tone examination. None of the assessors will have knowledge of the scores obtained by the other assessor at the time of his/her assessment.

CCI and Muscle Tone Examination

Modified Ashworth Scale, CCI will be performed as an entire set of examinations called 'CCI and Muscle Tone examination'. It will be performed on the study limb at baseline (Treatment 1, Day 1) and at all post-treatment visits, and in the non-study upper limb at each visit when the non-study upper limb is injected. The examination will include all of the following evaluations:

- CCI
- Elbow flexors MAS and C.
- Wrist flexors MAS and C.
- Finger flexors MAS.
- CCI

This examination must be performed by a different evaluator to the person performing the PGA.

Efficacy Evaluations

The efficacy evaluations described in the following sections will be evaluated at the following schedule:

- CCI, GAS, and CCI at baseline (Treatment 1, Day 1) and at each post-treatment visit to the study centre.
- Physician's Global Assessment at each post-treatment visit to the study centre.
- CCI
- Paediatric Quality of Life at baseline (Treatment 1, Day 1), Treatment 1, Week 16 and at the end of study visit or early withdrawal.

8.1.1 Modified Ashworth Scale

The MAS is a six-point scale which measures the amount of muscle tone by measuring the resistance of the muscle to passive lengthening or stretching [35]. The Investigator will grade muscle tone in the PTMG from 0 (no increase in tone) to 4 (affected part(s) rigid in flexion or extension). Further details are provided in Appendix 3.

8.1.2 Physician's Global Assessment of the Treatment Response

The PGA of treatment response will be assessed by asking the Investigator the following question: 'how would you rate the response to treatment in the subject's upper limb since the start of the study?' Answers will be made on a nine-point rating scale (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved and +4: markedly improved).

8.1.3 Goal Attainment Scale

The GAS is a functional scale used to measure progress towards individual therapy goals. Individual goals will be defined for each subject by the Investigator and the child's parents/guardians/caregivers prior to treatment. The GAS will be rated using a defined scale. Further details are provided in Appendix 4.

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]
[REDACTED]

8.1.8 Paediatric Quality of Life Inventory

Parents/guardians will be asked to complete questionnaires on their child's QoL [52] at each post-treatment visit to the study centre except Week 6. The PedsQL parent inventory measures healthcare concepts for children/adolescents of ages 2 to 18 years of age [53]. The Generic Core Scales cover four multidimensional scales including physical, emotional, social and school aspects with three summary scales of total scale score, physical health summary score and psychosocial health summary score.

Parents/guardians will also complete the Condition-specific Module in CP (in countries where translation is available) [53], which is a complement to the Generic Core Scale of the PedsQL. It is designed to provide greater measurement sensitivity for circumscribed populations.

Efficacy endpoints are defined in Section 4.2.1.

8.2 Safety Endpoints and Evaluations

8.2.1 Adverse Events

Adverse events will be monitored from the signing of informed consent up until the end of the study (as defined in Section 4.3.2). All AEs will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 10.

8.2.2 Physical Examination

A physical examination will be carried out by a physician, or by another qualified staff member designated by the Investigator, at the screening visit and at the end of study visit or early withdrawal. The physical examination should include (but is not restricted to) the following body systems: cardiovascular, respiratory, abdominal, eyes, ears, nose and throat, skin and musculoskeletal. If in the opinion of the Investigator there are any clinically significant changes in the physical examination findings (abnormalities) they will be recorded as AEs.

8.2.3 Vital Signs

Vital signs (systolic and diastolic BP and HR) will be measured at each visit to the study centre. Blood pressure will be measured with the subject in a sitting position. Absolute values and change from Baseline will be analysed.

8.2.4 Electrocardiogram Analysis

An ECG analysis will be included as a safety evaluation/endpoint in this study.

Subjects will have a set of three 12-lead ECG recordings taken at the screening visit (considered as baseline assessment), then subsequently one 12-lead ECG at Treatment 1, Week 6 and at the end of study visit or early withdrawal. The 12-lead ECG recordings will be performed at a paper speed of 25 mm/sec, recorded with the subject supine. Analysis of the ECG results will be performed in a central laboratory.

All ECGs that are performed post-treatment will be compared to baseline. Any clinically significant difference in the ECG parameters or morphology will be noted.

If at any time point the QTc exceeds 500 msec or the change from Baseline exceeds 60 msec, the ECG will be repeated until the parameters fall below these limits or the Investigator is satisfied that the subject is not at any significant risk.

Analysis of the duration of the QT/QTc interval, the HR and the presence of any of the following ECG abnormalities: new morphologies, arrhythmias, second degree AV block, third degree AV block, ST segment abnormalities, T-wave abnormalities, U-wave abnormalities, myocardial infarction, right bundle branch block, left bundle branch block, will be performed. These and any other clinically relevant abnormality will also be reported by the central provider to the Investigator and recorded as an AE.

The QT interval is defined as the time (in msec) from the beginning of the QRS complex to the end of the T-wave on the ECG. The QTc is defined as the corrected QT interval using the Fridericia and the Bazett formula. The duration of the QT/QTc interval in the ECGs taken for each subject and at each time point will be used for the analysis.

In summary, the ECG safety endpoints will include:

- Duration of the QT/QTc interval (in msec) at each ECG time point.
- Mean change from Baseline in the duration of the QT/QTc interval at each ECG time point.
- Proportion of subjects at each ECG time point with a duration of QT/QTc interval of: >450 to 480 msec, >480 to 500 msec and >500 msec.
- Proportion of subjects at each ECG time point with an increase from baseline in the QT/QTc interval of >30 msec and >60 msec.

- Proportion of subjects with any of the above listed ECG abnormalities at each ECG time point.

Electrocardiogram test results will be recorded by the central laboratory and provided to the study Sponsor, and to the study sites for evaluation of clinically significant changes. See Section 10.1.7 for recording clinically significant abnormal ECG findings that should be recorded as AEs in the eCRF.

8.2.5 *Clinical Laboratory Tests*

Blood samples for clinical chemistry (including serum ALP - total and bone isoenzyme, and HbA1c) will be collected at Treatment 1, Day 1 (baseline) and at the end of study visit or early withdrawal. In addition, a blood sample for serum ALP - total and bone isoenzyme, and HbA1c only will be collected at Treatment 1, Week 16. Absolute values and change from Baseline will be analysed.

The following will be assessed:

Clinical Chemistry (3.5 mL blood): urea, creatinine, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, serum ALP - total and bone isoenzyme, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, albumin, total protein, total cholesterol, triglycerides and HbA1c.

Pregnancy: At Day 1 of each treatment, the Tanner Grading Scale for breast development will be performed for all female subjects (further details are provided in Appendix 8) [54]. For all female subjects of childbearing potential and for those subjects reaching Tanner Stage II or more breast development, a urine sample will be collected for a pregnancy test. The test will be performed on site using a urine pregnancy test provided by the Sponsor.

If it is anticipated that urine collection may not be possible on site, parents will be instructed to collect a urine sample (at least 15 mL) at home in a clean dry vial on the day preceding the visit. The urine sample will be stored in the fridge (between 2°C and 8°C). Parents will take the urine sample to the investigational site where the test will be performed.

If the urine pregnancy test is found to be positive, it will be followed up with a serum pregnancy test (1 mL blood) conducted at the central laboratory.

Clinical laboratory tests will be performed by a central laboratory. Details of the methodology and reference ranges will be provided in the Trial Master File.

Laboratory test results will be recorded by the central laboratory and provided to the study Sponsor, and to the study sites for evaluation of clinically significant changes. All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor's medical monitor (or his/her designated representative), or until the abnormality is explained by an appropriate diagnosis. See Section 10.1.5 for abnormal laboratory tests that should be recorded as AEs in the eCRF.

8.2.6 *Prior and Concomitant Medications*

Prior and concomitant medications will be included as a safety evaluation in this study and will be monitored from the time that the child's parent(s)/guardian(s) give informed consent to the end of the study (as defined in Section 4.3.2).

8.2.7 *Body Weight and Height*

Body weight will be measured at screening, at Day 1 of each treatment, at Week 16 of each treatment and at the end of study visit or early withdrawal.

Height will be measured at Day 1 of Treatment 1, at Week 16 of each treatment and at the end of study visit or early withdrawal.

8.3 Total Blood Volume

The volume of blood to be taken for clinical chemistry and putative antibodies is described below:

For subjects' weighing ≥ 20 kg, the total scheduled volume of blood taken per subject during the course of the study will not exceed 39 mL. For subjects' weighing < 20 kg, the total scheduled volume of blood taken per subject during the course of the study will not exceed 29 mL. This is a safe and standard blood volume, appropriate to this study, and should cause no safety concerns.

8.4 Blood Samples for Putative Antibodies

Subjects will have blood samples collected prior to study treatment administration at baseline and at the end of study or early withdrawal, to test for the presence of BTX-A-Abs. CCI

[REDACTED]

Refer to Appendix 9 for a detailed description of sample collection.

9 STUDY TREATMENTS

9.1 Treatments Administered

It is forbidden to use the study treatment for purposes other than as defined in this protocol. Administration of the study treatment will be supervised by the Investigator, or designee.

At study entry, subjects will be randomised into one of the following three treatment groups for Treatment 1:

- Group A: Dysport 16 U/kg in one upper extremity (the study limb).
- Group B: Dysport 8 U/kg in the study limb.
- Group C: Dysport 2 U/kg in the study limb.

For Treatments 2, 3 and 4, subjects are planned to receive Dysport 8 U/kg or 16 U/kg according to the treatment allocation by the IRS and will remain double blind throughout the study.

CCI

[REDACTED] The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

9.1.1 *Dysport*

Dysport will be provided in a 3.0 mL glass vial containing 500 U (nominal) of BTX-A-HAC as a white lyophilised powder for reconstitution. Details of the drug composition and excipients are provided in the current Investigator's brochure for Dysport [24].

