PROTOCOL TITLE: An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis

STUDY PROTOCOL
STUDY number: F-FR-52120-228
**Study Short Title: ENGAGE**
Dysport® / 52120
EudraCT number: 2016-001989-29
Final Version (including Amendment #1): 02 December 2016
Final Version (including Amendment #2): 24 January 2018

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## INVESTIGATOR'S AGREEMENT

**Investigator Agreement and Signature:**

I have read and agree to Protocol F-FR-52120-228 entitled "An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), 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.

NAME:

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

OFFICE:

**Sponsor's Representative Signature:**

NAME: PPD

TITLE: PPD SIGNATURE:

DATE:

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# COORDINATING INVESTIGATOR'S AGREEMENT

**Coordinating Investigator Agreement and Signature:**

I have read and agree to Protocol F-FR-52120-228 entitled "An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis". I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), 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.

NAME: Professor JM Gracies, MD, PhD

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:

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## SUMMARY OF CHANGES

The current version of the protocol was released on 02 December 2016 and includes Amendment 1. The amendment forms were prepared and are provided in Appendix 1 and Appendix 2 (Table 1).

**Table 1 List of Protocol Amendments**

| Amendment | Release date | Amendment form |
|---|---|---|
| 1 | 02 December 2016 | Appendix 1 |
| 2 | 24 January 2018 | Appendix 2 |

## SYNOPSIS

| | |
|---|---|
| **Name of sponsor/company**: Ipsen Pharma SAS | |
| **Name of finished product**: Dysport® <br> **Name of active ingredient(s)**: AbobotulinumtoxinA | |
| **Title of study**: An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis <br> **Study number**: F-FR-52120-228 | |
| **Number of planned centres**: 20 | |
| **Planned study period**: <br> December 2016 to July 2018 | **Phase of development**: <br> Phase IIIb/Phase IV (depending on country) |

**Objectives**:

Primary Objective:

The primary objective is to assess the responder rate as defined by the improvement of composite active range of motion (AROM) in the primary targeted limb, either upper limb (UL) or lower limb (LL), depending on which one has been selected as a primary treatment target (TT), following two consecutive AbobotulinumtoxinA injections combined with a Guided Self-rehabilitation Contract (GSC) in subjects with spastic hemiparesis following acquired brain injury (ABI).

Secondary Objectives:

The secondary objectives are as follows:

- to assess the effectiveness of AbobotulinumtoxinA combined with a GSC on:
  - the responder rate as defined by the improvement of composite active range of motion (AROM) in the primary targeted limb, either upper limb (UL) or lower limb (LL), depending on which one has been selected as a primary treatment target (TT), following one AbobotulinumtoxinA injection combined with a Guided Self-rehabilitation Contract (GSC).
  - AROM against 10 prespecified muscle groups: 5 in upper and 5 in lower limbs
  - composite AROM against injected muscle groups (any of the 10 prespecified muscles) of each limb
  - full composite AROM against five UL muscle groups or full composite AROM against five LL muscle groups, regardless of whether the muscle groups were injected or not
  - active function in the upper and lower limbs using the Modified Frenchay Scale (MFS) and maximal Walking Speed (WS) barefoot, respectively.
- to assess subject satisfaction with regard to the use of a GSC
- to measure the changes in subject and physiotherapist beliefs that a GSC will help to improve function
- to assess subject compliance with the GSC
- to assess global benefits by both the investigator and the subject (or caregiver)

- in subjects not reinjected at Week 12, to assess satisfaction with longer than 12 weeks interval between 2 injections
- to assess health-related quality of life
- to assess safety parameters.

Exploratory objective:

The exploratory objective is as follows:

- to assess correlation between full composite AROM and active function (MFS in UL and WS in LL).

**Methodology**:

This is a multicentre, prospective, single-arm study to evaluate the efficacy and safety of two consecutive injections of AbobotulinumtoxinA administered in both upper and lower limbs (total dose of 1500 U per injection) plus daily GSC therapy, in adults with spastic hemiparesis due to ABI. The effect of treatment (i.e. AbobotulinumtoxinA+GSC) on voluntary movements will be assessed. Each subject will undergo two injection (treatment) cycles, receiving AbobotulinumtoxinA 1500 U on Day 1 of each cycle; the two dosing occasions will be separated by at least 12 weeks (maximum 20 weeks).

At the Baseline Visit (Cycle 1), all subjects will undergo screening procedures and baseline study assessments after written informed consent has been provided. The primary TT limb (UL or LL) will be defined by the investigator, following discussion with the subject. AbobotulinumtoxinA (1500 U) will be administered as a split dose, in both the UL and LL; the dose given in each limb will be decided by the investigator, based on which was considered the primary TT limb at the Baseline Visit and in accordance with the following dosing rules:

- electrical stimulation (ES) will be used to target the injection sites; Ultrasound guiding could be used in addition to ES in case this technique is used in routine clinical practice;
- at least half the total dose (i.e. ≥750 U) must be injected in the primary TT limb (the rest of the dose is injected in the secondary TT limb);
- a maximum of 1000 U can be injected in an UL (even if it is the primary TT limb);
- there is no maximum dose that can be injected in a LL, provided that some remainder dose (out of the 1500 U total) is used for the UL injections;
- the second AbobotulinumtoxinA injection (Cycle 2) may be given in a different split to the first injection (Cycle 1), at the discretion of the investigator. However, the same minimal/maximal rules apply, as described above. The primary TT remains the same for both AbobotulinumtoxinA injections and the study duration.

Each subject will also receive a personalised GSC and will be asked to perform daily GSC therapy throughout the study. The subject will record in a diary each of the performed exercises of the GSC therapy. Telephone calls will be made to the subject every 2 weeks to check how the GSC therapy is being performed and that the diary is being filled out every day.

In **Cycle 1**, postinjection follow-up (FU) visits will be held after the first AbobotulinumtoxinA administration, as follows:

- at Week 6;
- at Week 12: the investigator will decide if the subject is still responding to treatment

or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If a second injection is not given, the subject will return at Week 16;

- at Week 16: the investigator will again decide if the subject is still responding to treatment or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If a second injection is not given, the subject will return at Week 20;
- at Week 20: the investigator will again decide if the subject is still responding to treatment or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If the investigator decides that a second injection should not be given, based on his/her clinical judgement, the subject will be withdrawn from the study.

In **Cycle 2**, postinjection FU visits will be held after the second AbobotulinumtoxinA administration, as follows:

- at Week 6;
- at Week 12: the investigator will decide if the subject is still responding to treatment or if a further injection is needed, based on his/her clinical judgement. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection outside the study is given) (i.e. Final Visit). If a further injection is not needed, the subject will return at Week 16;
- at Week 16: the investigator will again decide if the subject is still responding to treatment or if a further injection is needed, based on his/her clinical judgement. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection outside the study is given) (i.e. Final Visit). If a further injection is not needed, the subject will return at Week 20;
- at Week 20: the subject completes the study after study assessments have been performed, regardless of whether a further injection is needed (i.e. Final Visit).

The overall duration of the study for each subject will be between 24 and 40 weeks (from Baseline Visit to Final Visit).

**Number of subjects planned**:

It is planned to recruit approximately 155 subjects at approximately 20 sites in Europe and United States of America (USA), in order to achieve 145 evaluable subjects. Recruitment will be stratified by country to ensure that 50% of subjects have the UL as primary TT and 50% of subjects have the LL as primary TT (with ±10% flexibility).

**Diagnosis and criteria for inclusion**:

Inclusion criteria:

1) Subjects aged at least the national legal adult age.
2) Subjects with hemiparesis due to ABI (i.e. stroke or traumatic brain injury (TBI)) presenting with muscle overactivity impeding motor function based on investigator's judgement including, but not limited to, at least one of the following requiring botulinum neurotoxin (BoNT) treatment: typical clenched fist; flexed wrist; flexed elbow; or plantar flexed foot pattern.
3) At least 12 months since the ABI.
4) Naïve or non-naïve to BoNT treatment; if non-naïve, at least 4 months after the last

BoNT injection, of any serotype.

5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS locally rated score, if the primary TT limb is the UL.
6) A 10-metre maximal WS barefoot between 0.2 and 1.4 m/s, if the primary TT limb is the LL. Maximal WS barefoot will be performed without walking aids. However, a cane may be permitted if absolutely necessary (although this may prevent detection of treatment-induced improvements). In this case, the same aid will have to be used for all WS assessments during the study.
7) Subjects must provide written informed consent to participate in the study prior to any study-related procedures.
8) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study until the last visit of the subjects and for at least 12 weeks post injection. Acceptable methods of contraception include total abstinence, male partner has had a vasectomy, double barrier method (e.g. male condom plus spermicide, or female diaphragm plus spermicide), intrauterine device, or hormonal contraceptive (oral, transdermal, implanted and injected)..
9) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow-up evaluation as specified in the protocol.

Exclusion criteria:

1) Inability to understand protocol procedures and requirements, which, in the opinion of the investigator, could negatively impact on protocol compliance, in particularly inability to exercise according to the GSC.
2) Previous surgery on the affected muscles and ligaments, tendons, nerve trunks, or bones of the treated upper or lower limb.
3) Previous treatment with phenol and/or alcohol in any of the treated limbs any time before the study.
4) Any medical condition (including severe dysphagia or breathing difficulties) that may increase, in the opinion of the investigator, the likelihood of adverse events (AEs) related to BoNT-A treatment.
5) Subjects treated, or likely to be treated, with intrathecal baclofen during the course of the study or during the 4 weeks before study entry.
6) Current, planned or received within the last 4 weeks prior to study treatment, treatment with any drug that interferes either directly or indirectly with neuromuscular function (for example, aminoglycosides).
7) Major neurological impairment other than spastic paresis (including major proprioceptive ataxia or apraxia on the paretic side) that could negatively impact on the functional performance of the subject.
8) Known disease of the neuromuscular junction (such as Lambert-Eaton myasthenic syndrome or myasthenia gravis).
9) Known sensitivity to BoNT-A or any excipient of Dysport.
10) Infection at the injection site(s).
11) Current pregnancy or lactation. A pregnancy test will be performed at the start of the

study for all female subjects of childbearing potential (i.e. not surgically sterile or 2 years postmenopausal).

12) Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.
13) Abnormal baseline findings or any other medical condition(s) that, in the opinion of the investigator, might jeopardise the subject's safety.
14) Subjects who have participated in any therapeutic clinical study/received any investigational agent within 30 days of enrolment.

**Test product, dose, mode of administration**:

AbobotulinumtoxinA (Dysport®) will be supplied as a white lyophilised powder in a vial containing 500 U of botulinum toxin type A (BTX-A)-haemagglutinin complex. A total dose of 1500 U (split between the UL and LL) will be used in each of two injection (treatment) cycles. Each Dysport vial (500 U) will be reconstituted with 2.5 mL sodium chloride for intramuscular (i.m.) injection (0.9%). The total volume to be injected on each dosing occasion will be 7.5 mL.

**Duration of treatment**:

Each subject will receive two injections of AbobotulinumtoxinA, separated by an interval of at least 12 weeks (maximum 20 weeks). Individual subject participation in the study (first injection to last FU visit) will be between 24 and 40 weeks.

**Reference therapy, dose and mode of administration**:

Not applicable.

**Criteria for evaluation**:

Efficacy:

A goniometer will be used to measure AROM in the UL and LL at baseline and all postinjection FU visits. The MFS will be used to measure active function in the UL and the 10-metre Walking Speed Test (WST) barefoot at maximal speed will be used to measure active function in the LL, at baseline and Week 12, in each injection cycle. Subject satisfaction with the GSC will be assessed using a Likert scale at all postinjection FU visits but also at baseline for patients who had any GSC done previously. Changes in the subject's and Physiotherapist's beliefs that the GSC will help to improve functional capacity will be assessed using a Likert scale at baseline and all postinjection FU visits. Subjects will record in a diary every day the performed exercises of the GSC therapy; the diary will be checked at each postinjection FU visit. The diary will be used by the investigator to ensure the prescription has been properly followed. The number of days without GSC therapy will be derived from the diary data by the investigator and entered into the electronic case report form (eCRF): compliance to GSC will be accordingly estimated over the study duration for each subject. A global assessment of benefits will be made by both the investigator and subject (or caregiver) at the end of both injection cycles using a Likert scale. For the subjects who will have an injection planned at either Visit 4 or Visit 5 for the first cycle and Visit 8 or Visit 9 for the second cycle (i.e. Week 16 or 20 of each cycle) satisfaction with longer treatment interval will be collected at the corresponding reinjection visit or at the last cycle visit. Subject quality of life will be assessed by the subject using the European Quality of Life 5 Dimensions (EQ-5D 5L) and Short Form 12 (SF-12) scales at baseline and the last study visit.

Safety:

Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study or subject withdrawal. Vital signs will also be measured at baseline, the second injection and the last study visit.

**Statistical Methods**:

Study Endpoints

*Primary Efficacy Endpoint and Evaluation:*

The primary efficacy endpoint is as follows:

- the percentage of responder subjects at Week 6 after the second injection, according to composite AROM in the primary TT limb.

Composite AROM ($X_A$), regardless of whether the muscle groups were injected or not, as measured by goniometer in the primary TT limb (either UL or LL, depending on which one has been selected as the primary TT limb), will be calculated as follows:

- composite $X_A$ UL: $X_A\,UL = X_{AEF} + X_{AWF} + X_{AFF}$
- composite $X_A$ LL: $X_A\,LL = X_{Asol} + X_{AGN}$

*where for UL: EF=elbow flexors, WF=wrist flexors and FF=extrinsic finger flexors, and for LL: Sol=soleus and GN=gastrocnemius muscles.*

Definition of a responder: a subject will be considered a responder if he/she achieves at least the predefined improvement threshold - larger or equal to 35° in UL or 5° in LL - in the primary TT limb (based on the composite AROM individual change from baseline to Week 6 after the second injection).

*Secondary Efficacy Endpoints and Evaluations:*

The secondary efficacy endpoints are as follows:

- the percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb
- AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- composite AROM against injected muscle groups (any of the 10 prespecified), in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- full composite AROM against five UL muscle groups ($X_A$ full UL = $X_{ASE} + X_{AEF} + X_{AWF} + X_{AFF} + X_{APT}$) or full composite AROM against five LL muscle groups ($X_A$ full LL = $X_{Asol} + X_{AGN} + X_{AGM} + X_{AHS} + X_{ARF}$), regardless of whether the muscle groups were injected or not: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only

  *where for UL: SE=shoulder extensors, EF=elbow flexors, WF=wrist flexors, FF=extrinsic finger flexors and PT=pronator teres,*
  *and for LL: Sol=soleus, GN=gastrocnemius muscles, GM=gluteus maximus, HS=hamstrings and RF=rectus femoris*
- active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks assessed locally and centrally by a reviewer blinded regarding the date of the video recording/visit number) at Week 12 after each injection cycle
- active LL function measured using maximal WS barefoot without walking aids or, if

absolutely necessary, with a cane, measured on a 10-metre WST: mean change from baseline at Week 12 after each injection cycle. (If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.)

- subject satisfaction with the GSC: at baseline (only for patients who had GSC performed previously), Week 6, Week 12 and re-injection/last cycle visits only
- changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)
- global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle
- in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- quality of life changes, measured on the EQ-5D 5L and SF-12 scales: change from baseline to Final Visit.

*Secondary Safety Endpoints and Evaluations:*

- Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study. Other safety data will include vital signs.

*Exploratory Endpoint and Evaluation:*

- Correlation between full composite AROM and active function (MFS in UL and WS in LL) will be explored.

Statistical analyses

All statistical analyses will be primarily descriptive and, when p-values are presented, this will be for exploratory purposes only. It is planned to perform an interim analysis when all subjects are recruited in order to describe baseline data and more specifically injection details, for example, dose per limb/injected muscles; this baseline data interim analysis is planned after subject enrolment has been completed.

Sample size calculation

The sample size was determined based on the primary efficacy endpoint (percentage of responder subjects at Week 6 after the second injection according to composite AROM). A 60% response rate was assumed based on previous studies (adult UL/LL) with an additional benefit of +10% compared with that observed in these studies (approximately 50% response rate at Week 4 of Cycle 2). The aim of this study will be to estimate this proportion with an accuracy of ±8%. Given a two-sided 95% confidence interval, 145 subjects are required; with an assumed 5% dropout rate, 153 subjects will have to be enrolled to achieve a target of 145 evaluable subjects.

