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STATISTICAL AND ANALYSIS PLAN - Final analysis

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

PROTOCOL VERSION AND DATE: FINAL (INCLUDING AMENDMENT #2) – 24 JANUARY 2018

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Version 2.0	05 October 2018

STUDY NUMBER:	F-FR-52120-228
EUDRACT NUMBER	2016-001989-29
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
SAP VERSION:	Version 2.0
SAP DATE:	05 October 2018

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
All	All	22 November 2017	05 October 2018	Update for final analysis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABI:	Acquired Brain Injury
AE:	Adverse Event
AESI:	Adverse Event for Special Interest
ANCOVA:	ANalysis of COVAriance
ATC:	Anatomic Therapeutic Class
AROM:	Active Range Of Motion
BMI:	Body Mass Index
BoNT:	Botulinum NeuroToxin
CI:	Confidence Interval
CRO:	Clinical Research Organisation
DMC:	Data Monitoring Committee
eCRF:	electronic Case Report Form
EF:	Elbow Flexors
EQ-5D-5L:	European Quality of Life 5 Dimensions
ES:	Electrical Stimulation
FF:	extrinsic Finger Flexors
FU:	Follow-Up
GM:	Gluteus Maximus
GN:	GastrocNemius
GSC:	Guided Self-rehabilitation Contract
HS:	HamStrings
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
ITT:	Intention-To-Treat
KM:	Kaplan-Meier
LL:	Lower Limb
MedDRA:	Medical Dictionary for Regulatory Activities
MFS:	Modified Frenchay Scale
mITT:	modified Intent-To-Treat
PP:	Per Protocol
PT:	Pronator Teres
QC:	Quality Control

RF:	Rectus Femoris
SAE:	Serious Adverse Event
SAP:	Statistical and Analysis Plan
SAS®:	Statistical Analysis System®
SD:	Standard Deviation
SE:	Shoulder Extensors
SF-12:	Short Form 12
SF-36:	Short Form 36
SFCO:	Specialty Franchise Clinical Operations
Sol:	Soleus
SOP:	Standard Operating Procedure
TBI:	Traumatic Brain Injury
TEAE:	Treatment Emergent Adverse Event
TFLs:	Tables, Figures and Listings
TT:	Treatment Target
UL:	Upper Limb
VAS:	Visual Analogue Scale
WF:	Wrist Flexors
WHO:	World Health Organization
WS:	Walking Speed
WST:	Walking Speed Test
X_A:	AROM (active range of motion)

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

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 acquired brain injury (ABI).

1.1.2 Secondary objectives

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 AROM in the primary targeted limb, either UL or LL, depending on which one has been selected as a primary TT, following one AbobotulinumtoxinA injection combined with a GSC
  - AROM against 10 prespecified muscle groups: 5 in upper and 5 in lower limbs
  - composite AROM against muscle groups of each limb
  - full composite AROM against five UL muscle groups or full composite AROM against five LL muscle groups or overall full composite AROM against ten prespecified 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.

1.1.3 Exploratory objective

The exploratory objective is to assess correlation between full composite AROM and active function (MFS (Local and central review) in UL and WS in LL).

1.2 Study design

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.

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 of the protocol.

- 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.