Dysport drug product should be stored at the recommended temperature (between 2°C and 8°C). The product does not contain any antimicrobial agent. It is therefore recommended that the product be used immediately after reconstitution. Dysport should not be frozen and should be protected from light.

9.1.2 *Administration Procedures*

Dysport will be reconstituted at the investigational site with preservative free 0.9% sodium chloride for injection. Detailed instructions will be provided for the volume which needs to be withdrawn from the reconstituted Dysport vials according to each subject's body weight and the group. The study treatment will be prepared by an independent reconstitutor (see Section 9.2.2) according to the instruction leaflet allocated for that treatment. The treatment allocation will be kept by the independent reconstitutor and must not be made available to any other members of the study team. A total of 1.6 mL of the reconstituted study treatment will be provided in syringes to the Investigators (or designee) performing the injection. This syringe will be labelled with the subject's study number without any dose information. Thus, the Investigator and subject will be completely blinded to the identity of the study treatment in the syringe and the dose. Regardless of the treatment group to which the subject is allocated, the volume of 1.6 mL will be constant across all dose groups.

All subjects will receive Dysport administered intramuscularly (see Section 9.1.3 for dosage). Electrical stimulation (ES) and/or ultrasound will be used to localise the targeted injection sites. Complementary techniques such as electromyography will be allowed in addition to ES and/or ultrasound. Description of the use of ES will be provided in the Study Manual.

For the injection, each participating centre should maintain their usual injection environment and procedures for their pain management strategies (e.g. use of general anaesthesia, topical anaesthesia, or oral, intranasal or rectal medication). The injection techniques and pain management strategies used will be recorded in the eCRF.

The study limb (left or right), the PTMG, muscles injected and volume injected (total and per muscle) will be documented in the eCRF.

9.1.3 *Treatment of the Study Upper Limb*

9.1.3.1 *Total Dose/Volume in the Study Upper Limb*

Subjects will receive Dysport 2 U/kg, 8 U/kg or 16 U/kg in the study limb in Treatment 1 and are planned to receive Dysport 8 U/kg or 16 U/kg in subsequent treatments according to the treatment allocation by the IRS (Table 1) and both Investigators and subjects will remain blinded to study treatment throughout the study. CCI

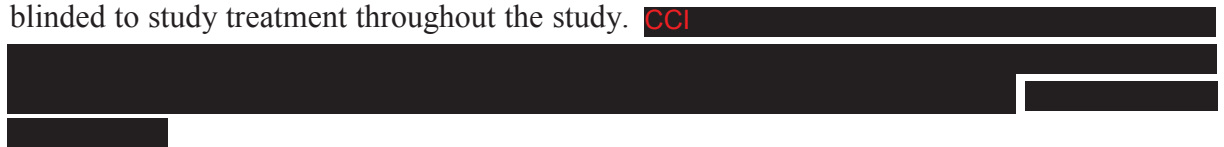


Table 1 Planned Dysport Dose Administered per Treatment Group

Group	Number of Subjects	Treatment 1 ^(a)	Treatments 2, 3 and 4 ^(a)
A	70	Dysport 16 U/kg	Dysport 16 U/kg
B	70	Dysport 8 U/kg	Dysport 8 U/kg
C ^(b)	70	Dysport 2 U/kg	Dysport 8 U/kg or Dysport 16 U/kg

^(a) The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

^(b) In this group, dynamic dose dispensing will be done by IRS at Treatment 2 to maintain a balance between subjects receiving 8 U/kg and 16 U/kg.

The dose for each subject will be calculated according to the subject's body weight, up to a maximum body weight of 40 kg (even if the subject weighs more than 40 kg and therefore a maximum total dose of 320 U in the 8 U/kg group and 640 U in the 16 U/kg group, [Table 2](#)). The allocated dose will be reconstituted with preservative free 0.9% sodium chloride for injection to a fixed volume of 1.6 mL for injection.

The IRS will be used to allocate packs and envelope numbers (to be considered to reconstitute the treatment) and then study treatment reconstitution will be performed by an independent reconstitutor who will not be involved in any other study related activities in order to maintain the blinding.

Study treatment will be supplied to the study centre in individual packs. Each pack will contain two vials of 500 U Dysport. The appropriate instruction leaflet, with detailed instructions for reconstitution will be provided outside of the treatment packs: one instruction leaflet for each of the possible doses 2 U/kg, 4 U/kg, 8 U/kg and 16 U/kg. The Sponsor will provide the injection materials (syringes and needles) for paediatric use to sites.

9.1.3.2 Primary Target Muscle Group

In Treatment 1, before performing the injection, the Investigator will select the study limb and the PTMG (either the elbow flexors or wrist flexors). The PTMG must have a baseline MAS score of greater or equal to 2 and must be the muscle group with the highest MAS score. The muscle group with the highest score will be the PTMG. If the baseline MAS score is the same for the elbow flexors and wrist flexors, the choice of PTMG will be left to the Investigator's judgement.

For Treatments 2, 3 and 4, the PTMG can be changed from elbow to wrist flexors or from wrist to elbow flexors, provided that the following criteria are fulfilled:

- The MAS score of the new PTMG must be higher than the MAS score of the previous PTMG, and
- The new PTMG must have a modified MAS score of greater or equal to 1+.
- The volume to be injected in the new PTMG should be equal to the volume presented in [Table 2](#) if clinically indicated.

9.1.3.3 Dose/Volume by Muscle

The entire volume for injection (1.6 mL) will be injected and will be divided between the PTMG (elbow flexors or wrist flexors) and a number of additional muscles selected by the Investigator according to the disease presentation.

The volume injected into the additional muscles must not exceed that specified in the dosing paradigm in [Table 3](#). No more than 0.5 ml will be injected per injection site.

The injection volume, number of injection sites and dose by muscles in the PTMG are provided in Table 2. Those are mandatory for the PTMG at treatment 1 and should be applied at other treatment cycles if clinically indicated.

- If elbow flexors are chosen as the PTMG, both brachialis and brachioradialis have to be injected at the injection volume specified in Table 2.
- If wrist flexors are chosen as the PTMG, both flexor carpi radialis and flexor carpi ulnaris have to be injected at the injection volume specified in Table 2.

Table 2 Injection Volumes, Dose per Muscle and Number of Injection Sites in the Primary Targeted Muscle Group

For Primary Targeted Muscle Group (PTMG)	Injection Volume (mL)	Number of Injection Sites	Dose per Muscle in U/kg / Maximum U		
			Low 2 U/kg	Medium 8 U/kg ^(a)	High 16 U/kg ^(a)
Elbow flexors					
Brachialis	0.6	2	0.75 U/kg/30 U	3 U/kg/120 U	6 U/kg/240 U
Brachioradialis	0.3	1	0.375 U/kg /15 U	1.5 U/kg/60 U	3 U/kg/120 U
Wrist flexors					
Flexor carpi radialis	0.4	1 - 2	0.5 U/kg /20 U	2 U/kg/80 U	4 U/kg/160 U
Flexor carpi ulnaris	0.3	1	0.375 U/kg /15 U	1.5 U/kg/60 U	3 U/kg/120 U

^a The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

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9.1.3.4 Dose/Volume at Treatment 2, 3 and 4

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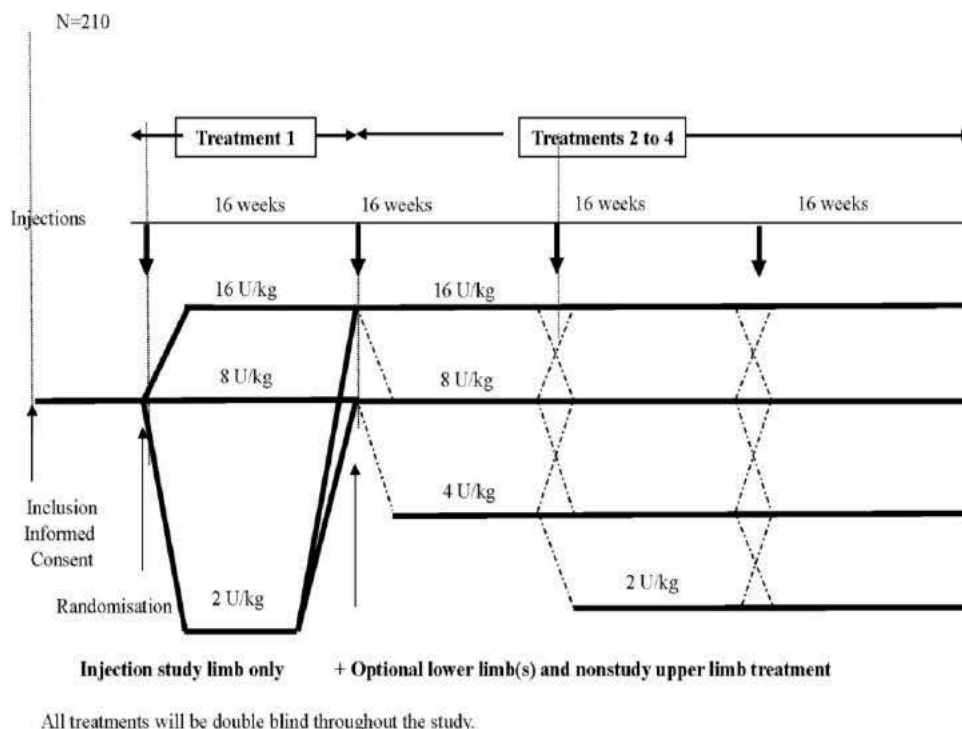
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[Redacted]	[Redacted]	[Redacted]
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Figure 2 Dose Modifications Available During the Study



9.1.3.6 Dosing Interval (Applicable to all Treatments) and reinjection criteria

The planned retreatment interval is 16 weeks and a maximum of four treatments will be administered.