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## LIST OF ABBREVIATIONS

| ABBREVIATION | Wording Definition |
|---|---|
| **ABI** | Acquired brain injury |
| **AE** | Adverse event |
| **ALLS** | Adult lower limb spasticity |
| **ANCOVA** | Analysis of covariance |
| **AROM** | Active range of motion |
| **BoNT** | Botulinum neurotoxin |
| **BoNT-A** | Botulinum neurotoxin type A |
| **BTX-A** | Botulinum toxin type A |
| **CA** | Competent authority |
| **CFR** | Code of Federal Regulations (United States of America) |
| **CI** | Confidence interval |
| **CRO** | Contract research organisation |
| **CSR** | Clinical study report |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **EF** | Elbow flexors |
| **e.g.** | Exempli gratia |
| **ES** | Electrostimulation |
| **EQ-5D 5L** | European Quality of Life 5 Dimensions |
| **FDA** | Food and Drug Administration |
| **FF** | Extrinsic finger flexors |
| **FU** | Follow-up |
| **GCP** | Good Clinical Practice |
| **GM** | Gluteus maximus |
| **GN** | Gastrocnemius muscles |
| **GSC** | Guided Self-rehabilitation Contract |
| **HS** | Hamstrings |
| **IB** | Investigator’s brochure |
| **ICH** | International Conference on Harmonisation |
| **i.e.** | Id est |
| **IEC** | Independent ethics committee |
| **i.m.** | Intramuscular |

| ABBREVIATION | Wording Definition |
|---|---|
| **IMP** | Investigational medicinal product |
| **INR** | International normalised ratio |
| **IRB** | Institutional review board |
| **ITT** | Intent-to-treat |
| **LL** | Lower limb |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MFS** | Modified Frenchay Scale |
| **mITT** | Modified intent-to-treat |
| **n, N** | Number |
| **PI** | Package insert |
| **PK** | Pharmacokinetic |
| **PP** | Per protocol |
| **PT** | Pronator teres |
| **RF** | Rectus femoris |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SAS®** | Statistical Analysis System |
| **SE** | Shoulder extensors |
| **SF-12** | Short Form 12 |
| **SmPC** | Summary of product characteristics |
| **Sol** | Soleus |
| **SOP** | Standard operating procedure |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TBI** | Traumatic Brain Injury |
| **TEAE** | Treatment-emergent adverse event |
| **TT** | Treatment target |
| **UL** | Upper limb |
| **US(A)** | United States (of America) |
| **VAS** | Visual analogue scale |
| **WF** | Wrist flexors |
| **WHODRUG** | World Health Organization Drug Dictionary |
| **WS** | Walking speed |
| **WST** | Walking speed test |

| **ABBREVIATION** | Wording Definition |
|---|---|
| $\mathbf{X_A}$ | AROM (active range of motion) |

# 1 BACKGROUND INFORMATION

## 1.1 Disease Review

Spasticity is an increase in velocity-dependent stretch reflexes, with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome [1, 2]. Spasticity is associated with various neurological disorders (for example, multiple sclerosis, cerebral or spinal cord injuries and cerebrovascular disorders), contributing to functional motor disability/impairment, pain and discomfort [3]. For example, globally, 15 million people suffer a stroke every year [4] and around half of these may eventually develop post-stroke upper-limb (UL) spasticity. As the population ages and medicine advances, disability due to post-stroke spasticity will increase and is now emerging as a significant global health issue with substantial socioeconomic burdens [5]. Post-stroke UL symptoms associated with spasticity include impairment of active and passive functioning of the limb (for example, hygiene-related actions, dressing and splint application) and can significantly impair both the patient's and the carer's quality of life [5].

Adult lower limb spasticity (ALLS) is one of the disabling complications of multiple neurological disorders such as stroke, multiple sclerosis, spinal cord injury and even some central neurodegenerative disorders. People with ALLS can present with a variety of abnormal postures. The increased tone due to spasticity can cause significant discomfort and patients describe it as, for example, a spasm, cramp or dull pain. If insufficiently managed, patients with ALLS are often predisposed to secondary complications of reduced mobility such as muscle shortening and joint deformity [6]. These secondary complications can themselves cause more systemic complications including deep vein thrombosis and pressure ulcers. The integral role of botulinum neurotoxin (BoNT) in the management of focal spasticity is recognized by guidelines from around the world [7].

## 1.2 Compound Review

Botulinum toxin type A (BTX-A) is a neurotoxin isolated and purified from Clostridium botulinum type A bacteria. It acts selectively on peripheral cholinergic nerve endings to inhibit acetylcholine release. This produces a weakening of voluntary and involuntary muscle contraction, an effect that can be used to therapeutic advantage in the treatment of focal dystonias, muscle spasms and muscle spasticity. Dysport® is a BTX-A-haemagglutinin complex (United States [US] generic name: AbobotulinumtoxinA), which was first approved in the United Kingdom in 1990 and is now licensed in more than 80 countries for various indications, including: spastic equinus deformity due to spasticity in adults following a stroke, blepharospasm, adult upper and lower limb spasticity, hemifacial spasm, spasmodic torticollis (cervical dystonia), paediatric lower limb spasticity and dynamic equinus foot deformity due to cerebral palsy, axillary hyperhidrosis and glabellar lines. It is of note that not all indications are approved across all regions; for example, Dysport has approval in France for the treatment of adult UL and lower limb (LL) spasticity but, in other regions such as the United States of America (USA) and Czech Republic, it has approval for adult UL spasticity but not LL spasticity (hence, the current study will be a phase IV study in France but a phase IIIb study in other countries).

A more detailed description of the product is given in the investigator's brochure (IB) [8] and Section 3.4, and a detailed description of administration procedures is given in Section 6.1.

## 1.3 Findings from Nonclinical and Clinical Studies

Nonclinical pharmacology studies have demonstrated the efficacy of low doses of BTX in various cholinergic pathways. Pharmacokinetic (PK) and distribution studies performed with BTX-A have demonstrated that the majority of the toxin remains localised at the injection site, supporting the local effect of the toxin. The results of single- and repeat-dose toxicity studies demonstrated that BTX-A administered in striated muscle possesses no potential for producing toxicity unrelated to its pharmacological activity or specific target organ. The effects on injected muscles (decrease in muscle and myofibre size) were related to the pharmacological activity of BTX-A and were consistent with the results of the pharmacodynamic Rat Muscle Force Test. Intramuscular (i.m.) administration of Dysport in healthy juvenile rats did not alter male or female rat fertility with toxicological profiles in juvenile animals observed to be similar to adults. After local administration, the amount of BTX-A in the systemic circulation of animals is below the limit of detection of bioanalytical methods validated for use on clinical samples. Therefore, no PK studies have been performed in humans. The drug was not teratogenic in rats and rabbits and no effects were observed in the pre- and postnatal study on the first (F1 generation) in rats.

Clinical studies conducted in adult subjects with UL spasticity have shown Dysport 500 U and 1000 U to be superior to placebo on muscle tone, spasticity, active range of motion (AROM), passive function and clinical benefit after a single treatment cycle. Maintenance of this efficacy and progressive improvement of active function could be seen after repeated administrations with a trend towards higher efficacy of the 1500 U dose (including 500 U in the shoulder) on both passive and active function [9]. Overall, across all studies, Dysport was well tolerated in the treatment of subjects with adult UL spasticity.

Clinical studies conducted in subjects with adult LL spasticity have shown substantial evidence of the efficacy of Dysport 1000 U and 1500 U on muscle tone and spasticity (statistically significant difference versus placebo with 1500 U), translating into clinical benefit. The effect observed after a single treatment cycle was enhanced and accompanied by progressive improvements of spasticity, active ankle dorsiflexion and walking speed (WS) over repeated cycles. Overall, across all studies, Dysport was well tolerated in the treatment of subjects with adult LL spasticity.

Further details of nonclinical studies, as well as clinical studies in all indications, may be found in the IB [8].

## 1.4 Known and Potential Risks and Benefits to Human Subjects

In subjects who were treated with Dysport in numerous clinical trials, approximately 25% experienced a treatment-emergent adverse event (TEAE). Dysport is generally well tolerated although temporary paresis of nontargeted muscle groups can occur. In general, the TEAE profile will be dependent on the site of injection. Most TEAEs are of mild or moderate severity and of limited duration. Adverse reactions that were seen and are considered expected in subjects treated across a variety of indications, including blepharospasm, hemifacial spasm, cervical dystonia, spasticity associated with either cerebral palsy or stroke and axillary hyperhidrosis, can be found in the Dysport Company Core Safety Information. In the following research indications, adverse reactions were reported as follows:

- In paediatric patients treated with Dysport for upper limb spasticity (alone or concomitantly with lower limb spasticity) in an observational study CCI , reported events (of any causality) included injection site reaction, muscle weakness, somnolence, constipation, dysphagia, fatigue, flu-like syndrome, ptosis, speech disorder, urinary incontinence and ulcerative stomatitis.

- In adult patients treated with Dysport for neurogenic detrusor overactivity in an interventional study CCI, the following events were reported as treatment-related by the investigator: muscular weakness, asthenia, suprapubic pain, pain in extremity and procedural pain.
- The profile of adverse reactions reported during postmarketing use reflects the pharmacology of the product and those seen during clinical trials.

The following information should be taken into consideration when prescribing Dysport:

- Dysport is contraindicated in individuals with known hypersensitivity to any BTX preparation or to any of the components in the formulation.
- Adverse effects resulting from distribution of the effects of the toxin to sites remote from the site of administration have been reported. Patients treated with therapeutic doses may present with excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose.
- Very rare cases of death, occasionally in a context of dysphagia, pneumopathy and/or in patients with significant asthenia have been reported after treatment with BTX-A or B. Patients with disorders resulting in defective neuromuscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the risk.
- Dysport should be administered with caution to patients with pre-existing swallowing or breathing problems including inhalation pneumopathy as these problems can worsen following distribution of its effect into the relevant muscles. Aspiration has occurred in rare cases and is a risk when treating patients who have a chronic respiratory disorder.
- Dysport should only be used with caution and under close supervision in patients with subclinical or clinical evidence of marked defective neuromuscular transmission (for example, myasthenia gravis). Such patients may have an increased sensitivity to agents such as Dysport, which may result in excessive muscle weakness.
- The recommended posology and frequency of administration for Dysport must not be exceeded.
- As with any i.m. injection, Dysport should be used only where strictly necessary in patients with prolonged bleeding times, or infection/inflammation at the proposed sites(s) of injection.
- Dysport contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood or blood products.
- Following Dysport treatment, a low number of patients developed neutralising antibodies.
- The effects of BTX may be enhanced by drugs interfering directly or indirectly with the neuromuscular function (for example, aminoglycosides, curare-like nondepolarising blockers) and such drugs should be used with caution in patients treated with BTX.
- The risk of excessive muscle weakness may impair the ability to drive or operate machinery.
- Patients and their caregivers must be warned of the necessity to seek immediate medical treatment in case of problems with swallowing, speech or respiratory problems.

- There are limited data from the use of Clostridium BTX-A-haemagglutinin complex in pregnant women. Animal studies do not indicate any direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development other than at high doses causing maternal toxicity. Dysport should be used during pregnancy only if the benefit justifies any potential risk to the foetus. Caution should be exercised when prescribing to pregnant women.
- It is not known whether Clostridium BTX-A-haemagglutinin complex is excreted in human milk. The excretion of Clostridium BTX-A-haemagglutinin complex in milk has not been studied in animals. The use of Clostridium BTX-A-haemagglutinin complex during lactation cannot be recommended.

It should also be noted that:

- Dysport units are specific to the preparation and are not interchangeable with other preparations of BTX-A.
- Excessive doses may produce distant and profound neuromuscular paralysis.
- Overdose could lead to an increased risk of the neurotoxin entering the bloodstream and may cause complications associated with the effects of oral botulinum poisoning (for example, dysphagia and dysphonia). Respiratory support may be required where excessive doses may cause paralysis of the respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. In the event of overdose, the patient should be medically monitored for any signs and/or symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.
- The safety profile of the indications under study can be in part predicted based on the overall experience with Dysport and the safety profile observed in studies performed with BTX-A (various brands; including Dysport used independent of Ipsen research) in these indications.

Additional information regarding risks and benefits to human subjects may be found in the IB [8].

## 1.5 Compliance Statement

The study will 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. As this is an electronic data capture (EDC) study, the following regulations must also be adhered to: Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures and FDA Guidance for Industry, Computerized Systems Used in Clinical Trials. Any episode of noncompliance will be documented.

In addition, the study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (for example, 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.

## 1.6 Clinical Trial Rationale

In hemiparetic patients, upper and lower limbs can be affected with spastic muscle overactivity and often need to be treated at the same time. The goals of management of spastic paresis include increasing mobility and range of motion (passive and active), improving function (passive and/or active), improving body image, facilitating splint wear and decreasing pain. Quite often, those goals can be achieved only when both affected limbs (UL and LL) are treated at the same time. However, there are limited published data concerning treatment strategies when both limbs require injection. The aim of this study is to provide efficacy and safety data on AbobotulinumtoxinA when upper and lower limbs are injected at the same time, to improve voluntary movements in subjects with spastic hemiparesis.

Botulinum neurotoxin type A (BoNT-A) has proven efficacy in treating muscle hypertonia of spastic paresis of various aetiologies, as measured by lowering the Modified Ashworth Scale score [10, 11]. The recently published results of AbobotulinumtoxinA for the treatment of adult UL spasticity (phase III study) demonstrated improvement in AROM and suggested that future research into the treatment of spastic paresis with botulinum toxin should use active movement and function as primary outcome measures [9]. Therefore, the primary endpoint in the current study will be based on AROM. Meaningful functional improvement has not been demonstrated consistently across the previous BoNT-A studies to date. The reasons for this may be associated with the outcome measures used but also which – if any – rehabilitation programs have been used. To date, there is insufficient evidence to support the preferential effect of adjunctive therapies following BoNT-A injections. A recent systematic review found limited evidence to support or refute the benefit of adjunctive therapies when provided in addition to BoNT-A injection for adult focal spastic paresis [7]. However, there is some evidence suggesting that a diary-based and antagonist-based rehabilitation system called the Guided Self-rehabilitation Contract (GSC) [12] may constitute a useful adjunct to BoNT-A injections in order to improve gait. Therefore, in this study, AbobotulinumtoxinA injections will be accompanied by GSC therapy for the whole study duration.

The primary efficacy endpoint will be based on the improvement of composite AROM in the primary treatment target (TT) limb (UL or LL). Secondary efficacy endpoints will include: other AROM assessments, as well as measures of active function in the UL (Modified Frenchay Scale (MFS)) and LL (Walking Speed Test (WST) barefoot at maximal speed); evaluations of GSC (subject satisfaction, subject beliefs that the GSC will help to improve functional capacity, and subject compliance with the GSC); global assessments of benefits of study therapy (by investigator and subject or caregiver); and quality of life assessments by the subject (European Quality of Life 5 Dimensions (EQ-5D 5L) and Short Form 12 (SF-12) scales). The study will also assess safety through the collection of adverse events (AEs) and the assessment of vital signs.

In clinical practice, Dysport is used at varying concentrations and doses, depending on the size, number and location of muscles involved, severity of spasticity, presence of local muscle weakness, response to previous treatment and/or AE history with Dysport [13]. In the current study, a total dose of 1500 U Dysport will be injected at each cycle, divided between UL and LL, with no more than 1000 U being administered into the UL. Although the maximum dose of Dysport in most regions is 1000 U, a dose of 1500 U is licensed for local symptomatic treatment of spasticity affecting lower limbs in adults in some countries (France, Spain, Italy and Brazil). Therefore, this is a tested and approved dose and will be permitted in the current study [8]. A maximum of 1000 U will be permitted for injection in the UL in the current study, in line with current marketing authorisations. A total of two injections are planned for each subject, with each injection separated by at least 12 weeks (maximum 20 weeks). This is

in line with clinical studies that have shown improved efficacy after repeated administrations (see Section 1.3).

This will be an open-label study with no placebo control. GSC, which cannot be replaced with placebo, is part of the study treatment; therefore, the study was not designed with a placebo control for the study treatment. With regard to AbobotulinumtoxinA, there is already extensive evidence demonstrating AbobotulinumtoxinA efficacy on spasticity versus placebo in upper and lower limbs. Furthermore, it would not be ethical to give subjects with spasticity placebo when an effective treatment exists.

The current study will enrol adult subjects with hemiparesis due to acquired brain injury (ABI), presenting with muscle overactivity impeding motor function based on the investigator's judgement, including potentially one of the following requiring BoNT treatment: typical clenched fist, flexed wrist, flexed elbow, or plantar flexed foot pattern. All subjects must have had the ABI at least 12 months before the study.

# 2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

## 2.1 Purpose of the Study

The aim of this study is to assess the effect of AbobotulinumtoxinA injected in both the UL and LL, given in conjunction with daily GSC therapy, on voluntary movements in subjects with hemiparesis due to ABI (see Section 1.6).

## 2.2 Study Objectives

The primary objective of the study is to assess the responder rate as defined by the improvement of composite active range of motion (AROM) in the primary targeted limb, either upper limb (UL) or lower limb (LL), depending on which one has been selected as a primary treatment target (TT), following two consecutive AbobotulinumtoxinA injections combined with a Guided Self-rehabilitation Contract (GSC) in subjects with spastic hemiparesis following ABI.