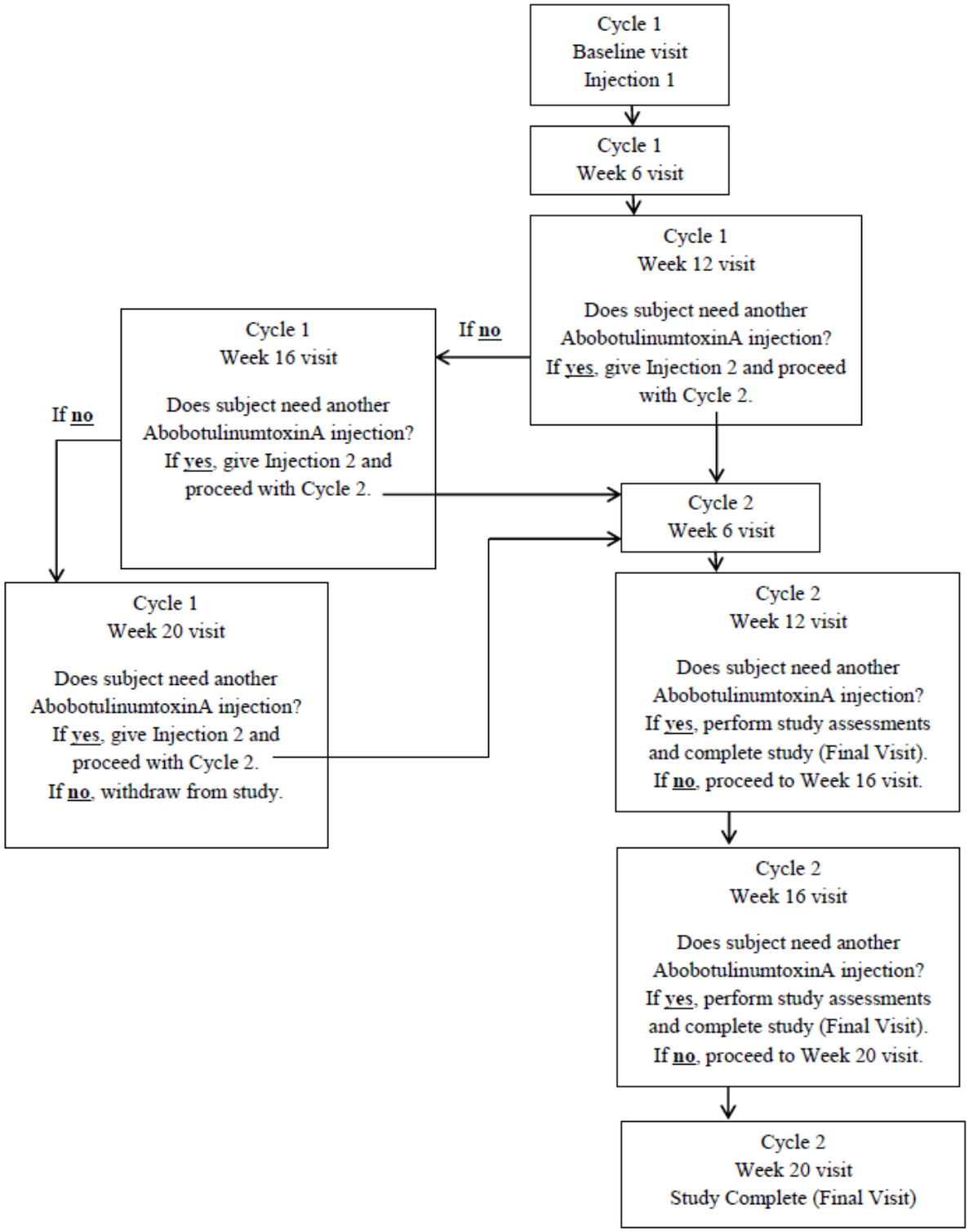
In **Cycle 2**, postinjection FU visits will be held after the second AbobotulinumtoxinA administration, as follows:

- 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).

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



1.2.1 Study population

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

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).

1.2.2 Study exposure

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.

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

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

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.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

1.3.2.1.1 Active Range of Motion (AROM)

The AROM will be assessed at baseline visit, at Week 6, Week 12, Week 16 (if applicable*) and Week 20 (if applicable*) of injection cycle 1, at Week 6, Week 12, Week 16 (if applicable*) and Week 20 (if applicable*) of injection cycle 2 and at Early withdrawal visit.

* *From Week 16 of each injection cycle, the visits are performed only if the injection was not given at the previous visit.*

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 not injected) 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).*

1.3.2.1.2 Modified Frenchay Scale (MFS)

The MFS will be assessed at baseline visit, at Week 12 of each injection cycle and at Early withdrawal visit.