At Week 16, subjects will be assessed for their eligibility to receive the next treatment. Subjects who are eligible for retreatment will be given the next treatment. In the unforeseeable event that the injection cannot be administered at the scheduled visit due to any technical or logistical reasons, an unscheduled visit can be arranged within the 2 week visit window.

The duration of the follow up period will be dependent upon the treatment interval as follows:

- All subjects whose first three treatment intervals fall between ≥ 16 and ≤ 22 weeks will receive four treatments and will exit the study as soon as a new injection is required and no later than 22 weeks after last injection (up to a maximum of 1 year and 9 months study duration).
- All other subjects will not be given any further study treatment after Week 52 and will exit the study after 16 weeks of follow up of the last treatment.

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9.1.4 *Concomitant Treatment of Lower Limb Spasticity and the Non-study Upper Limb*

For Treatments 2, 3 and 4, injection into the lower extremity/extremities and the non-study upper limb will be allowed at the same time as the study limb is injected. Muscle(s) for injection will be selected according to the Investigator’s judgement.

If there is no need to inject the lower limbs, and only the non-study upper limb is to be injected (on top of the study upper limb), the dose in the non-study upper limb should not exceed the dose detailed in Table 5 below:

Table 5 Maximum Dose for Non-study Upper Limb

Body Weight (kg)	Maximum Dose
10 to 40	5 U/kg, calculated up to 40 kg
40 and over	200 U

For dose by muscle, please refer to table 8

If there is no need to inject the non-study upper limb and only one or two lower limb(s) are to be injected (on top of the study upper limb), the dose in the lower limb(s) should not exceed the dose detailed in Table 6 below:

Table 6 Maximum Dose for the Lower Limb(s)

Body Weight (kg)	Maximum Dose
10 to 36	10 U/kg, calculated up to 36 kg
36 and over	360 U

For dose by muscle, please refer to table 9

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No more than 0.5 ml will be injected per injection site.

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9.2 Subject Identification and Allocation to Study Treatment

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required. At screening, potential subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be given a randomisation number and allocated to one of the treatment groups specified in Section 9.1.

9.2.1 *Randomisation*

Randomisation will be done with an IRS and will be in a 1:1:1 ratio. Stratification will be performed according to age range (2 to 9 years and 10 to 17 years) and BTX naïve or non-naïve status assessed at baseline.

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Any subject meeting the randomisation criteria will be assigned a randomisation number in his/her stratum and allocated to the associated treatment arm. At the randomisation and at each next dispensation, a treatment number and an envelope number will be then allocated to the subject and the corresponding treatment will be administered to the subject after the drug is reconstituted according to the subject's body weight and assigned leaflet.

This IRS service provides Investigators, site co-ordinators and project team members with a 24 hour per day, 7 day per week service. In case of medical or technical randomisation queries, a 24 hour helpline is available (see supporting information in the Investigator Site File). Additional details can be found in the IRS reference manual provided to each site.

Randomised subjects who terminate their study participation for any reason before administration of the drug assigned by IRS will retain their randomisation, envelope and treatment numbers, i.e. the envelope and treatment numbers will not be reused. The next subject is given another randomisation number, another envelope number and another treatment number even if he/she should receive the same treatment. Subjects who leave the study early will not be replaced.

The Sponsor's Randomisation Manager will keep the master lists. A copy of the list of randomisation and envelope numbers (Lists A and B) will be confidentially supplied to the independent statistician in the DSMB and the Contract Research Organisation (CRO) in charge of the central randomisation allocation. The master lists and the copies supplied to the CRO in

charge of the IRS will be kept confidential in a secure location. Access to the randomisation lists must be restricted until authorisation is given to unblind for final analysis.

9.2.2 *Blinding, Emergency Envelopes and Breaking the Blind*

All of the study treatment kits will contain two vials of Dysport 500 U. But, there will be four instruction leaflets (2 U/kg, 4 U/kg, 8 U/kg and 16 U/kg). Consequently, to maintain the blinding of study treatment, a nurse or a pharmacist, independent of the project team, will be in charge of the preparation of each individual subject's study treatment according to the assigned envelope number. This person will be fully trained in the method of preparing the syringes, and will be instructed not to convey the dose allocation to anyone else, including other members of the study team and Investigator. They will also be made aware of the importance of their role in maintaining the blind for the subject, the Investigator and the remainder of the project team. The randomisation manager will produce a treatment allocation envelope for each envelope number. So, an assigned envelope will have to be opened by the person in charge of the drug reconstitution to know the dose leaflet to be considered. The assigned envelope is strictly to be opened by the independent reconstitutor and annotated with the opener identification and the date in order to allow identification of the correct reconstitution leaflet to be used. Then after the drug preparation, it will be re-sealed by the independent reconstitutor. The unblinded monitor will open and check these envelopes for verification, then date, sign and reseal them. The independent reconstitutor will play no other part in any other study activities.

Whenever a situation arises necessitating knowledge of a subject's study treatment, the Investigator should first contact the Pharmacovigilance/Emergency contact, as outlined in the front of the protocol, prior to code-break to review the status of all pertinent information. The Pharmacovigilance/Emergency contact will discuss all pertinent information surrounding the case with the Investigator, to determine if the situation justifies knowledge of the dose allocation.

Where necessary the Investigator and the Central Department of Pharmacovigilance at Ipsen may break the blind by logging onto the IRS centre/system to obtain the subjects treatment dose identification. In addition, hard copy sealed code-break envelopes will be held by the Central Department of Pharmacovigilance at Ipsen, in case of IRS failure. This set of envelopes based on the envelope numbers, will be produced by the randomisation manager.

If code-break was performed using the IRS, the Investigator must store the email notification revealing unblinded treatment in a sealed envelope. The Investigator will then sign, date and provide reason for the code-break on the Emergency Code-break form, and on the sealed envelope. The date and reason for identifying the treatment group will be recorded in the eCRF.

9.3 *Study Treatment Supply, Packaging and Labelling*

The study treatment will be packaged and released by the CTSU, Beaufour Ipsen Industrie and delivered to the investigational sites or interim storage facility. A sufficient quantity of study treatment will be supplied as well as an acknowledgement of receipt form.

The Sponsor's representative will receive a Certificate of Analysis for which batch of study treatment has been used under their study, and the Certificate of Compliance which reflects the product release statement.

The core label texts for all treatment packs will be translated or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A description of the core text of the treatment pack labels is displayed below:

- Sponsor name, address and telephone number.
- Study number.
- Name of study treatment with strength and potency.
- Pharmaceutical dosage form and quantity of dosage unit.

- Route of administration.
- Batch number.
- Treatment number.
- Specific blank spaces to enter the subject number and envelope number (completed by the Investigator).
- For clinical study use only. In the US: ‘Caution: New Drug Limited by Federal (United States) Law to Investigational Use.’
- Investigator name/site (completed by the Investigator).
- Storage conditions.
- Expiry date.
- Directions for use.

The Investigator, or designee, will only dispense study treatment to subjects included in this study. Each subject will only be given the study treatment carrying his/her number. The dispensing for each subject will be documented in the eCRF.

9.4 Compliance

Study treatment will be administered intramuscularly at the clinic by the Investigator, thus, subject compliance with treatment is not expected to be an issue. Drug accountability records will be maintained by the independent reconstitutor documenting that subject received allocated drug.

9.5 Study Treatment Storage and Accountability

The Investigator, or an approved representative (e.g. pharmacist), will ensure that all study treatment is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements and will be reconstituted and dispensed by qualified staff members.

All study treatments are to be accounted for on the study treatment accountability log provided by the Sponsor. It is essential that all used and unused supplies are retained for verification (by the Sponsor or Sponsor’s representative). The Investigator should ensure adequate records are maintained via the study treatment accountability log.

The destruction of unused study treatments should be carried out on site only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. The study treatments will be destroyed preferably on site or at the interim storage facility or returned to CTSU CCI

9.6 Concomitant Medication/Therapy

The following concomitant medications/therapies are not permitted during this study (see also Section 6.3):

- Botulinum toxin for administration into any site of the body other than Dysport in the study limb (or in the non-study upper limb and/or in the lower limbs for Treatments 2, 3 and 4).
- Any investigational new drug or device or off label use of any drug.
- 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 ± 30 days of any study treatment.
- Intrathecal baclofen therapy.
- Phenol or alcohol injection affecting the study limb.

The following concomitant medications are permitted during this study but they must be monitored closely and every effort should be made to keep concomitant spasticity treatment

constant throughout the course of the study. However, changes in pain medication are acceptable if absolutely necessary and according to clinical judgement (see also Section 6.3):

- Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for the 4 weeks prior to study treatment and is expected to remain at this stable dose throughout the study.
- Concomitant treatment with dantrolene, tizanidine, gabaergic drugs, opioid, oral baclofen or other antispasticity agents like benzodiazepines should be kept at the same dose throughout the study.

The following conditions apply for physiotherapy, occupational therapy or use of splints and/or orthoses:

- If undergoing pre-study therapy, such physiotherapy, occupational therapy or use of splints and/or orthoses, therapy must have been initiated at least 30 days prior to the baseline visit and agreed to continue the therapy throughout the study and at the minimum, up to Week 16 following the first treatment administration.
- No physiotherapy, occupational therapy or use of splints and/or orthoses should be initiated less than 30 days prior to the baseline visit or during the course of the study up to Week 16 following the first treatment administration.
- Initiation of physiotherapy, occupational therapy or use of splints and/or orthoses after Week 16 following the first treatment administration will be allowed.
- Physiotherapy and occupational therapy sessions, or use of splints and/or orthoses will be documented in the subject diary and eCRF.
- Instructions for home exercises will be provided to the parents/guardians/caregivers and/or subjects to encourage use of the muscle groups injected in the study. These instructions will be given at the baseline visit and the instructions will be adapted based on the subject's need through the study. The use of home exercises will be documented in the eCRF. School therapy will also be allowed during term time.