The secondary objectives of the study are as follows:

- to assess the effectiveness of AbobotulinumtoxinA combined with a GSC on:
  - the responder rate as defined by the improvement of composite active range of motion (AROM) in the primary targeted limb, either upper limb (UL) or lower limb (LL), depending on which one has been selected as a primary treatment target (TT), following one AbobotulinumtoxinA injection combined with a Guided Self-rehabilitation Contract (GSC)
  - AROM against 10 prespecified muscle groups: 5 in upper and 5 in lower limbs
  - composite AROM against injected muscle groups (any of the 10 prespecified) of each limb
  - full composite AROM against five UL muscle groups or full composite AROM against five LL muscle groups, regardless of whether the muscle groups were injected or not
  - active function in the upper and lower limbs using the Modified Frenchay Scale (MFS) and maximal Walking Speed (WS) barefoot, respectively.
- to assess subject satisfaction with regard to the use of a GSC
- to measure the changes in subject and physiotherapist beliefs that a GSC will help to improve function
- to assess subject compliance with the GSC
- to assess global benefits by both the investigator and the subject (or caregiver)
- in subjects not reinjected at Week 12, to assess satisfaction with longer than 12 weeks interval between 2 injections
- to assess health-related quality of life
- to assess safety parameters.

The exploratory objective is as follows:

- to assess correlation between full composite AROM and active function (MFS in UL and WS in LL).

# 3 STUDY DESIGN

## 3.1 General Design and Study Schema

This is a multicentre, prospective, single-arm study to evaluate the efficacy and safety of two consecutive injections of AbobotulinumtoxinA administered in both upper and lower limbs (total dose of 1500 U) in conjunction with daily GSC therapy for at least a six-month duration, in adults with spastic hemiparesis due to ABI. The effect of treatment (i.e. AbobotulinumtoxinA+GSC) on voluntary movements will be assessed.

Each subject will undergo two injection (treatment) cycles, receiving AbobotulinumtoxinA 1500 U on Day 1 of each cycle; the two dosing occasions will be separated by at least 12 weeks (maximum 20 weeks). The study design is shown in Figure 1.

It is planned to recruit approximately 155 subjects at approximately 20 sites in Europe and the USA, in order to achieve 145 evaluable subjects. Recruitment will be stratified by country to ensure that 50% of subjects have the UL as primary TT and 50% of subjects have the LL as primary TT (with ±10% flexibility).

At the Baseline Visit (Cycle 1), all subjects will undergo screening procedures and baseline study assessments after written informed consent has been provided. The primary TT limb (UL or LL) will be defined by the investigator, following discussion with the subject. If the primary TT limb is the upper limb, the secondary TT limb will be the lower limb (and vice versa).

AbobotulinumtoxinA (1500 U) will be administered as a split dose, in both the UL and LL; the dose given in each limb will be decided by the investigator, based on which was considered the primary TT limb at the Baseline Visit and in accordance with the following dosing rules:

- electrical stimulation (ES) will be used to target the injection sites; Ultrasound guiding could be used in addition to ES in case this technique is used in routine clinical practice;
- at least half the total dose (i.e. ≥750 U) must be injected in the primary TT limb (the rest of the dose is injected in the secondary TT limb);
- a maximum of 1000 U can be injected in an UL (even if it is the primary TT limb);
- there is no maximum dose that can be injected in a LL, provided that some remainder dose (out of the 1500 U total) is used for the UL injections;

List of recommended UL and LL muscles and Dysport dose per muscle is provided in Sections 6.1.1.1 and 6.1.1.2.

- the second AbobotulinumtoxinA injection (Cycle 2) may be given in a different split to the first injection (Cycle 1), at the discretion of the investigator. However, the same minimal/maximal rules apply, as described above. The primary TT remains the same for both AbobotulinumtoxinA injections and the study duration.

Each subject will also receive a personalised GSC and will be asked to perform daily GSC therapy throughout the study, including the recording in a diary of the performed exercises of the prescribed GSC therapy. Telephone calls will be made to the subject every 2 weeks to check how the GSC therapy is being performed and that the diary is being filled out every day.

In **Cycle 1**, postinjection follow-up (FU) visits will be held after the first AbobotulinumtoxinA administration, as follows:

- at Week 6;

- at Week 12: the investigator will decide if the subject is still responding to treatment or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If a second injection is not given, the subject will return at Week 16;
- at Week 16: the investigator will again decide if the subject is still responding to treatment or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If a second injection is not given, the subject will return at Week 20;
- at Week 20: the investigator will again decide if the subject is still responding to treatment or if a second injection is needed, based on his/her clinical judgement. If a second injection is given, this marks the start of Cycle 2 (see below). If the investigator decides that a second injection should not be given, based on his/her clinical judgement, the subject will be withdrawn from the study.

In **Cycle 2**, postinjection FU visits will be held after the second AbobotulinumtoxinA administration, as follows:

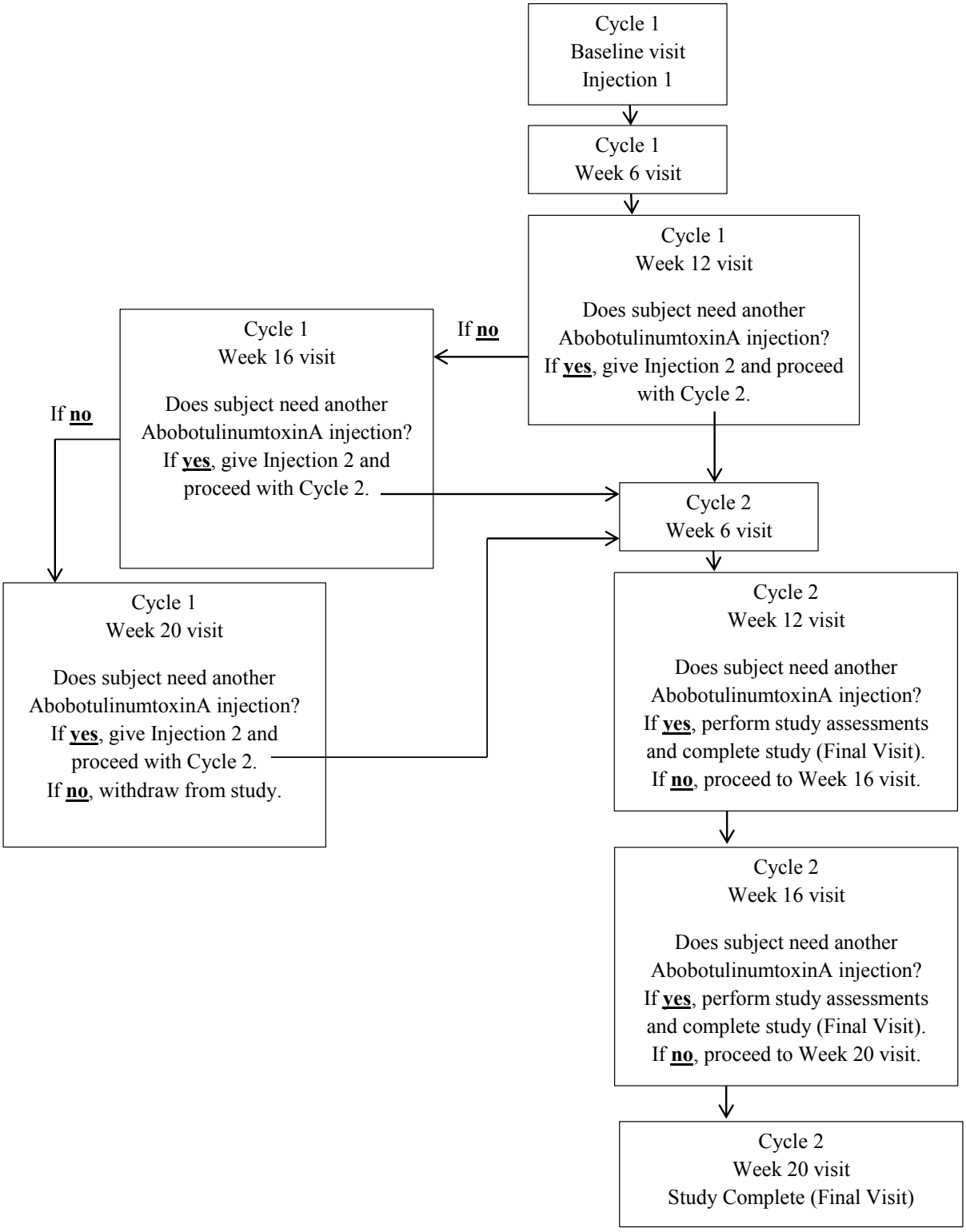
- at Week 6;
- at Week 12: the investigator will decide if the subject is still responding to treatment or if a further injection is needed, based on his/her clinical judgement. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection outside the study is given) (i.e. Final Visit). If a further injection is not needed, the subject will return at Week 16;
- at Week 16: the investigator will again decide if the subject is still responding to treatment or if a further injection is needed, based on his/her clinical judgement. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection outside the study is given) (i.e. Final Visit). If a further injection is not needed, the subject will return at Week 20;
- at Week 20: the subject completes the study after study assessments have been performed, regardless of whether a further injection is needed (i.e. Final Visit).

The overall duration of the study for each subject will be between 24 and 40 weeks (from Baseline Visit to Final Visit).

Subjects who receive two AbobotulinumtoxinA administrations and complete the required postinjection FU visits will be considered to have completed the study.

Subjects who withdraw from the study before completion of scheduled visits will have Early Withdrawal Visit assessments performed at their last visit.

**Figure 1 Study Design**



## 3.2 Primary and Secondary Endpoints and Evaluations

### *3.2.1 Primary Efficacy Endpoint and Evaluation*

The primary efficacy endpoint is as follows:

- the percentage of responder subjects at Week 6 after the second injection, according to composite AROM in the primary TT limb.

Composite AROM ($X_A$), regardless of whether the muscle groups were injected or not, as measured by goniometer in the primary TT limb (either UL or LL, depending on which one has been selected as the primary TT limb), will be calculated as follows:

- composite $X_A$ UL: $X_A$ UL = $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$
- composite $X_A$ LL: $X_A$ LL = $X_{Asol}$ + $X_{AGN}$

*where for UL: EF=elbow flexors, WF=wrist flexors and FF=extrinsic finger flexors, and for LL: Sol=soleus and GN=gastrocnemius muscles.*

Definition of a responder: a subject will be considered a responder if he/she achieves at least the predefined improvement threshold - larger or equal to 35° in UL or 5° in LL - in the primary TT limb (based on the composite AROM individual change from baseline to Week 6 after the second injection).

### *3.2.2 Secondary Efficacy Endpoints and Evaluations*

The secondary efficacy endpoints are as follows:

- the percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb
- AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- composite AROM against injected muscle groups (any of the 10 prespecified), in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- full composite AROM against five UL muscle groups ($X_A$ full UL = $X_{ASE}$ + $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$ + $X_{APT}$) or full composite AROM against five LL muscle groups ($X_A$ full LL = $X_{Asol}$ + $X_{AGN}$ + $X_{AGM}$ + $X_{AHS}$ + $X_{ARF}$), regardless of whether the muscle groups were injected or not: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only

  *where for UL: SE=shoulder extensors, EF=elbow flexors, WF=wrist flexors, FF=extrinsic finger flexors and PT=pronator teres,*
  *and for LL: Sol=soleus, GN=gastrocnemius muscles, GM=gluteus maximus, HS=hamstrings and RF=rectus femoris*
- active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks assessed locally and centrally by a reviewer blinded regarding the date of the video recording/visit number) at Week 12 after each injection cycle
- active LL function measured using maximal WS barefoot without walking aids or, if absolutely necessary, with a cane, measured on a 10-metre WST: mean change from baseline at Week 12 after each injection cycle. (If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.)
- subject satisfaction with the GSC: at baseline (only for patients who had GSC performed previously), Week 6, Week 12 and re-injection/last cycle visits only

- changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)
- global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle
- in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- quality of life changes, measured on the EQ-5D 5L and SF-12 scales: change from baseline to Final Visit.

### *3.2.3 Safety Endpoint and Evaluation*

Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study or subject withdrawal. Other safety data will include vital signs.

### *3.2.4 Exploratory Endpoint and Evaluation*

The correlation between full composite AROM and active function (MFS in UL and WS in LL) will be explored.

## 3.3 Randomisation and Blinding

This is a nonrandomised, open-label, single-arm study.

Recruitment will be stratified by country to ensure that 50% of subjects have the UL as primary TT and 50% of subjects have the LL as primary TT (with ±10% flexibility). This will be controlled at the country level.

## 3.4 Study Treatments and Dosage

A total dose of AbobotulinumtoxinA 1500 U will be used in each of two injection (treatment) cycles. In each subject, the dose of 1500 U will be split between the UL and LL, as determined by the investigator, based on which limb was considered the primary TT limb at the Baseline Visit and in accordance with prespecified limits. The primary TT will remain the same for both AbobotulinumtoxinA injections and the study duration.

A more detailed description of administration procedures is given in Section 6.1.1.

All subjects will also perform daily GSC therapy. A detailed description of GSC therapy is given in Section 6.1.2.

The investigational medicinal product (IMP) will be packaged by Dreux, France, and delivered to the investigational sites in Europe, or to interim storage in the USA (before delivery to study sites in the USA) and in other countries where interim storage will be needed. A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form.

The sponsor's representative will receive a Certificate of Analysis for the batch of IMP that has been used under their study, Material Data Safety Sheet for the active IMP, and Packaging Order which reflects the product release statement.

The core label texts for all packaging units 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 IMP labels is displayed below:

- sponsor name
- study number
- pharmaceutical dosage form
- route of administration
- quantity of dose units
- batch number
- specific blank space to enter the subject identification
- "Keep out of reach of children"
- "For clinical study use only" (for nonUS sites)
- "Caution: new drug limited by Federal Law to investigational use" (for US sites)
- name, address and telephone number of the sponsor, contract research organisation (CRO) or investigator (the main contact for information on the product, clinical study and emergency unblinding) (for sites in the European Union)
- storage conditions
- expiry date.

The investigator, or designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the electronic case report form (eCRF).

## 3.5 Study Duration

This study will consist of two open-label injection (treatment) cycles. Each cycle will include postinjection FU visits of up to 20 weeks (see Section 3.1). Subjects are expected to participate in this study for a minimum of 24 weeks (if they have postinjection FU visits up to Week 12 only, following both injections) and a maximum of 40 weeks (if they have postinjection FU visits up to Week 20, following both injections).

The subject's participation in the study will be considered to have ended at the time of the Final Visit. This will be no later than 20 weeks after the second AbobotulinumtoxinA injection.

The overall duration of the study will be between approximately 15 and 18 months. The study will be considered to have started when the first subject provides signed informed consent.

The study will be considered to have ended after the last subject has completed his/her Final Visit.

## 3.6 Stopping Rules and Discontinuation Criteria

In the following circumstances, subjects will be withdrawn from the study early:

- subject consent withdrawal
- subject lost to follow up
- occurrence of an AE that, in the opinion of the investigator, makes the administration of the study treatment undesirable
- investigator's and/or sponsor's decision to withdraw the subject if it is considered to be in the best interest of the subject
- occurrence of a new ABI

- continuous failure to comply with the provisions of the study protocol, which is likely to have an adverse impact on the safety or well-being of the subject, or could jeopardise the scientific value of the study
- investigator decides that subject does not need a second AbobotulinumtoxinA administration at Week 20 in Cycle 1.

Subject withdrawal criteria and procedures are described in Section 4.3.

## 3.7 Investigational Medicinal Product Preparation Storage and Accountability

### *3.7.1 Investigational Medicinal Product Storage and Security*

The investigator, or an approved representative (for example, pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature (2 to 8°C) monitored storage conditions, in accordance with applicable regulatory requirements.

### *3.7.2 Investigational Medicinal Product Preparation*

The investigator, or an approved representative (for example, pharmacist), will ensure that all IMP is reconstituted and dispensed by qualified staff members.

### *3.7.3 Investigational Medicinal Product Accountability*

All IMP and any other study related material is to be accounted for on the IMP 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 in the IMP accountability log.

All used or unused clinical study supplies should be destroyed locally and a certificate of destruction should be provided to the sponsor.

## 3.8 Maintenance of Randomisation and Blinding

Not applicable.

## 3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP, the sponsor-assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain 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), IMP 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.

Definition 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 (for example, 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 medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel and by local and possibly foreign, competent authorities (CAs). This information is included in the informed consent.

# 4 SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Inclusion Criteria

All subjects must fulfil all of following criteria to be included in the study:

(1) Subjects aged at least the national legal adult age.