The MFS will be used to measure active function in the UL [1]. 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 electronic Case Report Form (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 (i.e. mean score over the 10 tasks) 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 according to the central MFS reading charter. Videos will be provided for a given subject in a blinded manner for the visit order. All the videos for a given subject should be scored by only one reviewer and assessed only when the concerned subject has completed the study.

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

1.3.2.1.3 10-Metre Walking Speed Test (WST)

The WST will be assessed at baseline visit, at Week 12 of each injection cycle and at Early withdrawal visit.

The 10-metre WST will be used to measure active function in the LL [2]. 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.

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 be used in the efficacy endpoint analysis.

1.3.2.1.4 Guided Self-Rehabilitation Contract (GSC)

1.3.2.1.4.1 Subject satisfaction

Subjects will record their satisfaction with the GSC. The subject satisfaction will be assessed at baseline visit (only for subjects who had GSC previously), at Week 6

and Week 12 of injection cycle 1, at second injection visit (Week 12 or Week 16 or Week 20 of injection cycle 1), at Week 6 and Week 12 of injection cycle 2, at last study visit (including Early withdrawal visit).

Responses on the subject satisfaction with the GSC 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).

1.3.2.1.4.2 Subject's and physiotherapist's beliefs

Subjects and physiotherapists will record whether they believe the GSC will help to improve their functional capacity. The subject's and physiotherapist's beliefs will be assessed at baseline visit, at Week 6 and Week 12 of injection cycle 1, at second injection visit (Week 12, Week 16 or Week 20 of injection cycle 1), at Week 6 and Week 12 of injection cycle 2, at last study visit (including Early withdrawal visit).

Responses on the subject's and physiotherapist's beliefs 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).

1.3.2.1.4.3 Subject compliance with the GSC

As part of the GSC, the 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 post-baseline 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.

1.3.2.1.4.4 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 re-injection visit (Week 16 or Week 20 of injection cycle 1) or the last cycle visit (Week 16 or Week 20 of injection cycle 2). The possible answers will be: Yes, No or No opinion.

1.3.2.1.4.5 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. The subject's and investigator's global assessment of the benefits will be assessed at the end of each cycle (Week 12, Week 16 or Week 20 of each injection cycle) and at Early withdrawal visit.

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).

1.3.2.1.5 Subject quality of life

1.3.2.1.5.1 European Quality of Life 5 Dimensions (EQ-5D-5L)

The EQ-5D-5L questionnaire will be assessed at baseline visit, at the end of cycle 2 (Week 12, Week 16 or Week 20 of injection cycle 2) and at Early withdrawal visit.

Subjects will be asked to complete the EQ-5D-5L instrument to assess their current health status [3,4]. 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.

1.3.2.1.5.2 Short-Form 12 (SF-12)

The SF-12 questionnaire will be assessed at baseline visit, at the end of cycle 2 (Week 12, Week 16 or Week 20 of injection cycle 2) and at Early withdrawal visit.

Subjects will be asked to complete the SF-12 health survey to assess their general health and wellbeing [5]. The SF-12 is a short form survey consisting of 12 questions, which are a subset of the SF-36 health survey [6,7]. 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 [8].

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

1.3.2.2 Safety assessments

1.3.2.2.1 Adverse events

Adverse events (AEs) will be monitored from the time that the subject gives informed consent and throughout the study and will be elicited by direct, nonleading questioning or by spontaneous reports.

1.3.2.2.2 Vital signs

Vital signs will be measured at baseline visit, at the end of each cycle (Week 12, Week 16 or Week 20 of each injection cycle) and at Early withdrawal visit, including supine diastolic and systolic blood pressure, heart rate and weight. The body height will be measured at baseline visit only.

1.3.2.2.3 Physical examination

The physical examination will be assessed at baseline visit, at Week 6, Week 12, Week 16 (if applicable*) and Week 20 (if applicable*) of injection cycle 1, at Week 6, Week 12, Week 16 (if applicable*) and Week 20 (if applicable*) of injection cycle 2 and at Early withdrawal visit.