9.7 Treatment of Overdose of Investigational Medicinal Product

Excessive doses of BTX-A may produce distant and profound neuromuscular paralysis. Overdose may lead to an increased risk of the neurotoxin entering the bloodstream and may cause complications associated with the effects of oral BTX poisoning (e.g. deglutition disorder and dysphonia). Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. There is no specific antidote (antitoxin should not be expected to be beneficial) so general supportive care is advised. In the event of overdose, the subject should be medically monitored for any signs and/or symptoms of excessive muscle weakness and/or muscle paralysis. Symptomatic treatment should be instigated if necessary. The signs and/or symptoms of overdose may not present immediately following treatment. Should accidental treatment or oral ingestion occur, the person should be medically supervised for several weeks for any signs and symptoms of excessive muscle weakness or muscle paralysis.

Any appropriate treatment of overdose of study treatment will be determined by the Investigator according to the characteristics of the events and will be recorded in the subject's eCRF. An event resulting from an overdose of the study treatment is not considered as serious unless it meets the definition of a serious adverse event (SAE) and consequently should be reported on the SAE form (see Section 10.3).

10 ADVERSE EVENT REPORTING

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can

be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no study treatment has been administered.

This definition includes events occurring from the time of the child's parent(s)/guardian(s) giving informed consent until the end of the study (as defined in Section 4.3.2).

10.1 Categorisation of Adverse Events

10.1.1 Intensity/Severity Classification

Adverse events will be classified as mild, moderate or severe according to the following criteria:

- Mild: Symptoms do not alter the subject's normal functioning.
- Moderate: Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject.
- Severe: Symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.

10.1.2 Causality Classification

The relationship of an AE to the study treatment will be classified according to the following:

- Related: Where there is good reason(s) and sufficient evidence (e.g. plausible time sequence, dose response relationship, known pharmacology of study treatment) to assume a causal relationship with the study treatment in the sense that it is plausible, conceivable or likely.
- Not related: Where there is good reason(s) and sufficient evidence (e.g. implausible time sequence and/or event could be attributable to a concurrent disease or concomitant drug) to rule out a causal relationship with the study treatment.

10.1.3 Assessment of Expectedness

The reference safety document to be used for assessing the expectedness of AEs in this study will be the Investigator's brochure [24].

10.1.4 Adverse Events of Special Interest

The effects of Dysport and all BTX products may spread from the area of injection to produce symptoms consistent with BTX effects. These symptoms have been reported hours to weeks after injection. Remote spread of toxin that affects swallowing and breathing can be life threatening, and there have been reports of death. The risk of symptoms is increased in subjects who have underlying conditions (e.g. disorders of the neuromuscular junction) that would predispose them to these symptoms. Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation. Adverse events of special interest (AESIs) for Dysport are AEs that suggest a possible remote spread of effect of the toxin or hypersensitivity. A list of preferred terms of AESIs is provided in the Statistical Analysis Plan. All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. These AESIs will be further analysed to determine if there is a plausible possibility that they represent distant spread of toxin or hypersensitivity. In order to perform the analysis, variables including alternate aetiology (medical history, concomitant medication, or diagnosis which could account for the symptoms), location of Dysport administration, and temporal relationship to Dysport administration will be considered by the sponsor.

10.1.5 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in the schedule of administration (change in dosage, delay in administration, study treatment discontinuation).
- They require intervention or a diagnosis evaluation to assess the risk to the subject.
- They are considered as clinically significant by the Investigator.

10.1.6 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs.

10.1.7 Other Investigation Abnormal Findings

Abnormal objective test findings considered by the Investigator as clinically significant (e.g. ECG or vital signs changes) and that result in a change in study treatment dosage or administration schedule, or in discontinuation of the study treatment, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

10.2 Recording and Follow up of Adverse Events

At each study visit the subject should be asked a nonleading question such as: ‘do you feel different in any way since starting the new treatment/the last assessment?’

All observed (or volunteered by subject or parent/guardian) AEs, regardless of treatment group or suspected causal relationship to study treatment, will be recorded on the AE page(s) of the eCRF.

Any AEs already recorded in the eCRF and designated as ‘continuing’ should be reviewed at each subsequent visit and the AE log of the eCRF updated as appropriate to reflect the clinical evolution of the event (e.g. outcome changed from ongoing to recovered and event end date added).

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. study treatment or other cause).

For each AE recorded, the Investigator must provide their opinion on causal association (i.e. whether they consider the AE related/not related to study treatment). Follow up is required until the event and/or its sequelae either resolves completely or stabilises to a level acceptable to the Investigator and the Sponsor’s clinical monitor or his/her designated representative.

10.3 Serious Adverse Events

10.3.1 Definitions

All SAEs (as defined below) regardless of treatment group or suspected causal relationship to the study treatment must be reported immediately (within 24 hours of the Investigator’s knowledge of the event) to the Sponsors Pharmacovigilance department. If the immediate report is submitted by telephone, this must be followed up by a detailed written report using the SAE report form provided.

An SAE is any AE occurring that at any dose:

- (1) Results in death.

- (2) Is life threatening, that is any event that places the subject at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.
- (3) Results in inpatient hospitalisation or prolongation of an existing hospitalisation, excluding admission for social or administrative reasons (see further).
- (4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal daily life functions.
- (5) Results in a congenital anomaly/birth defect in the offspring of a subject who received the study treatment.
- (6) Is an important medical event that may not result in death, be life threatening, or require inpatient hospitalisation but where, based upon appropriate medical judgement, may jeopardise the subject and may require medical and/or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse.
 - **Hospitalisation** is defined as any formal inpatient admission. For any subjects already hospitalised, hospitalisation also includes any transfer within the hospital (or to another hospital) to an acute/intensive care unit.
 - **Prolongation of hospitalisation** is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for admission, **as determined by the Investigator or treating physician**.
 - **Prolongation in the absence of a precipitating, treatment emergent, clinical AE** (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for 'seriousness' but is not an AE and thus is not subject to immediate reporting to the Sponsor.
 - **Pre-planned or elective treatments/surgical procedures** should be noted in the subject's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

10.3.2 Reporting Requirements

All SAEs must be reported immediately (within 24 hours), irrespective of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period.

All SAEs that occur during the study period or within 90 days following the administration of study treatment (whichever is the greater), including those events occurring in drop outs, must be reported within 24 hours of the Investigator's knowledge of the event regardless of causality.

10.3.3 Mandatory Information for Reporting a Serious Adverse Event

For every SAE, the following information is the minimum that must be provided to the Sponsors' Pharmacovigilance department:

- Study number.
- Centre number.
- Subject number.
- The AE that met the seriousness criterion/criteria.
- Seriousness criteria.

- Causality assessment (if there is not enough information for the Investigator to provide definitive causality opinion, the Investigator must assign provisional causality based on the available information. The causality will be reassessed if more information becomes available).

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

10.3.4 Reporting Exemptions

There are no applicable exemptions for this study.

10.4 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication.

The outcome of any pregnancy will then need to be collected even if this occurs after the end of the study. Information regarding pregnancies must be collected on the AE page of the eCRF and on the Standard Pregnancy Report Form, including pregnancies with normal progress and outcome. A Standard Pregnancy Report Form must be completed by the Investigator and provided to the Sponsor's Pharmacovigilance department within 24 hours of the knowledge of the pregnancy in any study subject.

Investigators must instruct all female subjects to inform them immediately should they become pregnant during the treatment phase of this study. The Investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until the outcome of the pregnancy becomes known, which may involve follow up after the subject's involvement in the study has ended.

Pregnancies with a conception date within the study period or 90 days of the subject being dosed with study treatment including those occurring in drop outs must also be reported to the Investigator for onward reporting to the Sponsor.

10.5 Deaths

All AEs resulting in death that occur either during the study period or within 90 days following the administration of study treatment (whichever is greater), must be reported as an SAE within 24 hours of the Investigator's knowledge of the event.

The convention for recording death is as follows:

- Adverse event term/verbatim: should be the primary cause of death (e.g. pneumonia, myocardial infarction).
- Outcome: fatal.

The **only exception** is where the cause of death is unknown at the time of reporting. In this case and pending confirmation on the actual cause of death a verbatim of 'sudden death' or 'unexplained death' is appropriate. When the actual cause of death becomes known then the eCRF and the SAE report form should be updated to reflect the cause of death.

10.6 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to an AE should be distinguished from discontinuation/withdrawal due to insufficient response to the study treatment (see Section 6.4 and Section 6.5). Every effort should be made to try to attribute withdrawal to a single episode of a particular AE and not AEs in general.

If the study treatment is discontinued due to an SAE it must be reported immediately to the Sponsor (see Section 10.3).

In all cases, the Investigator must ensure the subject receives appropriate medical follow up (see Section 10.2).

10.7 Reporting to Competent Authorities/Independent Ethics Committees/Institutional Review Boards/Other Investigators

The Sponsor will ensure that processes are in place for the submission of reports of Suspected Unexpected Serious Adverse Reactions occurring during the study to the Competent Authorities (CAs), IECs, IRBs and all other Investigators concerned with the study treatment. Reporting will be done in accordance with the applicable regulatory requirements.

For study centres in the United States of America, Investigational New Drug Safety Reports will be submitted directly to the Investigators. It is the Investigators' responsibility to notify their IRB in a timely manner.

11 STATISTICAL CONSIDERATIONS

11.1 Subject Classification and Definitions

Enrolled subject:	Subject fully informed about the study whose parent(s)/guardian(s) have given written informed consent to participate (before any occurrence of study related procedure).
Screened failure subject:	Enrolled subject who fails to fulfil one or more entry criteria and thus does not proceed to the treatment phase of the study. Although not exposed to study treatment, they may have been exposed to some study related procedures. Records up to the time of premature termination should be completed including the reason for termination.
Treated subject:	Enrolled subject who is treated with at least one dose of study treatment.
Randomised subject:	Enrolled subject who is allocated to a treatment group at random.
Study completed subject:	Randomised/treated subject who has completed at least 52 weeks of follow up
Drop out:	Randomised/treated subject who did not complete the study and/or treatment.