(2) Subjects with hemiparesis due to ABI (i.e. stroke or Traumatic Brain Injury (TBI)) presenting with muscle overactivity impeding motor function based on investigator's judgement including, but not limited to, at least one of the following requiring BoNT treatment: typical clenched fist; flexed wrist; flexed elbow; or plantar flexed foot.

(3) At least 12 months since the ABI.

(4) Naïve or non-naïve to BoNT treatment; if non-naïve, at least 4 months after the last BoNT injection, of any serotype.

(5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS locally rated score, if the primary TT limb is the UL.

(6) A 10-metre maximal WS barefoot between 0.2 and 1.4 m/s, if the primary TT limb is the LL. Maximal WS barefoot will be performed preferably without walking aids. However, a cane may be permitted if absolutely necessary (although this may prevent detection of treatment-induced improvements). In this case, the same aid will have to be used for all WS assessments during the study.

(7) Subjects must provide written informed consent to participate in the study prior to any study-related procedures.

(8) Female subjects of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study until the last visit of the subjects and for at least 12 weeks post injection. Acceptable methods of contraception include total abstinence, male partner has had a vasectomy, double barrier method (e.g. male condom plus spermicide, or female diaphragm plus spermicide), intrauterine device, or hormonal contraceptive (oral, transdermal, implanted and injected)..

(9) Subjects must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period and willing to return to the clinic for the follow-up evaluation as specified in the protocol.

## 4.2 Exclusion Criteria

Subjects will not be included in the study if any of the following exclusion criteria are met:

(1) Inability to understand protocol procedures and requirements, which, in the opinion of the investigator, could negatively impact on protocol compliance, in particularly inability to exercise according to the GSC.

(2) Previous surgery on the affected muscles and ligaments, tendons, nerve trunks, or bones of the treated upper or lower limb.

(3) Previous treatment with phenol and/or alcohol in any of the treated limbs any time before the study.

(4) Any medical condition (including severe dysphagia or breathing difficulties) that may increase, in the opinion of the investigator, the likelihood of AEs related to BoNT-A treatment.

(5) Subjects treated, or likely to be treated, with intrathecal baclofen during the course of the study or during the 4 weeks before study entry.

(6) Current, planned or received within the last 4 weeks prior to study treatment, treatment with any drug that interferes either directly or indirectly with neuromuscular function (for example, aminoglycosides).

(7) Major neurological impairment other than spastic paresis (including major proprioceptive ataxia or apraxia on the paretic side) that could negatively impact on the functional performance of the subject.

(8) Known disease of the neuromuscular junction (such as Lambert-Eaton myasthenic syndrome or myasthenia gravis).

(9) Known sensitivity to BoNT-A or any excipient of Dysport.

(10) Infection at the injection site(s).

(11) Current pregnancy or lactation. A pregnancy test will be performed at the start of the study for all female subjects of childbearing potential (i.e. not surgically sterile or 2 years postmenopausal).

(12) Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.

(13) Abnormal baseline findings or any other medical condition(s) that, in the opinion of the investigator, might jeopardise the subject's safety.

(14) Subjects who have participated in any therapeutic clinical study/received any investigational agent within 30 days of enrolment.

### 4.3 Subject Withdrawal Criteria and Procedures

Subjects are free to withdraw completely from the study at any time upon request and subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects withdrawn from the study will not be replaced. Under no circumstances will subjects be enrolled more than once.

Whenever possible, if a subject withdraws from the study for whatever reason, they should still attend the Early Withdrawal Visit (see Section 5.2.3). If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Reasons for withdrawal of subjects from the study are given in Section 3.6.

If the subject is withdrawn 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 eCRF. Withdrawal due to AEs should be distinguished from withdrawal due to any other reason.

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 8.1 in order to assess the safety of the IMP.

# 5 STUDY PROCEDURES

## 5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 2.

A summary of the reinjection scenarios for this study is shown in Table 3.

**Table 2 Study Procedures and Assessments**

| Assessment[a] | Injection Cycle 1 | | | | | Injection Cycle 2 | | | | | Early withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline/ Inj 1 | Postinjection FU visits | | | | Inj 2[c] | Postinjection FU visits | | | | |
| | | W 6 (±7 days) | W 12[b] (+7 days) | W 16[b] (±7 days) | W 20[b] (±7 days) | | W 6 (±7 days) | W 12[d] (+7 days) | W 16[d] (±7 days) | W 20[d],[e] (±7 days) | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | | **6** | **7** | **8** | **9** | |
| Informed consent[f] | X | | | | | | | | | | |
| Eligibility criteria | X | | | | | | | | | | |
| Demographics[g] | X | | | | | | | | | | |
| Disease history[h] | X | | | | | | | | | | |
| Previous GSC / physiotherapy[i] | X | | | | | | | | | | |
| Previous BoNT injection(s)[j] | X | | | | | | | | | | |
| Significant medical or surgical history[k] | X | | | | | | | | | | |
| Prior/concomitant medications for UL and LL spasticity[l] | X | X | X | X | X | | X | X | X | X | X |
| Prior/concomitant medications and non-drug therapies[m] | X | X | X | X | X | | X | X | X | X | X |
| Concomitant surgical procedures | | X | X | X | X | | X | X | X | X | X |
| Urine pregnancy test[n] | X | | | | | | | | | | |
| Physical examination | X | X | X | X | X | | X | X | X | X | X |
| Vital signs[o] | X | | | | | X | | X[p] | X[p] | X[p] | X[p] |
| AROM in each muscle group of UL and LL[q] | X | X | X | X | X | | X | X | X | X | X |
| Selection of primary TT limb | X | | | | | | | | | | |
| MFS | X | | X | | | | | X | | | X |
| WST[r] | X | | X | | | | | X | | | X |
| Number of days without GSC therapy[s] | | X | X | X | X | | X | X | X | X | X |
| Subject satisfaction with GSC | X[v] | X | X | X[t] | X[t] | | X | X | X[p] | X[p] | X[p] |
| Subject satisfaction with longer interval between 2 injections | | | | X[t] | X[t] | | | | X[t] | X[t] | |

| Assessment[a] | Injection Cycle 1 | | | | | Injection Cycle 2 | | | | | Early withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline/ | Postinjection FU visits | | | | Inj 2[c] | Postinjection FU visits | | | | |
| Subject beliefs that GSC will help to improve functional capacity | X | X | X | X[t] | X[t] | | X | X | X[p] | X[p] | X[p] |
| Physiotherapist beliefs that GSC will help to improve functional capacity | X | X | X | X[t] | X[t] | | X | X | X[p] | X[p] | X[p] |
| Global assessment of benefits by investigator | | | X[t] | X[t] | X[t] | | | X[p] | X[p] | X[p] | X[p] |
| Global assessment of benefits by subject (or caregiver) | | | X[t] | X[t] | X[t] | | | X[p] | X[p] | X[p] | X[p] |
| EQ-5D 5L questionnaire | X | | | | | | | X[p] | X[p] | X[p] | X[p] |
| SF-12 questionnaire | X | | | | | | | X[p] | X[p] | X[p] | X[p] |
| AE reporting | X | X | X | X | X | | X | X | X | X | X |
| Study drug administration[u] | X | | (X) | (X) | (X) | X | | | | | |
| Visit status | X | X | X | X | X | | X | X | X | X | X |
| GSC | GSC therapy will be performed by the subject daily.<br>A telephone call will be made from the therapist to the subject every 2 weeks to check the subject is doing the GSC therapy daily and recording in the diary. | | | | | | | | | | |

ABI=Acquired brain injury; AE=Adverse event; AROM=Active range of motion; EQ-5D 5L=European Quality of Life 5 Dimensions; FU=Follow-up; GSC=Guided Self-rehabilitation Contract; Inj=AbobotulinumtoxinA injection; LL=Lower limb; MFS=Modified Frenchay Scale; SF-12=Short Form 12; TT=Treatment target; UL=Upper limb; W=Week; WST=Walking Speed Test.

a Assessments should be performed before the AbobotulinumtoxinA injection (if scheduled on an injection day).

b Cycle 1: The investigator decides if the subject is still responding to treatment or if a further AbobotulinumtoxinA injection is needed, based on his/her clinical judgement. At Week 12, if a second injection is given, this marks the start of Cycle 2; if a second injection is not given, the subject returns at Week 16. At Week 16, if a second injection is given, this marks the start of Cycle 2; if a second injection is not given, the subject returns at Week 20. At Week 20, if a second injection is given, this marks the start of Cycle 2; if the investigator decides that a second injection should not be given, based on his/her clinical judgement, the subject will be withdrawn from the study.

c Injection 2 will be performed at the Week 12, Week 16 or Week 20 visit after Injection 1, at the discretion of the investigator, based on his/her clinical judgement.

d Cycle 2: The investigator decides if the subject is still responding to treatment or if a further AbobotulinumtoxinA injection is needed, based on his/her clinical judgement. At Week 12, if a further injection is needed, the subject completes the study after study assessments have been performed (before the injection is given) (i.e. Final Visit); if a further injection is not needed, the subject returns at Week 16. At Week 16, if a further injection is needed, the subject completes the study after study assessments have been performed (before the injection is given) (i.e. Final Visit); if a further injection is not needed, the subject returns at Week 20. At Week 20, the subject completes the study after study assessments have been performed (regardless of whether a further injection is needed) (i.e. Final Visit).

e For all subjects attending the Week 20 visit (Cycle 2), this will be the Final Visit.

f Informed consent must be obtained before the subject undergoes any study-specific procedures.

g Demographics: sex and date of birth; race and ethnicity will also be collected if permitted according to local regulations.

h Disease history: date and type of ABI, date of spasticity development.

| | |
|---|---|
| i | Record all details of previous GSC or physiotherapy within 4 months before Baseline.. |
| j | Record if subject is naïve or non-naïve to BoNT treatment; if non-naïve to BoNT treatment, record dates of the first injection and last injection, which limbs were injected, and BoNT brand and dose used in the last injection. |
| k | Medical history: any significant past or ongoing medical or surgical conditions (not related to UL or LL spasticity). |
| l | Prior and concomitant medications for UL or LL spasticity: therapies taken from 4 weeks prior to baseline through the study (including the subject's last study visit). |
| m | Prior and concomitant medications and nondrug therapies: therapies taken from 4 weeks prior to baseline through the study (including the subject's last study visit). |
| n | Urine pregnancy test: recorded for females of childbearing potential only. |
| o | Measured at Baseline Visit, second injection visit and Final Visit, only (or early withdrawal). Vital signs: diastolic and systolic blood pressure and heart rate measured in the supine position after 5 minutes rest. Weight will be measured at baseline, second injection and last visit; height will be measured at baseline only. |
| p | To be performed at the Final Visit (which may be Week 12, Week 16 or Week 20 after Injection 2) or early withdrawal. |
| q | AROM is measured in each muscle group of the UL and LL (irrespective of whether injected or not). |
| r | WST is to be performed in the same condition as at Baseline Visit, for example, if a cane was used at the Baseline Visit, the same cane should be used for this test at other visits. |
| s | The number of days when GSC therapy was not performed since the last visit, as recorded in the subject diary, will be counted and recorded in the eCRF. |
| t | To be performed only at the last postinjection FU visit after Injection 1 (i.e. the visit where second injection is performed, which may be Week 12, Week 16 or Week 20). |
| u | AbobotulinumtoxinA (Dysport) (total dose 1500 U) will be administered by i.m. injection in the subject's UL and LL, according to the dose split decided by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits. |
| v | Only for subjects who had GSC previously |

**Table 3 Summary of Reinjection Scenarios**

| | Overall week number | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
| | <--------6 weeks----------> | | | | | | | <--------6 weeks----------> | | | | | | <--------6 weeks----------> | | | | | | <--------6 weeks----------> | | | | | <-----4 weeks-----> | | | | <-----4 weeks-----> | | | | | | | | | |
| [a] | x | | | | | | o | | | | | | x | | | | | | o | | | | | | o (FV) | | | | | | | | | | | | | | | | |
| [b] | x | | | | | | o | | | | | | x | | | | | | o | | | | | | o | | | | o (FV) | | | | | | | | | | | | |
| [c] | x | | | | | | o | | | | | | x | | | | | | o | | | | | | o | | | | o | | | | o (FV) | | | | | | | | |
| | <--------6 weeks----------> | | | | | | | <--------6 weeks----------> | | | | | | <----4 weeks---> | | | | <--------6 weeks----------> | | | | | | <--------6 weeks----------> | | | | | <-----4 weeks-----> | | | | <-----4 weeks-----> | | | | | | | | |
| [d] | x | | | | | | o | | | | | | o | | | | x | | | | | | o | | | | | | o (FV) | | | | | | | | | | | | |
| [e] | x | | | | | | o | | | | | | o | | | | x | | | | | | o | | | | | | o | | | | o (FV) | | | | | | | | |
| [f] | x | | | | | | o | | | | | | o | | | | x | | | | | | o | | | | | | o | | | | o | | | | o (FV) | | | | |
| | <--------6 weeks----------> | | | | | | | <--------6 weeks----------> | | | | | | <----4 weeks---> | | | | <----4 weeks---> | | | | <--------6 weeks----------> | | | | <--------6 weeks----------> | | | | | <-----4 weeks-----> | | | | <-----4 weeks-----> | | | | |
| [g] | x | | | | | | o | | | | | | o | | | | o | | | | x | | | | | | o | | | | o (FV) | | | | | | | | | | | | |
| [h] | x | | | | | | o | | | | | | o | | | | o | | | | x | | | | | | o | | | | o | | | | o (FV) | | | | | | |
| [i] | x | | | | | | o | | | | | | o | | | | o | | | | x | | | | | | o | | | | o | | | | o | | | | o (FV) | | |

FV=Final Visit; o=Postinjection follow-up visit; x=Injection.

Note: The investigator's decision whether to give an AbobotulinumtoxinA injection is based on his/her clinical judgement, depending on if the subject is still responding to treatment or if a further AbobotulinumtoxinA injection is needed (see Section 3.1).

a Injection 2 given at Week 12 relative to Injection 1, with 2 postinjection FU visits at Weeks 6 and 12 relative to Injection 2.

b Injection 2 given at Week 12 relative to Injection 1, with 3 postinjection FU visits at Weeks 6, 12 and 16 relative to Injection 2.

c Injection 2 given at Week 12 relative to Injection 1, with 4 postinjection FU visits at Weeks 6, 12, 16 and 20 relative to Injection 2.

d Injection 2 given at Week 16 relative to Injection 1, with 2 postinjection FU visits at Weeks 6 and 12 relative to Injection 2.

e Injection 2 given at Week 16 relative to Injection 1, with 3 postinjection FU visits at Weeks 6, 12 and 16 relative to Injection 2.

f Injection 2 given at Week 16 relative to Injection 1, with 4 postinjection FU visits at Weeks 6, 12, 16 and 20 relative to Injection 2.

g Injection 2 given at Week 20 relative to Injection 1, with 2 postinjection FU visits at Weeks 6 and 12 relative to Injection 2.

h Injection 2 given at Week 20 relative to Injection 1, with 3 postinjection FU visits at Weeks 6, 12 and 16 relative to Injection 2.

i Injection 2 given at Week 20 relative to Injection 1, with 4 postinjection FU visits at Weeks 6, 12, 16 and 20 relative to Injection 2.

## 5.2 Study Visits

### *5.2.1 Injection Cycle 1: Baseline Visit and Postinjection Follow-Up Visits*

#### *5.2.1.1 Baseline Visit*

A signed and dated informed consent form will be obtained before any study-specific procedures are performed.

After written informed consent is obtained, potential subjects will be allocated a subject number. Each investigator will maintain a record of all subjects who signed the informed consent form.

The following study assessments will be performed before the AbobotulinumtoxinA injection:

- eligibility check (inclusion/exclusion criteria)
- demographic data (sex and date of birth; race and ethnicity will also be collected if permitted according to local regulations)
- disease history: date and type of ABI, date of spasticity development
- previous GSC or physiotherapy history (within 4 months prior to baseline)
- subject satisfaction on previous GSC (if applicable)
- if subject is non-naïve to BoNT treatment: dates of the first injection and last injection, which limbs were injected, and BoNT brand and dose used in the last injection
- medical history, including any significant past or ongoing medical or surgical conditions (not related to UL or LL spasticity)
- prior and concomitant medications for UL or LL spasticity (taken from 4 weeks prior to baseline)
- other prior and concomitant medications and nondrug therapies (taken from 4 weeks prior to baseline)
- urine pregnancy test (females of childbearing potential only)
- physical examination
- vital signs (blood pressure and heart rate, weight, height)
- AEs (collected from after written informed consent and throughout the study)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- selection of the primary TT limb (UL or LL) by the investigator, based on his/her clinical judgement and in agreement with the subject
- MFS
- WST
- subject and Physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject completion of EQ-5D 5L questionnaire
- subject completion of SF-12 questionnaire

- preparation of individual subject GSC by the investigator/physiotherapist and diary provided to subject (see Section 6.1.2).