11.2 Analyses Populations Definitions

Screened population:	All subjects enrolled.
Randomised population:	All subjects randomised.
Safety population:	All randomised subjects who received at least one injection of the study treatment.
modified Intent to treat population (mITT):	All randomised subjects who received at least one injection of the study treatment and had a MAS score in the PTMG assessed both at baseline and at Treatment 1, Week 6.
Per protocol (PP) population:	All subjects from the mITT population who are not major protocol violators between baseline and the Treatment 1, Week 6 visit (inclusive).

11.2.1 Populations Analysed

For the efficacy analyses, the primary population will be the mITT population, a secondary population of interest will be the PP population.

The safety analyses will be performed based on the safety population.

11.2.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol Deviations Document (PDD) and its impact on the membership to each analysis population (i.e. mITT, PP and safety populations) for any subject having experienced it will be specified.

The list of major protocol deviations impacting the PP population membership in the latest version of the PDD will be reviewed during the blind data review meeting held prior to database lock, before any unblinding of treatment groups. If necessary, that list will be updated to include any additional major protocol deviation impacting the PP population membership.

11.3 Sample Size Determination

The sample size required for this study has been determined on the basis of the sample size estimate for each of the three criteria to be considered (superiority of any of the two tested Dysport doses to Dysport 2 U/kg on the primary efficacy endpoint, superiority of any of the two tested Dysport doses to Dysport 2 U/kg on the first secondary efficacy endpoint, and proper assessment of the long term safety of the two tested Dysport doses); the largest of these three estimates is used as the sample size of the study.

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Sample Size of the Study

Given the above sample size estimates, a targeted study sample size of 210 randomised subjects (i.e. 70 randomised subjects per treatment group) is considered sufficient to meet both the primary efficacy objective and the long term safety objectives.

Using a sample size of 210 as the largest of the three required figures means the actual power for the testing on the primary efficacy endpoint and the testing on the first secondary efficacy endpoint rises to 99% and 99%, respectively. As a result, the actual power of the study to detect a significant effect of any tested Dysport dose for both efficacy endpoints (US-targeted methodology) is 98% (= 99% x 99%).

11.3.1 Significance Testing and Estimations

The statistical testing of the primary efficacy endpoint is fully described in Section 11.4.3.

Unless otherwise specified, all statistical tests performed on Treatment 1 efficacy endpoints will be conducted at a two-tailed α level of 0.05 and each tested Dysport dose group (8 U/kg and 16 U/kg) will be compared to Dysport 2 U/kg separately.

Descriptive statistics will include n, n missing, and:

- Mean, standard deviation, minimum, median, maximum and 95% confidence for means for interval-type variables.
- Counts and percents of each category for categorical nominal variables.
- Both for categorical ordinal variables.

No statistical tests will be performed on the efficacy endpoints for Treatments 2, 3 or 4.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the Sponsor's Statistics Department.

A Statistical and Analysis Plan describing the planned statistical analysis in detail with table, figure and listing templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS®).

Unless otherwise specified, all summary efficacy tables will be presented by treatment group and overall. Unless otherwise specified, all summary safety tables will be presented by treatment group, total dose group and overall.

For the efficacy and safety parameters the Baseline (Treatment 1, Day 1) assessments will be considered for the analyses of the changes.

11.4.1 Demographic and Other Baseline Characteristics

All demographic and baseline characteristics will be listed by treatment group and subject identification (ID).

Summary statistics for demographic and baseline characteristics will be presented by treatment group for the mITT population.

11.4.1.1 Homogeneity of Treatment Groups

Demographic and baseline characteristics will be summarised, but not compared between treatment groups by formal statistical testing.

11.4.1.2 Subject Disposition and Withdrawals

A listing of all visit assessment dates (relative days) will be presented by treatment group and subject ID.

For each subject's population of interest, a summary table and a flow chart will present by treatment group the number of subjects assessed at each scheduled visit. Reasons for study withdrawal will be summarised at each visit.

A summary table will present the study duration, both overall and by treatment group.

Counts and percents of subjects with any major protocol violations will be tabulated by treatment group. Similarly, reasons for exclusion from the PP population will be presented by treatment group.

11.4.2 Pharmacokinetic Data

There are no pharmacokinetic analyses planned for this study.

11.4.3 Efficacy Evaluation

CCI
[Redacted]

CCI
[Redacted]

[Redacted]

11.4.3.3 Similarities Between the Two Statistical Methodologies Planned for the Efficacy Analyses

The following will be applied in the same way for the two statistical methodologies planned for the efficacy analyses:

Statistical Analyses

The primary efficacy endpoint will be analysed using an ANCOVA on the rank. This model will include treatment group, the baseline value, the two stratification factors (age range and BTX treatment naive status at baseline) and the pooled centre as fixed covariates. A sensitivity analysis will be performed using the Proportional Odds Model (POM).

The first secondary efficacy endpoints will be analysed using an ANCOVA on the rank. This model will include treatment group, the two stratification factors and the pooled centre as fixed covariates. A sensitivity analysis will be performed using the POM.

Other efficacy endpoints will be analysed according to their scale (categorical or continuous), using ANCOVA on the rank, ANCOVA or Logistic regression for Treatment 1. For Treatment 2 to treatment 4, only descriptive statistics will be performed.

Centre Effect

In order to assure that the centre effect will be properly estimated in both types of model, it is necessary to only consider the centres with a sufficient number of recruited subjects.

Therefore, it has been decided to apply the following approach:

- the centres having recruited at least six subjects will be taken into account for the estimate of the centre effect.
- the centres having recruited less than six subjects will be pooled with one (or several) centre(s) within the same country (or across countries within the same region) until the number of subjects in the resulting pooled centre(s) is at least equal to six. Then, only the pooled centre(s) will be taken into account for the estimate of the centre effect.

With such an approach, all the centres (original or pooled) considered for the estimate of the centre effect will account for at least six recruited subjects.

Missing Values

In order to assess the impact of the missing values of the primary efficacy endpoint for the withdrawals between the baseline visit and the Treatment 1, Week 6 visit, the primary analysis performed on the assessed values of the primary efficacy endpoint will be completed with a sensitivity analysis performed on the population of all randomised subjects who received at least one injection of study treatment. Within that population, any missing assessment on the MAS at Treatment 1, Week 6 visit will be imputed with the assessment on the MAS at the baseline visit (conservative approach).

The results of the sensitivity analysis will be taken into account to assess the robustness of the results of the primary analysis.

- In view of registration in the US only
In order to assess the impact of the missing values of the first secondary efficacy endpoint for the withdrawals between the baseline visit and the Treatment 1, Week 6 visit as well as for subjects not assessed in the mITT population, the primary analysis performed on the assessed values of the first secondary efficacy endpoint will be completed with the following two sensitivity analyses performed on the population of all randomised subjects who received at least one injection of study treatment:
 - First sensitivity analysis: any missing assessment on the PGA at Treatment 1, Week 6 visit will be imputed with the assessment 'markedly worse' (intermediate conservative approach).

- Second sensitivity analysis: any missing assessment on the PGA at Treatment 1, Week 6 visit for a subject in a higher dose Dysport group will be imputed with the assessment 'markedly worse' and any missing assessment on the PGA at Treatment 1, Week 6 visit for a subject in the low dose Dysport group will be imputed with the assessment 'markedly improved' (most conservative approach).

The results of the two sensitivity analyses will be taken into account to assess the robustness of the results of the primary analysis.

11.4.3.4 Adjustment for Country/Centre Effect

For the primary efficacy endpoint only, a sensitivity analysis will be conducted in order to investigate homogeneity of treatment response across centres: the ANCOVA on the rank will be re-run, adding the treatment by centre interaction term. If the p-value from the interaction term in the model is lower than 0.1 then the treatment by centre interaction will be deemed statistically significant and it will be concluded that the treatment effect is not constant from centre to centre. If this is the case then the influence of centre on the treatment effect will be investigated by estimating and plotting the treatment groups differences (for any of the two higher doses of Dysport, least square means difference Dysport higher dose - Dysport low dose) separately for each centre.

11.4.4 Safety Evaluation

The safety endpoints of the study are:

- Treatment emergent adverse events.
- Vital signs (systolic and diastolic BP and HR): absolute values and change from Baseline at each visit to the study centre.
- Body weight and height: absolute values and change from baseline at Week 16 of each treatment and at the end of study visit or early withdrawal.
- Clinical chemistry (including serum ALP - total and bone isoenzyme, and glycosylated HbA1c): absolute values and change from Baseline at Treatment 1, Week 16 (serum ALP - total and bone isoenzyme, and HbA1c only) and at the end of study visit or early withdrawal.
- Presence of BTX-A-Abs at baseline and at the end of study visit or early withdrawal.
- A 12-lead ECG: absolute values and change from Baseline in ECG parameters and morphology at Treatment 1, Week 6 and at the end of study visit or early withdrawal.

All safety data will be included in the safety data listings and summary tables will be produced on the safety population. Descriptive statistics will be provided for the safety endpoints.

Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version in force at the time of database freeze).

All AEs reported during the study will be presented in a listing which will be sorted by treatment group, subject ID, primary system organ class (SOC), preferred term, verbatim text and start date.

Listings of all SAEs, AEs leading to withdrawal and deaths reported during the study will also be presented by treatment group and subject ID.

A TEAE is defined as any AE that occurs during the treatment phase of this study if:

- (1) It was not present prior to the first of intake of study treatment, or
- (2) It was present prior to the first intake of study treatment but the intensity increases during the treatment phase of this study.
- (3) It was present prior to receiving the first dose of study treatment, the intensity is the same but the drug relationship became related during the active phase of the study.

An overall summary table of all AEs will be presented. In summaries of intensity, causality, and causality combined with intensity, subjects may be reported in more than one category in these tables according to how many different levels of intensity and causality are associated to the AEs they experience.

All TEAEs will be summarised overall and by treatment group with the number and percentage of subjects with TEAEs presented by primary SOC and preferred term. If a subject experiences more than one TEAE within a category (preferred term or primary SOC), the subject will be counted only once in that category.

In addition, TEAEs will be tabulated by decreasing overall preferred term frequency, intensity, causality, and causality combined with intensity.

In the event of multiple reports of the same preferred term for a subject, the maximum intensity (severe>missing>moderate>mild) and the most serious causality (related>not related) will be counted in the summary of TEAEs by intensity and causality.

The number of occurrences of TEAEs coded with the same preferred term will also be presented by treatment group.

All TEAEs will be flagged in the AE listing.

All SAEs and AEs leading to withdrawals will be summarised overall and by treatment group with the number and percentage of subjects with SAEs and AEs leading to withdrawals presented by primary SOC and preferred term.

Vital Signs

Vital signs data will be presented in a listing which will be sorted by treatment group, subject ID, and assessment visit. Any unscheduled assessments will be flagged in the listing.

Baseline values for each treatment group will be defined as the last measurements collected prior to administration of the study treatment.

For each treatment group, descriptive statistics on raw assessments and changes from baseline at each assessed study visit will be provided.

Laboratory Parameters

For clinical laboratory safety tests (clinical chemistry including serum ALP - total and bone isoenzyme, and HbA1c), all the abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented by treatment group and by subject ID for evaluations at baseline and at the end of study visit or early withdrawal.

Shift tables from baseline of the number and percentage of subjects with low, normal or high values will also be presented by treatment group.

The Presence of BTX-A-Abs

The number and percentage of subjects with the presence of BTX-A-Abs (both binding and neutralising) at baseline and at the end of study visit or early withdrawal will be compared between treatment groups.

Electrocardiograms

Summary statistics on the duration of QT/QTc interval and HR will be presented overall and by treatment group for each scheduled assessment visit and for both actual values and changes from baseline. Baseline values for each treatment group will be defined as the measurements collected at screening.

The number and percentage of subjects with duration of QT/QTc interval within the following three ranges of interest will also be presented overall and by treatment group for each scheduled assessment visit:

- >450 to 480 msec.
- >480 to 500 msec.
- >500 msec.

The number and percentage of subjects with an increase from baseline in the QT/QTc interval of >30 msec and >60 msec will also be presented overall and by treatment group for each scheduled post baseline assessment visit.

The number and percentage of subjects with any of the following ECG abnormalities will be provided overall and by treatment group for each scheduled assessment visit:

- Arrhythmias.
- Second degree AV block
- Third degree AV block.
- ST segment abnormalities.
- T-wave abnormalities.
- U-wave abnormalities.
- Myocardial infarction.
- Right bundle branch block
- Left bundle branch block.

Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the World Health Organisation Drug Dictionary (version in force at the time of database freeze).

The date of Day 1 will be used as the cut off date for the definition of a prior and a concomitant medication. A medication that started before the cut off date and is continuing will be considered as both prior and concomitant medications.

The number and percentages of subjects will be provided overall and by treatment group for prior and concomitant medications sorted by drug class and preferred drug name.

A listing will present by treatment group the prior and concomitant medications sorted by drug class and preferred drug name. Prior and concomitant medications will be flagged in the listing.

11.5 Subgroup Analyses

- Analysis on the primary and first secondary efficacy endpoints will be performed on the randomisation stratification factors i.e. age range and BTX status at baseline (naïve versus non-naïve) and on gender.
- Analysis on the MAS and PGA at Treatment 1 Week 6 and 16 will be performed according to physiotherapy/occupational therapy status at Treatment 1 Week 16 (subjects without physiotherapy nor occupational therapy before week 16 of treatment 1 versus subjects with physiotherapy and/or Occupational therapy without any change in the frequency between baseline and Week 16 of treatment 1).

Additional subgroup analyses may be performed according to clinical interest.

11.6 Final Analysis

A final analysis will be performed after the end of the study.

12 MONITORING PROCEDURES

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

12.1 Routine Monitoring

Sponsor assigned monitors will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's

activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs in a timely manner after the subject visit is performed and on an ongoing basis to allow regular review by the study monitor, both remotely via the internet and during site visits. This time period may be reduced at some specific stages of the study (e.g. end of study). The study monitors will use functions of the EDC system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the Sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as ID.

13 STUDY MANAGEMENT

13.1 Inspections and Auditing Procedures

Authorised personnel from external CAs and Sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 12.1, and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

13.2 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, should be clearly marked and permit easy ID of a subject's participation in the specified clinical study.

The Investigator must record all data relating to protocol procedures, study treatment administration, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The Investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF. Subject completed questionnaires will be printed.

All corrections on an eCRF and on source documents must be made in a way, which does not obscure the original entry. The correct data must be inserted, dated and initialled/authorised by study site personnel. If it is not obvious why a change has been made, a reason must be provided. The Investigator must, as a minimum, provide an e-signature to each eCRF casebook to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a casebook has been electronically signed, the Investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF. All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

13.3 Source Data Verification

As required by GCP, the Sponsor assigned monitor must verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The FDA 21 CFR Part 11 [42] is a regulation which provides criteria for acceptance by the FDA, under certain circumstances, of electronic records, e-signatures and hand written signatures executed to electronic records as equivalent to paper records and hand written signatures on paper.

The source documents must, as a minimum, contain the following: a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), study treatment administration, and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the Investigator and the Sponsor.

Definitions for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico technical departments involved in the clinical study).

The parent(s)/guardian(s) must have consented to the child's medical records being viewed by Sponsor authorised personnel, and by local, and possibly foreign, CAs. This information is included in the ICF.

13.4 Data Quality

Monitored eCRFs transferred from the investigational site to the assigned Data Management Group will be reviewed (secondary monitoring) for completeness, consistency and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator by the monitor for clarification/correction. The Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13.5 Data Management

Electronic data capture will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the e-signature of the person performing the action. This e-signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the hand written signature. Only Sponsor authorised users will get access to the eCRF as appropriate to their study responsibilities. Site users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO under the responsibility of the Sponsor's Data Management Department. All data management procedures will be completed in accordance with the Sponsor's and the CRO's Standard Operating Procedures.

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The Investigator will receive

their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail for the study, for archiving purposes and future reference.

Any queries generated during the data management process will be raised within the EDC system. It is the monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The Sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the Sponsor's Pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the Sponsor's Data Management Department. Concomitant medications will be coded using the World Health Organisation Drug Dictionary and AEs/medical history terms will be coded using MedDRA.

13.6 Study Management Committees

13.6.1 Data and Safety Monitoring Board

The DSMB will be composed of independent experts including one independent clinician who specialises in treating paediatric spasticity, one independent statistician and one independent pharmacovigilance expert. Data and Safety Monitoring Board meetings will take place as defined in the charter describing the operation of this committee and will depend on recruitment rate of the study. The first data review will take place after five subjects have been on treatment for at least 6 weeks or 4 months after the first subject has been randomised, whichever occurs first. Subsequent meetings will take place at intervals as defined by this committee.

Safety and efficacy data will be provided to the committee for their review. Possible recommendations that the DSMB can make regarding the conduct of the study are described in the charter. This includes recommending that the study is stopped for safety reasons.

The Chair of the DSMB will be responsible for communicating the committee's recommendations to Ipsen.

The DSMB charter will be available in the Trial Master File.

13.7 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

14 ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

As required by local regulations, the Sponsor's Regulatory Affairs Group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies and CAs prior to study initiation in regions where an approval is required.

14.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published or communicated to scientific meetings by the Investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical study agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical study agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period has expired as may be agreed in the contractual arrangements, including clinical study agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

14.3 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any child's parent(s)/guardian(s) have signed an ICF, regardless of whether the study is completed or prematurely terminated. Where appropriate, an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

14.4 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial Disclosure Statements will be completed, as required.

14.5 Insurance, Indemnity and Compensation

The Sponsor will provide product liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

15 PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required (see Section 5.1), it will be submitted per local regulations. However, for the countries within the European Union (EU), according

to the Directive 2001/20/EC, the protocol amendment will be classified into one of the following three categories:

- ***Nonsubstantial Amendments*** are those that are not considered ‘substantial’ (e.g. administrative changes) and as such only need to be notified to the IECs/IRBs or CAs for information purposes.
- ***Substantial Amendments*** are those considered ‘substantial’ to the conduct of the clinical study where they are likely to have a significant impact on:
 - the safety or physical or mental integrity of the subjects,
 - the scientific value of the study,
 - the conduct or management of the study, or
 - the quality or safety of the study treatment used in the study.

In the EU countries, substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the member states, approval or ‘favourable opinion’ can be assumed if the CA has raised no grounds for nonacceptance during an allocated time period (to be confirmed with the Sponsor’s Regulatory Affairs representative) following acknowledgment of receipt of a valid application to make a substantial amendment.

- ***Urgent Amendments*** are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.