After completion of study assessments and confirmation of eligibility, the following will be performed:

- selection of dose split in the UL and LL by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits (see Section 6.1.1)
- AbobotulinumtoxinA (Dysport) (total dose 1500 U) will be administered by i.m. injection in the subject's UL and LL, according to the agreed dose split.

Telephone calls will be made to the subject every 2 weeks to check the GSC therapy is being performed daily.

*5.2.1.2 Week 6 (± 7 days)*

The following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist.

*5.2.1.3 Week 12 (+7 days)*

The following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight) (to be measured only if second injection is given at this visit)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- MFS
- WST (in the same condition as at Baseline Visit, for example, if a cane was used at Baseline Visit, the same cane should be used for this test also)
- subject assessment of satisfaction with GSC

- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- global assessment of benefits by investigator (only if the second injection of AbobotulinumtoxinA is given at this visit)
- global assessment of benefits by subject (or caregiver) (only if the second injection of AbobotulinumtoxinA is given at this visit)
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist.

The investigator will decide if the subject is still responding to treatment or if a second AbobotulinumtoxinA injection is needed at this visit, based on his/her clinical judgement. If a second injection is not given, the subject will return at Week 16. If a second injection is given, this marks the start of Cycle 2 (see Section 5.2.2) and the following procedures will be performed:

- selection of dose split in the UL and LL by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits (see Section 6.1.1)
- AbobotulinumtoxinA (Dysport) (total dose 1500 U) will be administered by i.m. injection in the subject's UL and LL, according to the agreed dose split.

*5.2.1.4 Week 16 (± 7 days) (Only if AbobotulinumtoxinA Not Administered at Week 12 Postinjection FU Visit After Injection 1)*

This visit is performed only if the second injection of AbobotulinumtoxinA was not given at the previous visit.

If this visit is performed, the following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight) (to be measured only if second injection is given at this visit)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- global assessment of benefits by investigator (only if the second injection of AbobotulinumtoxinA is given at this visit)
- global assessment of benefits by subject (or caregiver) (only if the second injection of AbobotulinumtoxinA is given at this visit).

- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist.

The investigator will decide if the subject is still responding to treatment or if a second AbobotulinumtoxinA injection is needed at this visit, based on his/her clinical judgement. If a second injection is not given, the subject will return at Week 20. If a second injection is given, this marks the start of Cycle 2 (see Section 5.2.2) and the following procedures will be performed:

- in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- selection of dose split in the UL and LL by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits (see Section 6.1.1)
- AbobotulinumtoxinA (Dysport) (total dose 1500 U) will be administered by i.m. injection in the subject's UL and LL, according to the agreed dose split.

*5.2.1.5 Week 20 (± 7 days) (Only if AbobotulinumtoxinA Not Administered at Week 12 or Week 16 Postinjection FU Visit After Injection 1)*

This visit is performed only if the second injection of AbobotulinumtoxinA was not given at the previous visit.

If this visit is performed, the following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- global assessment of benefits by investigator
- global assessment of benefits by subject (or caregiver)
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist.

The investigator will decide if the subject is still responding to treatment or if a second AbobotulinumtoxinA injection is needed at this visit, based on his/her clinical judgement. If the investigator decides that a second injection should not be given, based on his/her clinical judgement, the subject will be withdrawn from the study. If a second injection is given, this marks the start of Cycle 2 (see Section 5.2.2) and the following procedures will be performed:

- in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- selection of dose split in the UL and LL by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits (see Section 6.1.1)
- AbobotulinumtoxinA (Dysport) (total dose 1500 U) will be administered by i.m. injection in the subject's UL and LL, according to the agreed dose split.

### *5.2.2 Injection Cycle 2: Postinjection Follow-Up Visits*

Telephone calls will be made to the subject every 2 weeks to check the GSC therapy is being performed daily.

#### *5.2.2.1 Week 6 (± 7 days)*

The following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- measurement of AROM in 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist.

#### *5.2.2.2 Week 12 (+7 days)*

The following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight) (to be measured only if this is the Final Visit)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- MFS
- WST (in the same condition as at Baseline Visit, for example, if a cane was used at Baseline Visit, the same cane should be used for this test also)
- subject assessment of satisfaction with GSC

- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist (if this is not the Final Visit).

The investigator will decide if the subject is still responding to treatment or if a further AbobotulinumtoxinA injection is needed at this visit, based on his/her clinical judgement. If a further injection is not given, the subject will return at Week 16. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection is given) (i.e. this is the Final Visit) and the following procedures will be performed:

- global assessment of benefits by investigator
- global assessment of benefits by subject (or caregiver)
- subject completion of EQ-5D 5L questionnaire
- subject completion of SF-12 questionnaire.

#### *5.2.2.3 Week 16 (± 7 days) (Only if AbobotulinumtoxinA Not Administered at Week 12 Postinjection FU Visit After Injection 2)*

If this visit is performed (see Section 5.2.2.2), the following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight) (to be measured only if this is the Final Visit)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- GSC exercises may be adjusted, based on the clinical judgement of the investigator or physiotherapist (if this is not the Final Visit).

The investigator will decide if the subject is still responding to treatment or if a further AbobotulinumtoxinA injection is needed at this visit, based on his/her clinical judgement. If a further injection is not given, the subject will return at Week 20. If a further injection is needed, the subject completes the study after study assessments have been performed (before the injection is given) (i.e. this is the Final Visit) and the following procedures will be performed:

- in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- global assessment of benefits by investigator
- global assessment of benefits by subject (or caregiver)

- subject completion of EQ-5D 5L questionnaire
- subject completion of SF-12 questionnaire.

#### *5.2.2.4 Week 20 (± 7 days) (Only if AbobotulinumtoxinA Not Administered at Week 16 Postinjection FU Visit After Injection 2)*

If this visit is performed (see Section 5.2.2.2), it will be considered the Final Visit and the following assessments will be performed:

- AE check
- concomitant medication review
- physical examination
- vital signs (blood pressure and heart rate, weight)
- measurement of AROM against 10 prespecified muscle groups of the UL and LL (irrespective of whether injected or not)
- subject assessment of satisfaction with GSC
- subject and physiotherapist completion of Likert scale to assess beliefs that GSC will help to improve functional capacity
- subject GSC diary check and record the number of days GSC not performed in eCRF
- global assessment of benefits by investigator
- global assessment of benefits by subject (or caregiver)
- in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- subject completion of EQ-5D 5L questionnaire
- subject completion of SF-12 questionnaire.

### *5.2.3 Early Withdrawal Visit*

If the subject withdraws early from the study, the procedures described for Injection Cycle 2, Week 12 (see Section 5.2.2.2) should be completed, if possible.

# 6 TREATMENT OF SUBJECTS

## 6.1 Study Drugs Administered

This is a single-arm study and all subjects will receive the same study treatment.

At the Baseline Visit (Cycle 1), all subjects will be allocated a subject number after giving written informed consent. Following baseline assessments and confirmation of eligibility for the study, AbobotulinumtoxinA (1500 U) will be administered by i.m. injection as a split dose, in both the UL and LL (see Section 6.1.1).

In Cycle 2, all subjects will receive a second administration of AbobotulinumtoxinA (1500 U) given as a split dose, in both the UL and LL. The dose split (per limb and per muscle) may be different to the dose split given for the first administration of AbobotulinumtoxinA, but it must follow the same limits (see Section 6.1.1).

Each subject will also receive a personalised GSC and will be asked to perform GSC therapy daily throughout the study (from Baseline Visit to Final Visit). Details are provided in Section 6.1.2.

*Note: For subjects receiving antivitamin K therapy the Investigator will have to ensure that the International Normalised Ratio (INR) is below 3.5 within 1 week prior to study treatment administration.*

*Subjects currently receiving oral anti-spasticity medications (e.g. Baclofen) may be included provided the dose will be kept constant during the study.*

### *6.1.1 AbobotulinumtoxinA (Dysport)*

The IMP, AbobotulinumtoxinA (Dysport®), will be supplied as a white lyophilised powder in a vial containing 500 U of BTX-A-haemagglutinin complex. A total dose of 1500 U will be used in each of two injection (treatment) cycles.

Each Dysport vial containing 500 U will be reconstituted with 2.5 mL sodium chloride for i.m. injection (0.9%). For the total dose of 1500 U, three vials will be used for each subject on each dosing occasion The total volume to be injected on each dosing occasion will be 7.5 mL.

In each subject, the dose of AbobotulinumtoxinA 1500 U will be split between the UL and LL. The dose given in each limb will be decided by the investigator, according to his/her clinical judgement, based on which limb was considered the primary TT limb at the Baseline Visit and prespecified limits (see dosing rules below).

The second administration of AbobotulinumtoxinA 1500 U will be given at the Week 12, Week 16 or Week 20 visit (after the first AbobotulinumtoxinA injection) (see Section 3.1). The primary TT will remain the same for both AbobotulinumtoxinA injections and the study duration.

The following dosing rules will apply:

- electrical stimulation will be used to target the injection sites;
- at least half the total dose (i.e. ≥750 U) must be injected in the primary TT limb. The rest of the dose is injected in the secondary TT limb;
- a maximum of 1000 U can be injected in an UL (even if it is the primary TT limb);
- there is no maximum dose that can be injected in a LL, provided that some remainder dose (out of the 1500 U total) is used for the UL injections;

- the second injection (Week 12, 16 or 20) may be given in a different split to the first injection, at the discretion of the investigator. However, the same minimal/maximal rules apply, as described above.

Details of study drug packaging and supply are provided in Section 3.4.

Dose administration details will be recorded in the eCRF, including the doses administered and details of the muscle groups that were injected. List of recommended muscles to be injected based on subject needs is presented in Section 6.1.1.1 for upper limb and Section 6.1.1.2 for lower limbs. Any muscle injected will be recorded in the eCRF.

#### *6.1.1.1 List of muscles recommended to be injected and Dysport Dosing by Muscle for Upper Limb Spasticity*

| MUSCLES | DOSES |
|---|---|
| Flexor carpi radialis (FCR) | 100 – 200 U |
| Flexor carpi ulnaris (FCU) | 100 – 200 U |
| Flexor digitorum profundus (FDP) | 100 – 200 U |
| Flexor digitorum superficialis (FDS) | 100 – 200 U |
| Flexor Pollicis Longus | 100 – 200 U |
| Adductor Pollicis | 25 – 50 U |
| Brachialis | 200 – 400 U |
| Brachioradialis | 100 – 200 U |
| Biceps Brachii (BB) | 200 – 400 U |
| Pronator Teres | 100 – 200 U |
| Triceps Brachii (long head) | 150 – 300 U |
| Pectoralis Major | 150 – 300 U |
| Subscapularis | 150 – 300 U |
| Latissimus Dorsi | 150 – 300 U |

#### *6.1.1.2 List of muscles recommended to be injected and Dysport Dosing by Muscle for Lower Limb Spasticity*

| MUSCLES | DOSES |
|---|---|
| Soleus muscle | 300 – 550 U |
| Gastrocnemius Medial Head | 100 – 450 U |
| Gastrocnemius Lateral Head | 100 – 450 U |
| Tibialis posterior | 100 – 250 U |
| Flexor digitorum longus | 50 – 200 U |
| Flexor digitorum brevis | 50 – 200 U |
| Flexor hallucis longus | 50 – 200 U |
| Flexor hallucis brevis | 50 – 100 U |
| Rectus femoris | 100 – 400 U |
| Hamstrings | 100 – 400 U |
| Adductor magnus | 100 – 300 U |
| Adductor Longus | 50 – 150 U |
| Adductor Brevis | 50 – 150 U |
| Gracilis | 100 – 200 U |
| Gluteus maximus | 100 – 400 U |

### *6.1.2 Second Study Therapy: GSC*

At the first visit, the investigator will prescribe the rehabilitation programme for the GSC [12]. The GSC is a motivational tool, which will be described in detail in the Study Operational Manual. The physiotherapist will teach each subject the stretching postures and exercises to perform on a daily basis throughout the study. These will be tailored to the individual subject's needs and will form the GSC therapy. The main focus will be on the primary TT limb (as determined at the Baseline Visit) and then the other limb. All muscle groups requiring active training and/or stretching should be trained.

The subjects will be given a diary at the Baseline Visit. As part of the GSC, they will be asked to record in this diary each day whether they have performed the GSC therapy. A copy of the diary and details regarding diary completion will be provided in the Study Operational Manual.

Telephone calls will be made to the subjects every 2 weeks to encourage them, check the GSC therapy is being performed daily and that they are completing the diary. The exercises may be adjusted at study visits, based on the clinical judgement of the investigator or physiotherapist.

At each postbaseline FU visit, the subjects will return the diary. The investigator will count the number of days when GSC therapy was not performed and will record this in the eCRF.

## 6.2 Concomitant Medication/Therapy

All previous GSC or physiotherapy will be recorded in the eCRF.

It will be recorded if subject is naïve or non-naïve to BoNT treatment. If non-naïve to BoNT treatment, the dates of the first injection and last injection, details of which limbs were injected, and the BoNT brand and dose used in the last injection will be recorded in the eCRF.

Prior and concomitant medications for UL or LL spasticity, taken from 4 weeks prior to baseline through the study (including the subject's last study visit) will be recorded in the eCRF. Other prior and concomitant medications and nondrug therapies taken from 4 weeks prior to baseline through the study (including the subject's last study visit) will also be recorded in the eCRF.

For each therapy, the generic name or trade name, dosage, route, start and end dates and indication will be recorded in the eCRF.

The following concomitant medications are not permitted during this study (see also Section 4.2):

- any other form of BoNT is not allowed;
- drugs which affect neuromuscular transmission, such as aminoglycoside antibiotics, should be used with caution;
- any anti-spasticity medication (such as Baclofen, tizanidine, eperisone or benzodiazepines), which is expected to change in dosage during the study is not allowed (anti-spasticity medications on a stable dose are permitted).

The following concomitant medications are permitted during this study but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study:

- changes in pain medication are acceptable if absolutely necessary and according to clinical judgment and will be recorded in the eCRF;
- concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for 6 weeks prior to study treatment and is expected to remain at this stable dose throughout the study;

- anticoagulant treatment if INR > 3.5 during the study.

## 6.3 Procedures for Monitoring Subject Compliance

Administrations of AbobotulinumtoxinA will be administered at the clinic by the investigator.

Telephone calls will be made every 2 weeks to the subject to remind him/her to perform the GSC therapy every day and fill out the diary. At each postbaseline FU visit, subjects will return their diary. The diary will be checked and the number of days when GSC therapy was not performed since the last visit will be recorded in the eCRF.

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol (see Section 3.6).

# 7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 2.

## 7.1 Primary Efficacy Endpoint and Evaluation

The primary efficacy endpoint is as follows:

- the percentage of responder subjects at Week 6 after the second injection, according to composite AROM in the primary TT limb.

Composite AROM ($X_A$), regardless of whether the muscle groups were injected or not, as measured by goniometer in the primary TT limb (either UL or LL, depending on which one has been selected as the primary TT limb), will be calculated as follows:

- composite $X_A$ UL: $X_A$ UL = $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$
- composite $X_A$ LL: $X_A$ LL = $X_{Asol}$ + $X_{AGN}$

*where for UL: EF=elbow flexors, WF=wrist flexors and FF=extrinsic finger flexors, and for LL: Sol=soleus and GN=gastrocnemius muscles.*

Definition of a responder: a subject will be considered a responder if he/she achieves at least the predefined improvement threshold - larger or equal to 35° in UL or 5° in LL - in the primary TT limb (based on the composite AROM individual change from baseline to Week 6 after the second injection).

## 7.2 Secondary Efficacy Endpoints and Evaluations

The secondary efficacy endpoints are as follows:

- the percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb
- AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- composite AROM against injected muscle groups (any of the 10 prespecified), in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- full composite AROM against five UL muscle groups ($X_A$ full UL = $X_{ASE}$ + $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$ + $X_{APT}$) or full composite AROM against five LL muscle groups ($X_A$ full LL = $X_{Asol}$ + $X_{AGN}$ + $X_{AGM}$ + $X_{AHS}$ + $X_{ARF}$), regardless of whether the muscle groups were injected or not: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only

  *where for UL: SE=shoulder extensors, EF=elbow flexors, WF=wrist flexors, FF=extrinsic finger flexors and PT=pronator teres,*
  *and for LL: Sol=soleus, GN=gastrocnemius muscles, GM=gluteus maximus, HS=hamstrings and RF=rectus femoris*
- active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number) at Week 12 after each injection cycle
- active LL function measured using maximal WS barefoot without walking aids or, if absolutely necessary, with a cane, measured on a 10-metre WST: mean change from baseline at Week 12 after each injection cycle. (If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.)

- subject satisfaction with the GSC: at baseline (only for subject who had GSC performed previously), Week 6, Week 12 and re-injection/last cycle visits only
- changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)
- global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle
- in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit
- quality of life changes, measured on the EQ-5D 5L and SF-12 scales: change from baseline to Final Visit.