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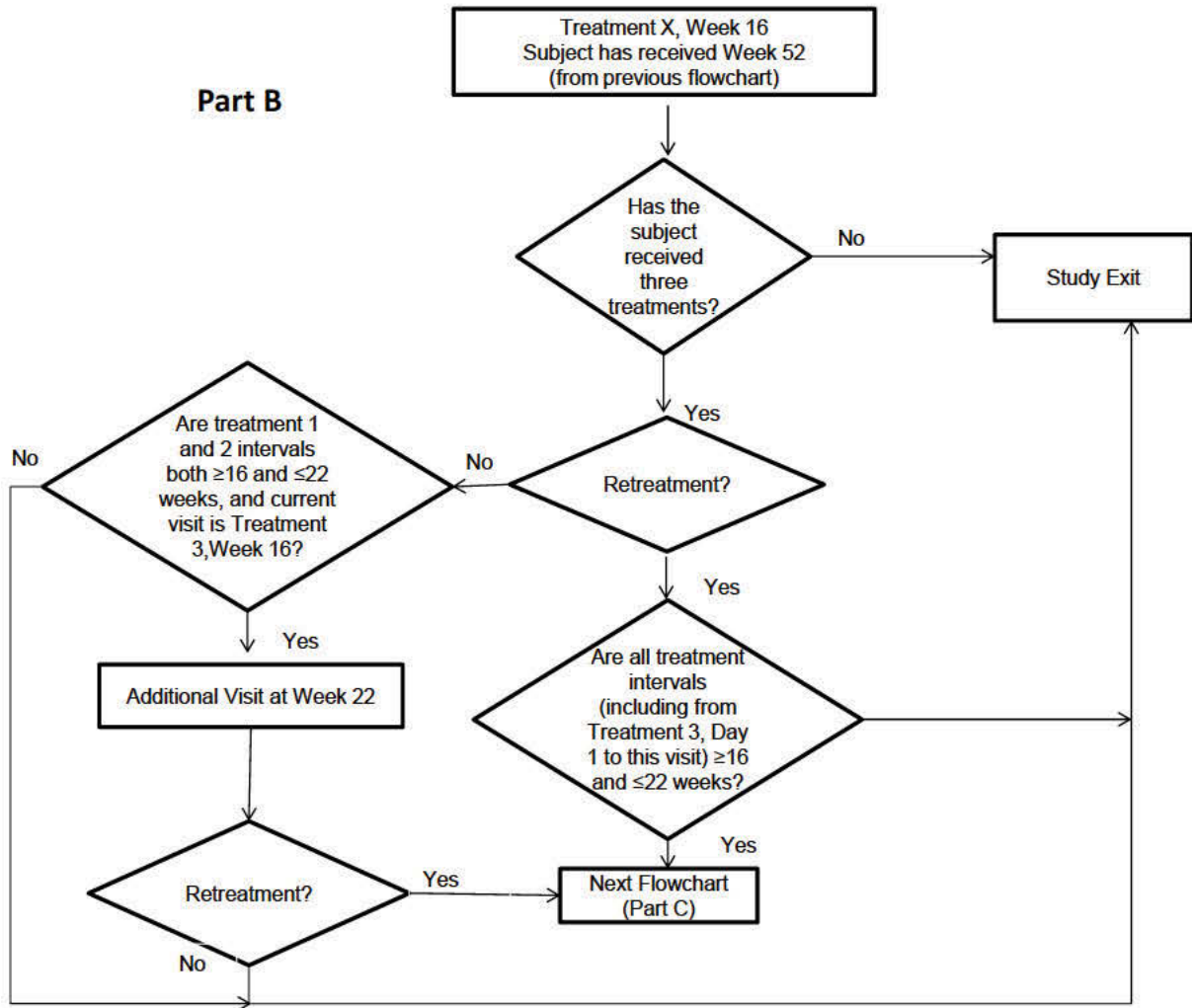
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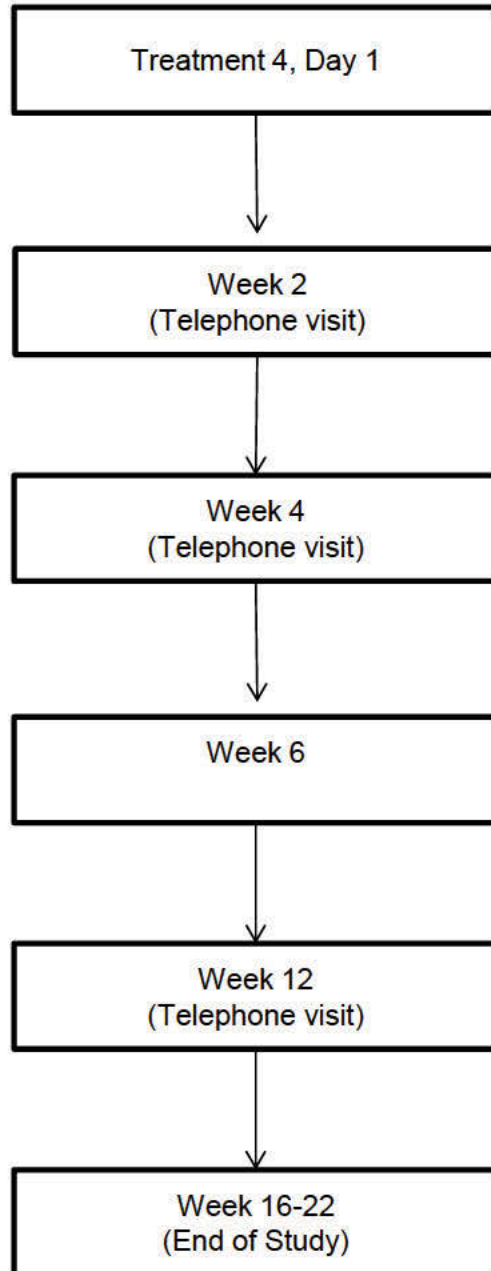
Appendix 2 Study Flow Chart

Figure 3 Study Flow Chart





Part C



Appendix 3 Modified Ashworth Scale

Modified Ashworth Scale

Muscle tone will be scored as follows:

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

Appendix 4 Goal Attainment Scale

Goal Attainment Scale For Measurement of Individual Therapy Goals

The GAS is a functional scale used to measure progress towards individual therapy goals. Individual goals will be defined for each subject by the physician, with the child's parents/guardians, prior to each treatment. Detailed instruction of goal setting and scaling is available in the study manual.

Identification of Goals and Goal Weighting

Parent(s)/guardian(s) and child, under the supervision of the physician should identify between one to three goals and categorise them into the sub-domains as listed in Table 13 for achievement. Goals chosen should fulfil the principle of SMART – Specific, Measurable, Attainable, Measurable and Timely. These chosen goals will be ranked according to their importance to the parent(s)/guardian(s)/child. If choosing more than one goal, one of them has to be chosen as very important and rank the other chosen goals accordingly (a little or moderately important). If only one goal is chosen, that goal will be rated as very important. After goal identification, the physician and/or therapist will rate the level of difficulty of each chosen goal.

Table 13 Domains / Subdomains of GAS Goals

Domain	Subdomain
Active Functions	Reaching
	Grasp and release
	Use of limb as a 'helping hand'/'to stabilise
	Involving affected arm more in daily activities
Passive Functions	Overall ease of care
	Hygiene
	Dressing
	Improve range of movement
	Donning/tolerating splints
Pain	Pain
Others	Other (please specify)

Importance Rating Scale:

- 1 = A little (important)
- 2 = Moderately (important)
- 3 = Very (important)

Difficulty Rating Scale:

- 0 = Not at all
- 1 = A little
- 2 = Moderately
- 3 = Very

Goal Attainment Scaling

Once the goals have been set, the next step is to define 'expected' outcome of each goal and scale it into the 5-point scale below. The outcome required in order to reach each score of the scale has to be determined at baseline (Treatment 1, Day 1) and before any subsequent treatment (Day 1 of Treatments 2, 3 and 4).

+2 = Much more than expected outcome

+1 = Somewhat more than expected outcome

0 = Expected outcome

-1 = Somewhat less than expected outcome

-2 = Much less than expected outcome

Post-treatment Visits Assessment

At each post-treatment visit, each chosen goal set for that treatment will be evaluated using the following scale:

+2 = Much more than expected outcome

+1 = Somewhat more than expected outcome

0 = Expected outcome

-1 = Somewhat less than expected outcome

-2 = Much less than expected outcome

The score for each goal is based on whether the subject has reached the predetermined level of achievement set out at the baseline and subsequent treatment visits.

Appendix 7 Manual Ability Classification System (MACS)

Information for users

The Mini-Manual Ability Classification System (Mini-MACS) is a classification system that describes how children with cerebral palsy (CP) aged 1–4 years use their hands when handling objects in daily activities. Ability is ranked on five levels based on the children's self-initiated ability and their need for assistance or adaptation when handling objects. This brochure also describes differences between adjacent levels to make it easier to determine the most appropriate level. Mini-MACS is a functional description that can be used as a complement to the supposed diagnose of CP and its subtypes.

The description concern how the children handle objects relevant for age. The objects referred to are those commonly found in the children's environment which they use when performing tasks, such as playing, drawing, eating, or dressing. How children handle toys often gives a good idea of their manual ability. Obviously, a 12-month-old child does not handle the same toys and other objects as a 4-year-old. A child's motivation and cognitive ability also influence the ability to handle objects and, consequently, the Mini-MACS level.

When assessing a child's Mini-MACS level, choose the level that best describes the child's usual performance in the daily environment. To better understand what a child usually does, and how he or she performs this activity, it is necessary to ask someone who knows the child well. The questions should be phrased to obtain a description of the type of objects the child handles, in what situations, and how. Mini-MACS levels reflect what the child usually does, not his or her best performance as demonstrated in a specific test situation.

Mini-MACS assesses the child's general ability to handle everyday objects, not the function of each hand separately. Mini-MACS does not intend to explain the underlying reasons for impaired manual capacity.

The Mini-MACS system spans the entire spectrum of functional limitation found among children with CP and covers all CP sub diagnoses. Level I includes children with minor limitations, if any, while children with severe disabilities are usually classified on level V. Certain CP subtypes can be found at all levels, e.g., bilateral CP, while unilateral CP usually occurs at levels I–III. Mini-MACS does not include children without physical disabilities; if it did, they would be classified as level "0". However, no such level exists!

Since Mini-MACS consists of only five levels, each level includes children with relatively varied function. Consequently, Mini-MACS is a classification system, probably not sensitive to changes and should therefore not be used to evaluate development or interventions. Mini-MACS can be used to describe and differentiate into five levels functional aspects on how a suspected CP diagnosis affects children's manual ability.