Secondary efficacy endpoints and evaluations are summarised in Table 4.

**Table 4 Secondary Efficacy Endpoints and Evaluations**

| Measure | Timepoint | Variable | Endpoint |
|---|---|---|---|
| Voluntary movements measured using goniometer to determine AROM | Baseline, Week 6, Week 12 and re-injection/last cycle visits | AROM ($X_A$) | • Percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb<br>• Mean change from baseline to each postbaseline timepoint in AROM against 10 prespecified muscle groups<br>• Mean change from baseline to each postbaseline timepoint in composite AROM against injected muscle groups (any of the 10 prespecified)<br>• Mean change from baseline to each postbaseline timepoint in full composite AROM against five UL muscle groups or five LL muscle groups, regardless of whether the muscle groups were injected or not |
| Active function in the UL measured using MFS | Baseline, Week 12 (postinjections 1 and 2) | MFS overall score | • Mean change from baseline to Week 12 in MFS overall score assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number |
| Active function in the LL measured using 10-metre WST[a] | Baseline, Week 12 (postinjections 1 and 2) | Maximal WS (m/s) | • Mean change from baseline to Week 12 in maximal WS |
| Subject satisfaction with the GSC measured on a Likert scale | Baseline[b], Week 6, Week 12 and re-injection/last cycle visits | Likert scale scores | • Scores at each timepoint |

| Measure | Timepoint | Variable | Endpoint |
|---|---|---|---|
| Subject's beliefs that GSC will help to improve functional capacity | Baseline, Week 6, Week 12 and re-injection/last cycle visits | Likert scale scores | • Change from baseline to each postbaseline timepoint in scores |
| Physiotherapist's beliefs that GSC will help to improve functional capacity | Baseline, Week 6, Week 12 and re-injection/last cycle visits | Likert scale scores | • Change from baseline to each post baseline timepoint in scores |
| Subject compliance with the GSC | Baseline to Final Visit | Days when GSC therapy was documented | • Percentage of days over study period when GSC therapy was performed (as determined from the subject diary) |
| Subject satisfaction with longer interval between 2 injections | Week 16 or Week 20, depending on which is last visit cycle 1 and cycle 2 | Likert scale scores | • Scores at each timepoint |
| Benefits of treatment assessed by investigator and subject (or caregiver) | Last visit of each injection cycle (i.e. Week 12 or Week 16 or Week 20, depending on which is last visit postinjection) | Global assessment | • Scores at each timepoint |
| Quality of life measured using the EQ-5D 5L and SF-12 scales | Baseline, Final Visit (postinjection 2) | EQ-5D 5L descriptive data and VAS, SF-12 scores | • Change from baseline in scores |

AROM=Active range of motion; EQ-5D 5L= European Quality of Life 5 Dimensions; GSC=Guided Self-rehabilitation Contract; LL=Lower limb; MFS=Modified Frenchay Scale; SF-12=Short Form 12; UL=Upper limb; VAS=Visual analogue scale; WS=Walking Speed.

a The WST is to be performed barefoot without walking aids or, if absolutely necessary, with a cane. If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.

b for previously GSC treated subjects

## 7.3 Methods and Timing of Assessing, Recording and Analysing Efficacy Data

All scales and methods of measurement will be described in detail in the Study Operational Manual. Methods for assessing efficacy data are summarised below. The timing of assessments is discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1 and methods of analyses are discussed in Section 10.4.5.

### *7.3.1 Active Range of Motion (AROM)*

The AROM will be measured in the UL and LL using a goniometer, using zero as the theoretical position of minimal stretch for the muscle assessed. The subject will be asked to perform the active movement as far as possible against that muscle and the angle will be measured.

The investigator will use the goniometer to measure the angle of joint movement with respect to the following 10 prespecified muscle groups (injected or noninjected) in the UL and LL:

- UL: shoulder extensors, elbow flexors*, wrist flexors*, extrinsic finger flexors* and pronator teres
- LL: soleus*, gastrocnemius muscles*, gluteus maximus, hamstrings and rectus femoris.

* These measurements will be used for determination of the composite AROM against the injected muscle groups of the primary TT limb, for the primary efficacy endpoint (depending on whether the primary TT limb is the UL or LL).

Details will be provided in the Study Operational Manual. The definition of responders and details of calculations using the AROM measurements are provided in Section 10.4.5.

### *7.3.2 Modified Frenchay Scale (MFS)*

The MFS will be used to measure active function in the UL [14]. The MFS consists of 10 tasks (for example, opening and closing a jam jar), each of which is assessed on a visual analogue scale (VAS) from "No movement" to "Normal".

While performing the tasks, each subject will be videotaped. The investigator will record the MFS scores in the eCRF. The baseline mean MFS score assessed by each local investigator will be used for the purpose of the eligibility check. When evaluating active function at postbaseline FU visits, the investigator will review the baseline video for comparison purposes. Details will be provided in the Study Operational Manual.

At each visit and for each rating, the MFS overall scores will be obtained by averaging all individual task scores, provided that at least 8 out of the 10 are not missing. If 3 or more individual task scores are missing, the overall score will be left missing.

On top of the local MFS scores assessed by the investigators, a central review will be conducted at the Coordinating investigator's site of Prof Gracies: if possible, videos will be scored by only one reviewer. Videos will be provided for a given subject in a blinded manner for the visit order. All videos should be assessed only when the subject has completed the study.

The efficacy endpoint analysis will be performed both on the locally rated MFS mean score and on the centrally rated MFS mean score. if available

### *7.3.3 10-Metre Walking Speed Test (WST)*

The 10-metre WST will be used to measure active function in the LL [15]. The subject will perform the WST barefoot without a walking aid. If it is absolutely necessary that the subject uses a cane, this may be permitted provided that the same cane is used at the Baseline Visit and all other WS assessments for that subject. The subject will be given instructions to walk at his/her maximum speed. Details will be provided in the Study Operational Manual.

The time taken (in seconds) for the subject to walk from the start to the end of the 10 metres will be recorded in the eCRF. Walking speed (m/s) over the 10-metre distance will used in the efficacy endpoint analysis.

### *7.3.4 Guided Self-Rehabilitation Contract (GSC)*

Information regarding the GSC is provided in Section 6.1.2. Details will be provided in the Study Operational Manual.

Efficacy measures associated with the GSC are described below.

#### *7.3.4.1 Subject Satisfaction*

Subjects will record their satisfaction with the GSC. To assess this, subjects will be asked the following question:

"*How satisfied are you TODAY regarding the GSC?*"

Responses will be recorded using a 5-level Likert scale, as follows:

- completely satisfied (+2)

- rather satisfied (+1)
- neither satisfied nor dissatisfied (0)
- rather dissatisfied (-1)
- completely dissatisfied (-2).

*7.3.4.2 Changes in the Subject's and Physiotherapist's Beliefs*

Subjects and physiotherapists will record whether they believe the GSC will help to improve their functional capacity. To assess this, subjects and physiotherapists will be asked the following question:

- for subjects: "*Do you believe that GSC will help to improve your arm and leg function?"*
- for physiotherapists: "*Do you believe that GSC will help to improve your patient's arm and leg function?*"

Responses will be recorded using a 5-level Likert scale, as follows:

- very true of what I believe (+2)
- somewhat true of what I believe (+1)
- no opinion / don't know (0)
- somewhat untrue of what I believe (-1)
- very untrue of what I believe (-2).

Changes in subject and physiotherapist beliefs from baseline to postinjection timepoints will be assessed.

*7.3.4.3 Subject Compliance with the GSC*

As part of the GSC, she subjects will be given a diary at the Baseline Visit. They will be asked to record in this diary each day whether they have performed the GSC therapy. At each postbaseline FU visit, subjects will bring the GSC diary. The investigator will count the number of days when GSC therapy was not performed since the last visit and will record this in the eCRF.

Using the total number of study days and the total number of days when GSC therapy was not performed, the number of days when GSC was performed will be calculated. This will be used to determine the percentage subject compliance with GSC therapy.

### *7.3.5 Subject Satisfaction regarding Longer Injection Intervals (only for Subjects with an Injection Planned at Week 16 or 20 of Each Cycle)*

For subjects who will not be reinjected at Week 12 of a given cycle, subjects will record their satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit (week 16 or week 20 for each cycle). To assess this, subjects will be asked the following question:

*"Are you satisfied with a longer interval between 2 injections?"*

- Yes
- No
- No opinion

### *7.3.6 Global Assessment of Benefits*

A global assessment of the benefits of the study therapy (i.e. AbobotulinumtoxinA+GSC) will be made by the investigator and the subject (or the caregiver). The subject's caregiver will perform the global assessment only in those cases when the subject is not capable to do this.

To assess the global assessment of benefits, the following question will be asked:

*"How would you rate the overall response to study therapy (AbobotulinumtoxinA plus GSC) since baseline?"*

Responses on the global assessment will be recorded using a 5-level Likert scale, as follows:

- much better (+2)
- a bit better (+1)
- the same (0)
- a bit worse (-1)
- much worse (-2).

### *7.3.7 Subject Quality of Life*

#### *7.3.7.1 European Quality of Life 5 Dimensions (EQ 5D-5L)*

Subjects will be asked to complete the EQ 5D-5L instrument to assess their current health status [16, 17]. The EQ 5D-5L is a generic, preference-based measure of health-related quality of life. The questions are answered based on how the subject is feeling "today".

The EQ 5D-5L instrument consists of two parts: the EQ 5D descriptive system and the EQ VAS. The EQ 5D descriptive system includes questions for each of the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the subject's self-rated health on a vertical 20-cm VAS where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". This measure can be used as a quantitative measure of health, as judged by the individual subjects.

#### *7.3.7.2 Short-Form 12 (SF-12)*

Subjects will be asked to complete the SF-12 health survey to assess their general health and wellbeing [18]. The SF-12 is a short form survey consisting of 12 questions, which are a subset of the SF-36 health survey [19, 20]. Most of the questions are answered based on how the subject has been feeling over the previous 4 weeks. The SF-12 was updated with improvements (Version 2) and this version will be used in this current study [21].

The SF-12 covers eight domains, including physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional and mental health.

# 8 ASSESSMENT OF SAFETY

## 8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

### *8.1.1 Definition of an Adverse Event*

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, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).

### *8.1.2 Categorisation of Adverse Events*

#### *8.1.2.1 Intensity 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 well being, significant impairment of function or incapacitation.

#### *8.1.2.2 Causality Classification*

The relationship of an AE to IMP administration will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

#### *8.1.2.3 Assessment of Expectedness*

The reference document for assessing expectedness of AEs/events in this study will be the IB.

#### *8.1.2.4 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 IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation);
- they require intervention or a diagnosis evaluation to assess the risk to the subject;

- they are considered as clinically significant by the investigator.

*8.1.2.5 Abnormal Physical Examination Findings*

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

*8.1.2.6 Other Investigation Abnormal Findings*

Abnormal test findings as judged by the investigator as clinically significant (for example, vital signs changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

### *8.1.3 Recording and Follow up of Adverse Events*

At each visit and each phone call, the subject should be asked a non leading question such as: "How have you felt since starting the new treatment/the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation's of pre-existing illnesses should be recorded.

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

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 a serious adverse event (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. IMP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

### *8.1.4 Reporting of Serious Adverse Events*

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE that:

(1) results in death

(2) is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death

(3) results in in-patient hospitalisation or prolongation of 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 life functions

(5) results in congenital anomaly/birth defect in the offspring of a subject who received the IMP

(6) is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. 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 adverse experience and thus is not subject to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned 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.

Any SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor pharmacovigilance contact within 24 hours for each SAE:

- study number
- centre number
- subject number
- AE (including investigator assessment of causality)
- investigator's name and contact details.

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. 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.

### *8.1.5 Pregnancy*

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected poststudy and it may be necessary to discontinue administration of the IMP.

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor within 24 hours. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the 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 conclusion of the pregnancy, which may involve follow up after the subject's involvement in the study has ended.

Pregnancies with a conception date within 180 days after subject's last dose of IMP must be reported to the investigator for onward reporting to the sponsor.

### *8.1.6 Deaths*

All AEs resulting in death during the study period 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:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction)
- outcome: fatal.

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

### *8.1.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events*

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to other reasons (see Section 4.3).

If the IMP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4).

In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.3).

### *8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators*

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the CAs, IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

For study centres in the USA, Investigational New Drug application Safety Reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their IRB in a timely manner.

## 8.2 Physical Examination

Physical examinations will be performed by a physician at the visits indicated in Table 2.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs.

A urine pregnancy test will be performed at the Baseline Visit for all female subjects of childbearing potential.

## 8.3 Vital Signs

Blood pressure and heart rate will be recorded after 5 minutes of rest in a supine position at the visits indicated in Table 2.

Body weight will be measured at the visits indicated in Table 2. Height will be measured at the Baseline Visit only.

See Section 8.1.2.6 for abnormal vital signs results that should be recorded as AEs in the eCRF.

# 9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

# 10 STATISTICS

## 10.1 Analyses Populations

The following populations will be used during the statistical analyses:

- **Screened population:** all subjects screened (i.e. who signed the informed consent).
- **Safety population:** all subjects who received at least one dose of study medication.
- **Intent-to-treat (ITT) population:** all subjects who received at least one dose of study medication. The ITT population will be identical to the safety population and will be denoted throughout as safety/ITT population.
- **Modified intent-to-treat (mITT) population:** all treated subjects having the primary efficacy outcome assessed at Week 6 after the second injection.
- **Per protocol (PP) population:** all subjects in the mITT population for whom no major protocol violations/deviations occurred.

### *10.1.1 Populations Analysed*

The primary analysis based on the primary efficacy endpoint will be performed on the mITT population. In addition, safety/ITT and PP analyses will be performed as secondary analyses.

### *10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses*

Any major protocol deviation will be described in the Protocol Deviation Document and its impact on inclusion in each analysis population (mITT, safety/ITT and PP populations) for any subject will be specified. The final list of protocol deviations impacting all populations will be reviewed during the final data review meeting held prior to database lock.

## 10.2 Sample Size Determination

The sample size was determined based on the primary efficacy endpoint (percentage of responder subjects at Week 6 after the second injection according to composite AROM). A 60% response rate was assumed based on previous studies (adult UL/LL) with an additional benefit of +10% compared with that observed in these studies (approximately 50% response rate at Week 4 of Cycle 2). The aim of this study will be to estimate this proportion with an accuracy of ±8%. Given a two-sided 95% confidence interval (CI), 145 subjects are required; with an assumed 5% dropout rate, 153 subjects will have to be enrolled to achieve a target of 145 evaluable subjects (i.e. subjects included in the mITT population). These calculations have been performed with nQuery using CI for proportions and assuming normal approximation.

## 10.3 Significance Testing and Estimations

As this is a descriptive efficacy study, no formal statistical testing will be performed and all the analyses will be primarily descriptive in nature. When appropriate and unless otherwise specified, two-sided 95% CIs will be displayed and if p-values are presented, they will be for exploratory purposes only.

Descriptive statistics will include number of measures (n), n missing and the following:

- mean, standard deviation, minimum, median, maximum and 95% CIs for means for interval-type variables
- counts and percentages of each category for categorical nominal variables
- both the above for categorical ordinal variables.

## 10.4 Statistical/Analytical Methods

The statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A statistical analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (Version 9 or higher).

### *10.4.1 Demographic and Other Baseline Characteristics*

All demographic and baseline characteristics will be listed for the safety/ITT population.

Descriptive summary statistics for demographic and baseline characteristics will be presented for the mITT population. If the safety/ITT population differs from the mITT population by more than 10%, summary statistics for demographic and baseline characteristics will also be presented for the safety/ITT population.

### *10.4.2 Homogeneity of Treatment Groups*

Not applicable as this is a single treatment arm study.

### *10.4.3 Subject Disposition and Withdrawals*

The numbers and percentages of subjects enrolled and included in each of the mITT, safety/ITT and PP populations will be tabulated by country and centre. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were treated, discontinued and completed the study treatment will be tabulated for each population. Primary reasons for discontinuation of study treatment will be tabulated.

### *10.4.4 Pharmacokinetic Data*

There are no PK analyses planned for this study.

### *10.4.5 Efficacy Evaluation*

#### *10.4.5.1 Primary Efficacy Endpoint*

As indicated in Section 7.1, the primary efficacy endpoint is as follows:

- the percentage of responder subjects at Week 6 after the second injection, according to composite AROM in the primary TT limb.

Composite AROM ($X_A$), regardless of whether the muscle groups were injected or not, as measured by goniometer in the primary TT limb (either UL or LL, depending on which one has been selected as the primary TT limb), will be calculated as follows:

- composite $X_A$ UL: $X_A$ UL = $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$
- composite $X_A$ LL: $X_A$ LL = $X_{Asol}$ + $X_{AGN}$

*where for UL: EF=elbow flexors, WF=wrist flexors and FF=extrinsic finger flexors, and for LL: Sol=soleus and GN=gastrocnemius muscles.*

Definition of a responder: a subject will be considered a responder if he/she achieves at least the predefined improvement threshold - larger or equal to 35° in UL or 5° in LL - in the primary TT limb (based on the composite AROM individual change from baseline to Week 6 after the second injection).

***Primary Efficacy Analysis of the Primary Efficacy Endpoint***

The primary efficacy endpoint will be summarized descriptively as a binary variable using the mITT population.

***Secondary Efficacy Analysis of the Primary Efficacy Endpoint***

The following analyses will be conducted in support of the primary efficacy analysis.

The primary efficacy analysis will be repeated using the safety/ITT population where subjects with missing responder status at Week 6 after the second injection will have their last postbaseline responder status used instead. Subjects with no postbaseline responder status are considered nonresponders.

Additionally, the primary efficacy analysis will be repeated based on the PP population.

***Exploratory Analysis of the Primary Efficacy Endpoint***

The odds ratio for the primary efficacy endpoint and its associated two-sided 95% CI will be estimated from a logistic regression model with primary TT and country as fixed factors and composite AROM value at baseline as covariate. Further details will be provided in the SAP.

*10.4.5.2 Secondary Efficacy Endpoints*

As discussed in Section 7.2, the secondary efficacy variables are as follows:

- the percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb
- AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- composite AROM against injected muscle groups (any of the 10 prespecified), in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only
- full composite AROM against five UL muscle groups ($X_A$ full UL = $X_{ASE}$ + $X_{AEF}$ + $X_{AWF}$ + $X_{AFF}$ + $X_{APT}$) or full composite AROM against five LL muscle groups ($X_A$ full LL = $X_{Asol}$ + $X_{AGN}$ + $X_{AGM}$ + $X_{AHS}$ + $X_{ARF}$), regardless of whether the muscle groups were injected or not: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only

  *where for UL: SE=shoulder extensors, EF=elbow flexors, WF=wrist flexors, FF=extrinsic finger flexors and PT=pronator teres,*
  *and for LL: Sol=soleus, GN=gastrocnemius muscles, GM=gluteus maximus, HS=hamstrings and RF=rectus femoris*
- active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number) at Week 12 after each injection cycle
- active LL function measured using maximal WS barefoot without walking aids or, if absolutely necessary with a cane, measured on a 10-metre WST: mean change from baseline at Week 12 after each injection cycle. (If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.)
- subject satisfaction with the GSC: at baseline (only for patients who had GSC performed previously), Week 6, Week 12 and re-injection/last cycle visits only
- changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only

- changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only
- subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)
- global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle
- in subjects with an injection planned at Week 16 or 20 of each cycle satisfaction with longer interval collected at the corresponding reinjection visit or the last cycle visit.
- quality of life changes, measured on the EQ-5D 5L and SF-12 scales: change from baseline to Final Visit.

***Analysis of the Secondary Efficacy Endpoints***

The secondary efficacy endpoints will be summarised descriptively at each relevant visit using the safety/ITT population. Unless otherwise specified, missing values will not be imputed.

Additionally, adjusted mean change from baseline in AROM variables at each relevant postbaseline timepoint and associated two-sided 95% CIs will be estimated from an analysis of covariance (ANCOVA) model with primary TT and country as fixed effects and the appropriate baseline AROM value as covariate. Active UL and LL functions and quality of life questionnaires will be summarised in a similar way as AROM variables.

Percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb, will be analysed in a similar way as for the primary efficacy endpoint.

Using the total number of study days and the total number of days when GSC therapy was not performed (as recorded in the eCRF from the subject diary), the number of days when GSC was performed will be calculated. This percentage of days over the study period when GSC therapy was performed will be calculated by subject and summarized descriptively as a categorical ordinal variable.

### *10.4.6 Adjustment for Country/Centre Effect*

Descriptive analysis of the primary efficacy endpoint will be performed by country.

### *10.4.7 Safety Evaluation*

All safety data will be included in the subject data listings using the safety population. Analyses and summary tables will be based on the safety population.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term and system organ class. Adverse event listings will be presented by subject, system organ class and preferred term.

The incidence of all reported AEs, TEAEs and SAEs will be tabulated separately. In addition, summary tables for TEAEs will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

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

- it was not present prior to receiving the first dose of IMP, or
- it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study.

All TEAEs will be flagged in the AE listings.

Concomitant medication will be coded using the World Health Organization Drug Dictionary (WHODRUG) and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, standard deviation, and range, as appropriate) will be presented for vital signs (blood pressure and heart rate, weight) at each assessment with change from baseline.

## 10.5 Subgroup Analyses

Descriptive statistics for the primary efficacy endpoint will be provided within each category of the following variables: race, ethnicity, sex, age (<65 years, ≥65 years), primary TT (UL, LL), naïve or non-naïve to BoNT treatment, and naïve or non-naïve to GSC. Additional subgroup analyses may be planned in the SAP according to clinical interest.

## 10.6 Interim Analyses

It is planned to perform an interim analysis in order to describe baseline data and more specifically injection details, for example, dose per limb/injected muscles; this baseline data interim analysis is planned after subject enrolment has been completed.

# 11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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 12.4 and to any other locations used for the purpose of the study in question (for example, laboratories).

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

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

## 12.1 Protocol Amendments and Protocol Deviations and Violations

### *12.1.1 Protocol Amendments*

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

### *12.1.2 Protocol Deviations, Violations and Exceptions*

A protocol deviation is nonadherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the eCRF.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the standard operating procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

## 12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (for example, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

## 12.3 Study Monitoring

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.

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 according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor 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 (for example, 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 identification.

### 12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

### 12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility 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 ETHICS

## 13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines, FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA Guidance, Industry Computerized Systems Used in Clinical Trials (Section 1.5).

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (for example, 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.

## 13.2 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, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. 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 language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject 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 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. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

### 13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

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, prior to study initiation in regions where an approval is required.

### 13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (for example, initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

# 14 DATA HANDLING AND RECORD KEEPING

## 14.1 Data Recording of Study Data

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

The investigator must record all data relating to protocol procedures, IMP 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 diaries and questionnaires will be printed or electronic.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and 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.

## 14.2 Data Management

Electronic data capture (EDC) 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 electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Monitoring Procedures). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

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 archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study 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 a CRO, directed by the sponsor's Biometry Group and reviewed and approved by the sponsor.

Concomitant medications will be coded using the WHODRUG and AEs/medical history terms will be coded using the MedDRA.

## 14.3 Record Archiving and Retention

During the prestudy 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.

# 15 FINANCING AND INSURANCE

## 15.1 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 need to be completed, as requested by FDA 21 CFR Part 54.

## 15.2 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.

# 16 REPORTING AND PUBLICATIONS OF RESULTS

## 16.1 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 trial 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 trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial 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.

## 16.2 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 subject has signed informed consent, 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.

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# 18 LIST OF APPENDICES

# Appendix 1 Amendment Form #1

| | |
|---|---|
| **STUDY NUMBER:** | F-FR-52120-228 |
| **PROTOCOL TITLE:** | An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis |
| **AMENDED PROTOCOL VERSION NUMBER & DATE** | Final Version (including Amendment #1): 02 December 2016 |
| | |

**THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:**

| **Version Date** | | **30 JUNE 2016** | **02 DECEMBER 2016** |
|---|---|---|---|
| **Page** | **Section** | **WAS** | **IS** |
| 1 | Cover page | PPD [redacted], QPPV, Global Patient Safety, Ipsen Group,<br>~~190 Bath Road, Slough, Berkshire SL1 3XE,~~ England | PPD [redacted] QPPV, Global Patient Safety, Ipsen Group,<br>**102 Park Drive, Milton Park, Abingdon, Oxfordshire OX14 4RY,** England |
| 5 | Synopsis: Secondary Objective | • AROM against ~~each injected~~ muscle group ~~of each~~ limb<br>• composite AROM against injected muscle groups of each limb | • AROM against **10 prespecified** muscle groups**: 5 in upper and 5 in lower** limbs<br>• composite AROM against injected muscle groups **(any of the 10 prespecified)** of each limb |
| 5 | Synopsis: Secondary Objective | • to measure the changes in subject beliefs that a GSC will help to improve function | • to measure the changes in subject **and physiotherapist** beliefs that a GSC will help to improve function |
| 6 | Synopsis: Secondary Objective | | • **in subjects not reinjected at Week 12, to assess satisfaction with longer than 12 weeks interval between 2 injections** |
| 6 | Synopsis: Methodology | • electrical stimulation will be used to target the injection sites; | • electrical stimulation **(ES)** will be used to target the injection sites; **Ultrasound guiding could be used in addition to ES in case this technique is used in routine clinical practice;** |

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| 7 | Synopsis: Diagnosis and criteria for inclusion | Inclusion criteria:<br><br>2) Subjects with hemiparesis due to ABI (…) | Inclusion criteria:<br><br>2) Subjects with hemiparesis due to ABI **(i.e. stroke or traumatic brain injury (TBI))** (…) |
| 8 | Synopsis: Diagnosis and criteria for inclusion | Exclusion criteria:<br><br>~~13) Anticoagulant treatment with international normalised ratio (INR) >3.5 within a week prior to injection.~~ | Exclusion criteria:<br>**5) Subjects treated, or likely to be treated, with intrathecal baclofen during the course of the study or during the 4 weeks before study entry.** (…)<br><br>*Deleted* |
| 9 | Synopsis: Criteria for evaluation efficacy | Subject satisfaction with the GSC will be assessed using a likert scale at all postinjection FU visits. Changes in the subject's beliefs that the GSC will help (…). A global assessment of benefits will be made by both the investigator and subject (or caregiver) at the end of both injection cycles using a Likert scale. | Subject satisfaction with the GSC will be assessed using a likert scale at all postinjection FU visits **but also at baseline for patients who had any GSC done previously**. Changes in the subject's **and physiotherapist's** beliefs that the GSC will help (…). A global assessment of benefits will be made by both the investigator and subject (or caregiver) at the end of both injection cycles using a Likert scale. **For the subjects who will have an injection planned at either Visit 4 or Visit 5 for the first cycle and Visit 8 or Visit 9 for the second cycle (i.e. Week 16 or 20 of each cycle) satisfaction with longer treatment interval will be collected at the corresponding reinjection visit or at the last cycle visit.** |
| 10 | Synopsis: Criteria for evaluation Safety | Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study. | Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study **or subject withdrawal.** |

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| 10 | Synopsis: Statistical method Secondary Endpoints and Evaluations | • AROM against each injected muscle group, in upper ~~of~~ lower limbs ~~;~~ mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups in upper and lower limbs; mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only | • AROM against **10 prespecified muscle groups, 5** in upper **and 5 in** lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups **(any of the 10 prespecified)** in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only |

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| 11 | Synopsis: Statistical Method | • subject satisfaction with the GSC: Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle | • subject satisfaction with the GSC: **at baseline (only for patients who had GSC performed previously),** Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br>• **changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only**<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit**<br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |
| 18 | Abbreviation | | **ES Electrostimulation**<br>**TBI Traumatic Brain Injury** |
| 25 | Section 2.2 | • AROM against ~~each injected muscle group of each~~ limb<br>• composite AROM against injected muscle groups of each limb | • AROM against **10 prespecified muscle groups: 5 in upper and 5 in lower** limbs<br>• composite AROM against injected muscle groups **(any of the 10 prespecified)** of each limb |

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| 25 | Section 2.2 | • to measure the changes in subject beliefs that a GSC will help to improve function | • to measure the changes in subject **and physiotherapist** beliefs that a GSC will help to improve function |
| 25 | Section 2.2 | | • **in subjects not reinjected at Week 12, to assess satisfaction with longer than 12 weeks interval between 2 injections** |
| 26 | Section 3.1 | • electrical stimulation will be used to target the injection sites; | • electrical stimulation **(ES)** will be used to target the injection sites; **Ultrasound guiding could be used in addition to ES in case this technique is used in routine clinical practice;**<br>• **(…)**<br><br>**List of recommended UL and LL muscles and Dysport dose per muscle is provided in Sections 6.1.1.1 and 6.1.1.2.** |
| 29 | Section 3.2.2 | • AROM against ~~each injected muscle group of each limb~~ ~~;~~ mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against ~~injected muscle groups of each~~ limb~~;~~ mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only | • AROM against **10 prespecified muscle groups, 5 in upper and 5 in lower limbs**: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups **(any of the 10 prespecified) in upper and lower** limb**s:** mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only |

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| 29-30 | Section 3.2.2 | • subject satisfaction with the GSC: Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle | • subject satisfaction with the GCS: **at baseline (only for patients who had GSC performed previously),** Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br>• **changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only**<br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |
| 30 | Section 3.2.3 | Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study. | Safety will be assessed by recording the number, nature and severity of AEs from the time that the subject gives informed consent to the end of study **or subject withdrawal.** |
| 34 | Section 4.1 | (2) Subjects with hemiparesis due to ABI | (2) Subjects with hemiparesis due to ABI **(i.e. stroke or Traumatic Brain Injury (TBI))** |

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| 35 | Section 4.2 | Exclusion criteria:<br><br>~~13) Anticoagulant treatment with international normalised ratio (INR) >3.5 within a week prior to injection.~~ | Exclusion criteria:<br>**5) Subjects treated, or likely to be treated, with intrathecal baclofen during the course of the study or during the 4 weeks before study entry.**<br>(…)<br><br>*Deleted* |
| 37-39 | Section 5.1 | Table 1<br>*W x*<br><br>Previous BoNT~~-A~~ injection(s)[j]<br><br>Subject satisfaction with GSC *measured at* W6, W12, w16 and W20 *for Cycle 1*<br><br>*Table Footnotes:*<br>i Record all details of previous GSC or physiotherapy<br>j Record if subject is naïve or non naïve to BoNT~~-A~~ treatment; if non naïve to BoNT~~-A~~ treatment, record dates of the first injection and last injection, which limbs were injected, and BoNT~~-A~~ brand and dose used in the last injection.<br>(…)<br>t To be performed only at the last postinjection FU visit after Injection 1 (which may be Week 12, Week 16 or Week 20).<br>(…) | Table 1<br>***W x* ± 7 days** *for all visits, except **W12 + 7 days***<br>Previous BoNT injection(s)[j]<br><br>Subject satisfaction with GSC *measured at* **Baseline**, W6, W12, w16 and W20 *for Cycle 1*<br><br>**Subject satisfaction with longer interval between 2 injections** *measured at* **W16 and W20** ***for both cycles***<br><br>**Physiotherapist beliefs that GSC will help to improve functional capacity** *measured at* ***all visits***<br><br>*Table Footnotes:*<br>i Record all details of previous GSC or physiotherapy **within 4 months before Baseline**<br>j Record if subject is naïve or non naïve to BoNT treatment; if non naïve to BoNT treatment, record dates of the first injection and last injection, which limbs were injected, and BoNT brand and dose used in the last injection.<br>(…)<br>t To be performed only at the last postinjection FU visit after Injection 1 **(i.e. the visit where second injection is performed,** which may be Week 12, Week 16 or Week 20**).**<br>(…)<br>**v Only for subjects who had GSC previously.** |

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| 41 | Section 5.2.1.1 | • previous GSC or physiotherapy history<br><br>• if subject is non-naïve to BoNT-~~A~~ treatment: dates of the first injection and last injection, which limbs were injected, and BoNT-~~A~~ brand and dose used in the last injection<br>• (…)<br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• Subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | • previous GSC or physiotherapy history **(within 4 months prior to baseline)**<br>• **subject satisfaction on previous GSC (if applicable)**<br>• if subject is non-naïve to BoNT treatment: dates of the first injection and last injection, which limbs were injected, and BoNT brand and dose used in the last injection<br>• (…)<br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• Subject **and Physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity |
| 42 | Section 5.2.1.2 | 5.2.1.2 Week 6<br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.1.2 Week 6 **(±7 days)**<br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity |
| 42 | Section 5.2.1.3 | 5.2.1.3 Week 12<br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.1.3 Week 12 **(+7 days)**<br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity |

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| 43 | Section 5.2.1.4 | 5.2.1.4 Week 16 (…)<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.1.4 Week 16 **(±7 days)** (…)<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity<br>(…)<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |
| 44 | Section 5.2.1.5 | 5.2.1.5 Week 20 (…)<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.1.5 Week 20 **(±7 days)** (…)<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity<br>(…)<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |

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| 45 | Section 5.2.2.1 | 5.2.2.1 Week 6<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• Subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.2.1 Week 6 **(±7 days)**<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity |
| 45 | Section 5.2.2.2 | 5.2.2.2 Week 12<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.2.2 Week 12 **(+7 days)**<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• (…)<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity |
| 46 | Section 5.2.2.3 | 5.2.2.3 Week 16 (…)<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• Subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.2.3 Week 16 **(±7 days)** (…)<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity<br>(…)<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |

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| 47 | Section 5.2.2.4 | 5.2.2.4 Week 20 (…)<br><br>• measurement of AROM against ~~each~~ muscle group of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject completion of Likert scale to assess beliefs that GSC will help to improve functional capacity | 5.2.2.4 Week 20 **(±7 days)** (…)<br><br>• measurement of AROM against **10 prespecified** muscle group**s** of the UL and LL (irrespective of whether injected or not)<br>• subject assessment of satisfaction with GSC<br>• subject **and physiotherapist** completion of Likert scale to assess beliefs that GSC will help to improve functional capacity<br>(…)<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |
| 48 | Section 6.1 | | **Note: For subjects receiving antivitamin K therapy the Investigator will have to ensure that the International Normalised Ratio (INR) is below 3.5 within 1 week prior to study treatment administration.**<br>**Subjects currently receiving oral anti-spasticity medications (e.g. Baclofen) may be included provided the dose will be kept constant during the study.** |
| 49 | Section 6.1.1 | | **List of recommended muscles to be injected based on subject needs is presented in Section 6.1.1.1 for upper limb and Section 6.1.1.2 for lower limbs. Any muscle injected will be recorded in the eCRF.** |

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| 49 | Section 6.1.1 | | **6.1.1.1 List of muscles recommended to be injected and Dysport Dosing by Muscle for Upper Limb Spasticity** |

| MUSCLES | DOSES |
|---|---|
| Flexor carpi radialis (FCR) | 100 – 200 U |
| Flexor carpi ulnaris (FCU) | 100 – 200 U |
| Flexor digitorum profundus (FDP) | 100 – 200 U |
| Flexor digitorum superficialis (FDS) | 100 – 200 U |
| Flexor Pollicis Longus | 100 – 200 U |
| Adductor Pollicis | 25 – 50 U |
| Brachialis | 200 – 400 U |
| Brachioradialis | 100 – 200 U |
| Biceps Brachii (BB) | 200 – 400 U |
| Pronator Teres | 100 – 200 U |
| Triceps Brachii (long head) | 150 – 300 U |
| Pectoralis Major | 150 – 300 U |
| Subscapularis | 150 – 300 U |
| Latissimus Dorsi | 150 – 300 U |

**6.1.1.2 List of muscles recommended to be injected and Dysport Dosing by Muscle for Lower Limb Spasticity**

| MUSCLES | DOSES |
|---|---|
| Soleus muscle | 300 – 550 U |
| Gastrocnemius Medial Head | 100 – 450 U |
| Gastrocnemius Lateral Head | 100 – 450 U |
| Tibialis posterior | 100 – 250 U |
| Flexor digitorum longus | 50 – 200 U |
| Flexor digitorum brevis | 50 – 200 U |
| Flexor hallucis longus | 50 – 200 U |
| Flexor hallucis brevis | 50 – 100 U |
| Rectus femoris | 100 – 400 U |
| Hamstrings | 100 – 400 U |
| Adductor magnus | 100 – 300 U |
| Adductor Longus | 50 – 150 U |
| Adductor Brevis | 50 – 150 U |
| Gracilis | 100 – 200 U |
| Gluteus maximus | 100 – 400 U |

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| 50 | Section 6.2 | It will be recorded if subject is naïve or non-naïve to BoNT~~-A~~ treatment. If non-naïve to BoNT~~-A~~ treatment, the dates of the first injection and last injection, details of which limbs were injected, and the BoNT~~-A~~ brand and dose used in the last injection will be recorded in the eCRF. | It will be recorded if subject is naïve or non-naïve to BoNT treatment. If non-naïve to BoNT treatment, the dates of the first injection and last injection, details of which limbs were injected, and the BoNT brand and dose used in the last injection will be recorded in the eCRF. |
| 52 | Section 7.2 | • AROM against ~~each injected~~ muscle group, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• (…)<br>• subject satisfaction with the GSC: at Week 6, Week 12 and re-injection/last cycle visits only | • AROM against **10 prespecified** muscle group**s**, **5** in upper and **5 in** lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups **(any of the 10 prespecified)**, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• (…)<br>• subject satisfaction with the GSC: at **baseline (only for patients who had GSC performed previously),** Week 6, Week 12 and re-injection/last cycle visits only |

| | | | |
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| 53 | Section 7.2 | • changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br><br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle | • changes in subject's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only<br>• **changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re injection/last cycle visits only**<br>• subject compliance with the GSC: percentage of days over study period when GSC therapy was performed (as determined from the subject diary)<br>• global assessment of benefits, evaluated by both the investigator and the subject (or caregiver): at the end of each cycle<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle: subject satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit** |
| 53-54 | Section 7.2 | Table ~~3~~<br>Measure: Voluntary movements measured using goniometer to determine AROM<br>• Endpoint: Mean change from baseline to each postbaseline timepoint in AROM against ~~each injected~~ muscle group<br>• Mean change from baseline to each postbaseline timepoint in composite AROM against injected muscle groups<br><br>Measure: Subject satisfaction with the GSC measured on a Likert scale<br>Timelines: Week 6, Week 12 and re-injection/last cycle visits | Table **4**<br>Measure: Voluntary movements measured using goniometer to determine AROM<br>• Endpoint: Mean change from baseline to each postbaseline timepoint in AROM against **10 prespecified** muscle group**s**<br>• Mean change from baseline to each postbaseline timepoint in composite AROM against injected muscle groups **(any of 10 prespecified)**<br><br>Measure : Subject satisfaction with the GSC measured on a Likert scale<br><br>Timelines: **Baseline,** Week 6, Week 12 and re-injection/last cycle visits<br><br>*New raw added*<br>**Measure : Physiotherapist's beliefs that GSC will help to improve functional capacity**<br>**Timelines: Baseline, Week 6, Week 12** |

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| | | | **and re-injection/last cycle visits**<br>**Variable: Likert scale scores**<br>**Endpoint: Change from baseline to each post baseline timepoint in scores**<br>(…)*New raw added*<br>**Measure : Subject satisfaction with longer interval between 2 injections**<br>**Timelines: Week 16 or Week 20, depending on which is last visit cycle 1 and cycle 2**<br>**Variable: Likert scale scores**<br>**Endpoint: Scores at each timepoint**<br><br>*Footnote added*<br>**AROM=Active range of motion; EQ-5D 5L= European Quality of Life 5 Dimensions; GSC=Guided Self-rehabilitation Contract; LL=Lower limb; MFS=Modified Frenchay Scale; SF-12=Short Form 12; UL=Upper limb; VAS=Visual analogue scale; WS=Walking Speed.**<br>**a The WST is to be performed barefoot without walking aids or, if absolutely necessary, with a cane. If a cane is used at the Baseline Visit, the same cane is to be used during all WS assessments.**<br>**b for previously GSC treated subjects** |
| 54 | Section 7.3.1 | The investigator will use the goniometer to measure the angle of joint movement with respect to ~~all~~ the following muscle groups (injected or noninjected) in the UL and LL: | The investigator will use the goniometer to measure the angle of joint movement with respect to the following **10 prespecified** muscle groups (injected or noninjected) in the UL and LL: |
| 55 | Section 7.3.2 | The MFS overall score (i.e. mean score over the 10 tasks) will be used in the efficacy endpoint analysis. At each visit and for each rating, the MFS overall score will be obtained by averaging all individual task scores, provided that at least ~~7~~ out of the 10 are not missing. If **4** or more individual task scores are missing, the overall score will be left missing. | The MFS overall score (i.e. mean score over the 10 tasks) will be used in the efficacy endpoint analysis. At each visit and for each rating, the MFS overall score will be obtained by averaging all individual task scores, provided that at least **8** out of the 10 are not missing. If **3** or more individual task scores are missing, the overall score will be left missing. |

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| 55-56 | Section 7.3.4.2 | 7.3.4.2 Changes in the Subject's Beliefs<br><br>Subjects will record whether they believe the GSC will help to improve their functional capacity. To assess this, subjects will be asked the following question:<br><br>• ~~"Do you believe that GSC will help to improve your arm and leg function?"~~<br><br>(…)<br>Changes in subject beliefs from baseline to postinjection timepoints will be assessed. | 7.3.4.2 Changes in the Subject's **and Physiotherapist's** Beliefs<br><br>Subjects **and physiotherapists** will record whether they believe the GSC will help to improve their functional capacity. To assess this, subjects **and physiotherapists** will be asked the following question:<br>• **for subjects: "Do you believe that GSC will help to improve your arm and leg function?"**<br>• **for physiotherapists: "Do you believe that GSC will help to improve your patient's arm and leg function?"**<br>(…)<br>Changes in subject **and physiotherapist** beliefs from baseline to postinjection timepoints will be assessed. |
| 56 | Section 7.3.5 | | **7.3.5 Subject satisfaction regarding longer injection intervals (only for subjects with an injection planned at Week 16 or 20 of each cycle)**<br><br>**For subjects who will not be reinjected at Week 12 of a given cycle, subjects will record their satisfaction with longer interval between 2 injections collected at the corresponding reinjection visit or the last cycle visit (week 16 or week 20 for each cycle). To assess this, subjects will be asked the following question:**<br>**"Are you satisfied with a longer interval between 2 injections?"**<br>• **Yes**<br>• **No**<br>• **No opinion** |
| 59 | Section 8.1.3 | At each visit, the subject should be asked a non leading question such as: "How have you felt since starting the new treatment/the last assessment?" | At each visit **and each phone call**, the subject should be asked a non leading question such as: "How have you felt since starting the new treatment/the last assessment?" |

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| 62 | Section 8.3 | Blood pressure and heart rate will be recorded after 5 minutes of rest in a supine position at the visits indicated in Table 2. ~~Diastolic and systolic blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer.~~ | Blood pressure and heart rate will be recorded after 5 minutes of rest in a supine position at the visits indicated in Table 2. |
| 66-67 | Section 10.4.5.2 | • AROM against ~~each injected~~ muscle group, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• (…)<br>• subject satisfaction with the GSC: at Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only | • AROM against **10 prespecified** muscle group**s**, **5** in upper and **5 in** lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• composite AROM against injected muscle groups **(any of the 10 prespecified)**, in upper and lower limbs: mean change from baseline at Week 6, Week 12 and re-injection/last cycle visits only<br>• (…)<br>• subject satisfaction with the GSC: at **baseline (only for patients who had GSC performed previously),** Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only<br>• changes in Physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12 and re-injection/last cycle visits only<br>• (…)<br>• **in subjects with an injection planned at Week 16 or 20 of each cycle satisfaction with longer interval collected at the corresponding reinjection visit or the last cycle visit.** |
| 68 | 10.5 | BoNT~~-A~~ | BoNT |

**SUMMARY & OUTCOME OF CHANGES:**

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|---|---|---|
| **STUDY NUMBER** | F-FR-52120-228 | |
| **AMENDED PROTOCOL VERSION NUMBER & DATE** | Final Version (including Amendment #1): 02 December 2016 | |
| **SUBSTANTIAL** ☒ | **NON-SUBSTANTIAL** ☐ | |
| **REASON(S) FOR CHANGES** | - To clarify the ABI diseases authorised<br>- To exclude subjects who have received (within 4 weeks before study entry) or might receive intrathecal baclofen<br>- To remove the INR>3,5 in exclusion criteria as this is not an exclusion but a recommendation for dosing and clarify this is only for antivitamin K and no new oral anticoagulant in Section 6.1<br>- To clarify the recommended dose and muscles to be injected according to Study Drug labelling<br>- To add the subject satisfaction with GSC at baseline in case he/she had GSC previously<br>- To add new assessment such as the Physiotherapist belief in the GSC therapy at study start and during the study.<br>- To add the subject satisfaction in case of longer interval of injection<br>- To authorise the use of Ultrasound guiding in addition to ES in case this technique is used in routine clinical practice<br>- To add a visit windows of ± 7 days for all visits and +7 days only for W12 visit<br>- To add the record of any AE during the routine phone call done by the physiotherapist<br>- To remove the automated device for taking blood pressure.<br>- To clarify that previous BoNT treatment will be collected for all previous BoNT | |
| **OTHER ACTION REQUIRED?** | CRF UPDATE | Yes ☒<br>No ☐<br>*(tick one)* |
| | LOCAL CONSENT FORM UPDATE | Yes ☒<br>No ☐<br>*(tick one)* |
| | DATABASE UPDATE | Yes ☒<br>No ☐<br>*(tick one)* |
| | REPORTING & ANALYSIS PLAN (RAP) UPDATE | Yes ☒<br>No ☐<br>*(tick one)* |

# Appendix 2 Amendment Form #2

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| **STUDY NUMBER:** | F-FR-52120-228 |
| **PROTOCOL TITLE:** | An International, Multicentre, Prospective, Single-Arm Study to Assess the Effect on Voluntary Movements of AbobotulinumtoxinA 1500 U Administered in Both Upper and Lower Limbs in Conjunction with a Guided Self-Rehabilitation Contract in Adult Subjects with Spastic Hemiparesis |
| **AMENDED PROTOCOL VERSION NUMBER & DATE** | Final Version (including Amendment #2): 24 January 2018 |

**THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:**

| **Version Date** | | **02 DECEMBER 2016** | **24 JANUARY 2018** |
|---|---|---|---|
| **Page** | **Section** | **WAS** | **IS** |
| 1 | Cover | PPD —— —— —— —— —— —— ~~QPPV, Global Patient Safety, Ipsen Group,~~ | PPD **EU Qualified Person for Pharmacovigilance, Ipsen Biopharm Ltd** |
| 8 | Synopsis Diagnosis and criteria for inclusion | 5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS, if the primary TT limb is the UL. | 5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS **the locally rated score**, if the primary TT limb is the UL. |
| 10 | Synopsis Statistical Methods | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks ~~score~~) at Week 12 after each injection cycle | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks **assessed locally and centrally by a reviewer blinded regarding the dates of video recording/visit number)** at Week 12 after each injection cycle |
| 30 | Section 3.2.2 | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks score) at Week 12 after each injection cycle | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks **assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number**) at Week 12 after each injection cycle |

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| 35 | Section 4.1 | 5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS, if the primary TT limb is the UL. | 5) Upper limb active function with an overall score between 2 and 7, as assessed by MFS **locally rated score**, if the primary TT limb is the UL. |
| 54 | Section 7.2 | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks ~~score~~) at Week 12 after each injection cycle | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks **assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit name**) at Week 12 after each injection cycle |
| 55 | Table 4 Column End point | Mean change from baseline to Week 12 in MFS overall score | Mean change from baseline to Week 12 in MFS overall score **assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number**) |
| 57 | Section 7.3.2 | ~~When evaluating active function at postbaseline FU visits, the investigator will review the baseline video for comparison purposes. Details will be provided in the Study Operational Manual.~~<br>~~The central MFS overall score (i.e. mean score over the 10 tasks) will be used in the~~ efficacy endpoint analysis. | **At each visit and for each rating, the MFS overall scores will be obtained by averaging all individual task scores, provided that at least 8 out of the 10 are not missing. If 3 or more individual task scores are missing, the overall score will be left missing.**<br>**On top of the local MFS scores assessed by the investigators, a central review will be conducted at the Coordinating investigator's site of Prof Gracies: if possible, videos will be scored by only one reviewer. Videos will be provided for a given subject in a blinded manner for the visit order. All videos should be assessed only when the subject has completed the study.**<br>**The efficacy endpoint analysis will be performed both on the locally rated MFS mean score and on the centrally rated MFS mean score, if available** |

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| 68 | Section 10.4.5.2 | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks) at Week 12 after each injection cycle | • active UL function measured using MFS: mean change from baseline in MFS overall score (i.e. mean score over the 10 tasks **assessed locally and centrally by a reviewer blinded regarding the date of video recording/visit number**) at Week 12 after each injection cycle |

**SUMMARY & OUTCOME OF CHANGES:**

| | | | |
|---|---|---|---|
| **STUDY NUMBER** | F-FR-52120-228 | | |
| **AMENDED PROTOCOL VERSION NUMBER & DATE** | Final Version (including Amendment #2): 24 January 2018 | | |
| **SUBSTANTIAL** ☐ | **NON-SUBSTANTIAL** ☒ | | |
| **REASON(S) FOR CHANGES** | - To add the central scoring of MFS | | |
| **OTHER ACTION REQUIRED?** | CRF UPDATE | Yes ☐<br>No ☒<br>*(tick one)* | |
| | LOCAL CONSENT FORM UPDATE | Yes ☒<br>No ☐<br>*(tick one)* | |
| | DATABASE UPDATE | Yes ☒<br>No ☐<br>*(tick one)* | |
| | REPORTING & ANALYSIS PLAN (RAP) UPDATE | Yes ☒<br>No ☐<br>*(tick one)* | |