The five-level Mini-MACS scale is ordinal, which means that the differences between levels are not necessarily equal, nor are children with CP equally distributed across the five levels.

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Mini-MACS

Mini-Manual Ability Classification System for children with cerebral palsy 1 - 4 years of age

The Manual Ability Classification System (MACS) described how children aged 4–18 years with CP use their hands when handling objects in daily activities. Mini-MACS is an adaptation of MACS for children aged 1–4 years.

- Mini-MACS classifies children's ability to handle objects that are relevant for their age and development as well as their need for support and assistance in such situations.
- Mini-MACS describes how children usually use their hands to handle objects, such as toys, in various settings. In other words, it describes what they ordinarily do, rather than what is known to be their best capacity.
- Mini-MACS classifies the child's overall ability to handle objects, not the ability of each hand separately.
- To find out how a child handles various objects in everyday life, it is necessary to ask someone who knows the child well. Such knowledge cannot be obtained through specific testing. The questions should be phrased to obtain a description of the type of objects the child handles daily, in what situations, and how.

Mini-MACS

What do you need to know to use Mini-MACS?

Mini-MACS users need to find out what objects the child usually handles and how they handle them: with ease or difficulty, quickly or slowly, with precision or randomly? For example, you can ask about and/or observe how the child uses his or her hands when playing and during meals, or when participating in usual activities of daily living.

Ask questions about the child's self-initiated ability and how much adult help and support the child needs to handle everyday objects, e.g. toys.

Below is a description of the five Mini-MACS levels of children's self-initiated ability and their need for assistance or adaptation when handling objects.

- I. **Handles objects easily and successfully.** The child may have a slight limitation in performing actions that require precision and coordination between the hands but they can still perform them. The child may need somewhat more adult assistance when handling objects compared to other children of the same age.
- II. **Handles most objects, but with somewhat reduced quality and/or speed of achievement.** Some actions can only be performed and accomplished with some difficulty and after practice. The child may try an alternative approach, such as using only one hand. The child need adult assistance to handle objects more frequently compared to children at the same age.
- III. **Handles objects with difficulty.** Performance is slow, with limited variation and quality. Easily managed objects are handled independently for short periods. The child often needs adult help and support to handle objects.
- IV. **Handles a limited selection of easily managed objects in simple actions.** The actions are performed slowly, with exertion and/or random precision. The child needs constant adult help and support to handle objects.
- V. **Does not handle objects and has severely limited ability to perform even simple actions.** At best, the child can push, touch, press, or hold on to a few items, in constant interaction with an adult.

Distinctions between Levels I and II

Children in Level I may have slightly more difficulty handling items that require good fine motor skills compared to children without disabilities of the same age.

Children in Level II handle essentially the same objects as children in Level I, but they may encounter problems performing tasks and/or take longer to perform them, so they often ask for help. Functional differences between hands may cause performance to be less effective. They may need more guidance and practice to learn how to handle objects compared with children in Level I.

Distinctions between Levels II and III

Children in Level II can handle most objects, though they may take longer and do so with somewhat less quality, and they may need a lot of guidance and practice to learn how to handle objects.

Level III children manage to use easily handled objects but often need help placing objects in an easy position in front of them. They perform actions with few subcomponents. Performance is slow.

Distinctions between Levels III and IV

Children in Level III manage to use easily handled objects independently for short periods. They perform actions with few subcomponents, and the actions take a long time to perform.

At best, children in Level IV can perform simple actions such as grasping and releasing easily handled objects that are offered in an adapted position. They need constant help.

Distinctions between Levels IV and V

Children in Level IV perform individual actions with a very limited selection of objects and need constant help.

At best, children in Level V perform simple movements in special situations. For example, they can press a simple button or hold single, simple objects.

Information for users

The Manual Ability Classification System (MACS) describes how children with cerebral palsy (CP) use their hands to handle objects in daily activities. MACS describes five levels. The levels are based on the children's self-initiated ability to handle objects and their need for assistance or adaptation to perform manual activities in everyday life. The MACS brochure also describes differences between adjacent levels to make it easier to determine which level best corresponds with the child's ability to handle objects.

The objects referred to are those that are relevant and age-appropriate for the children, used when they perform tasks such as eating, dressing, playing, drawing or writing. It is objects that are within the children's personal space that is referred to, as opposed to objects that are beyond their reach. Objects used in advanced activities that require special skills, such as playing an instrument are not included in this considerations.

When establishing a child's MACS level, choose the level that best describes the child's overall usual performance, in the home, school or community setting. The child's motivation and cognitive ability also affect the ability to handle objects and accordingly influence the MACS level. In order to obtain knowledge about how a child handles various everyday objects it is necessary to ask someone who knows the child well. MACS is intended to classify what the children usually do, not their best possible performance in a specific test situation.

MACS is a functional description that can be used in a way that is complementary to the diagnosis of cerebral palsy and its subtypes. MACS assesses the children's overall ability to handle everyday objects, not the function of each hand separately. MACS does not take into account differences in function between the two hands; rather, it addresses how the children handle age-appropriate objects. MACS does not intend to explain the underlying reasons for impaired manual abilities.

MACS can be used for children aged 4–18 years, but certain concepts must be placed in relation to the child's age. Naturally there is a difference in which objects a four-year old should be able to handle, compared with a teenager. The same applies to independence—a young child needs more help and supervision than an older child.

MACS spans the entire spectrum of functional limitations found among children with cerebral palsy and covers all sub-diagnoses. Certain sub-diagnoses can be found at all MACS levels, such as bilateral CP, while others are found at fewer levels, such as unilateral CP. Level I includes children with minor limitations, while children with severe functional limitations will usually be found at levels IV and V. If typically developed children were to be classified according to MACS, however, a level "0" would be needed.

Moreover, each level includes children with relatively varied function. It is unlikely that MACS is sensitive to changes after an intervention; in all probability, MACS levels are stable over time.

The five levels in MACS form an ordinal scale, which means that the levels are 'ordered' but differences between levels are not necessarily equal, nor are children with cerebral palsy equally distributed across the five levels.

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Eliasson AC, Krumlinde-Sundholm L, Rösblad B, Beckung E, Arner M, Öhrvall AM, Rosenbaum P. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Developmental Medicine and Child Neurology*. 2006;48:549-554



Manual Ability Classification System for Children with Cerebral Palsy 4-18 years

MACS classifies how children with cerebral palsy use their hands to handle objects in daily activities.

- MACS describes how children usually use their hands to handle objects in the home, school, and community settings (what they do), rather than what is known to be their best capacity.
- In order to obtain knowledge about how a child handles various everyday objects, it is necessary to ask someone who knows the child well, rather than through a specific test.
- The objects the child handles should be considered from an age-related perspective.
- MACS classify a child's overall ability to handle objects, not each hand separately.



What do you need to know to use MACS?

The child's ability to handle objects in important daily activities, for example during play and leisure, eating and dressing.

In which situation is the child independent and to what extent do they need support and adaptation?

- I. **Handles objects easily and successfully.** At most, limitations in the ease of performing manual tasks requiring speed and accuracy. However, any limitations in manual abilities do not restrict independence in daily activities.
- II. **Handles most objects but with somewhat reduced quality and/or speed of achievement.** Certain activities may be avoided or be achieved with some difficulty; alternative ways of performance might be used but manual abilities do not usually restrict independence in daily activities.
- III. **Handles objects with difficulty; needs help to prepare and/or modify activities.** The performance is slow and achieved with limited success regarding quality and quantity. Activities are performed independently if they have been set up or adapted.
- IV. **Handles a limited selection of easily managed objects in adapted situations.** Performs parts of activities with effort and with limited success. Requires continuous support and assistance and/or adapted equipment, for even partial achievement of the activity.
- V. **Does not handle objects and has severely limited ability to perform even simple actions.** Requires total assistance.

Distinctions between Levels I and II

Children in Level I may have limitations in handling very small, heavy or fragile objects which demand detailed fine motor control, or efficient coordination between hands. Limitations may also involve performance in new and unfamiliar situations. Children in Level II perform almost the same activities as children in Level I but the quality of performance is decreased, or the performance is slower. Functional differences between hands can limit effectiveness of performance. Children in Level II commonly try to simplify handling of objects, for example by using a surface for support instead of handling objects with both hands.

Distinctions between Levels II and III

Children in Level II handle most objects, although slowly or with reduced quality of performance. Children in Level III commonly need help to prepare the activity and/or require adjustments to be made to the environment since their ability to reach or handle objects is limited. They cannot perform certain activities and their degree of independence is related to the supportiveness of the environmental context.

Distinctions between Levels III and IV

Children in Level III can perform selected activities if the situation is prearranged and if they get supervision and plenty of time. Children in Level IV need continuous help during the activity and can at best participate meaningfully in only parts of an activity.

Distinctions between Levels IV and V

Children in Level IV perform part of an activity, however, they need help continuously. Children in Level V might at best participate with a simple movement in special situations, e.g. by pushing a button or occasionally hold undemanding objects.

Appendix 9 Tanner Grading Scale

Tanner Grading Scale for Measurement of Breast Development

Breast development will be assessed using the original version of the Tanner grading scale [54]. Pubertal Staging: The Tanner Grading Scale for breast development will be performed for female subjects at Day 1 of each treatment, as described in [Table 14](#).

Table 14 Tanner Grading Scale for Breast Development

Grade	Description
Tanner I	No glandular tissue; areola follows the skin contours of the chest (prepubertal). Typically age ≤ 10 years.
Tanner II	Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen. Typically age 10 to 11.5 years.
Tanner III	Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast. Typically age 11.5 to 13 years.
Tanner IV	Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast. Typically age 13 to 15 years.
Tanner V	Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla. Typically age ≥ 15 years.