* *From Week 16 of each injection cycle, the visits are performed only if the injection was not given at the previous visit.*

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

1.3.2.3 Other assessments

Demography and baseline characteristics: Data collected will include sex and date of birth. Race and ethnicity will also be collected, except for French centers. This will be recorded at baseline visit.

Disease history: date and type of ABI, and onset date of spasticity will be recorded at baseline visit.

Previous BoNT injections: previous BoNT treatment will be recorded for each subject and for each limb (upper and lower) at baseline visit. If subject is non-naïve to BoNT treatment for a given limb: dates of the first injection and last injection, BoNT brand and total dose used in the last injection will be recorded.

Previous GSC: previous GSC followed within the last four months prior to study entry will be recorded at baseline visit.

Selection of primary TT limb (UL or LL): the selection of the TT limb will be recorded at baseline visit according to the clinical judgement of the investigator, in agreement with the subject and in accordance with the dosing rules detailed in the section 1.2.

Urine pregnancy test: this will be recorded at baseline visit for females of childbearing potential only.

Medical and surgical history: Complete medical history will include evaluation for any significant past or ongoing medical or surgical conditions not related to UL or LL spasticity. Data will be collected at baseline visit.

Study drug administration: Dose administration details will be recorded in the eCRF at each injection. These include the total doses administered (in each limb and for both limbs), the techniques used to target injection with the laterality, and details of the muscles that were injected for each limb and each muscle group (site of administration, number of injection sites and the dose administered by muscle).

Prior and concomitant medications (excluding UL or LL spasticity): General prior medications (excluding UL or LL spasticity) taken from four weeks prior to baseline will be reviewed for each subject at baseline visit. Any general concomitant medications (excluding UL or LL spasticity) will be recorded in the eCRF at each visit.

Concomitant medications for UL or LL spasticity: Any concomitant medication for UL or LL spasticity will be recorded in the eCRF at each visit.

Prior and concomitant non-drug therapies for UL or LL spasticity: Prior non-drug therapies for UL or LL spasticity, including physiotherapy history, taken from four weeks prior to baseline will be reviewed for each subject at baseline visit. Any concomitant non-drug therapies for UL or LL spasticity will be recorded in the eCRF at each visit.

Prior and concomitant non-drug therapies for other indication: Prior non-drug therapies for indication other than UL or LL spasticity taken from four weeks prior to baseline will be reviewed for each subject at baseline visit. Any concomitant non-drug therapies for other indication will be recorded in the eCRF at each visit.

Concomitant surgical procedures: Any concomitant surgical procedures will be recorded in the eCRF at each visit.

1.3.2.4 Withdrawal/discontinuation

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.

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 of the protocol in order to assess the safety of the investigational medicinal product (IMP).

1.3.3 Schedule of assessments

Table 1 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]	
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. 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 2 Summary of Re-injection 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.

1.3.4 Planned sample size

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 Modified intent-to-treat (mITT) population). These calculations have been performed with nQuery using CI for proportions and assuming normal approximation.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Enrolled population

The enrolled population is all subjects who signed the informed consent.

2.2 Efficacy

2.2.1 Intention-To-Treat population (ITT)

Two ITT populations will be defined: one for the interim analysis and one for the final analysis.

- The ITT population for the interim analysis is all subjects who were injected at least once with the study treatment and for whom a primary Target Treatment limb has been defined.
- The ITT population for the final analysis is all subjects who were injected at least once with the study treatment, who received at least one day of GSC therapy during the study and for whom a primary Target Treatment limb has been defined.

2.2.2 Modified intention-to-treat population (mITT)

The mITT population is all subjects who were injected at least once with the study treatment, who received at least one day of GSC therapy during the study, for whom a primary Target Treatment limb has been defined and who have the primary efficacy outcome assessed at Week 6 after the second injection (i.e. Visit 6).

2.2.3 Per Protocol population (PP)

The PP population is all subjects included in the mITT population for whom no major protocol violations/deviations occurred.

2.3 Safety

The safety population is all subjects who were injected at least once with the study treatment.

2.4 Pharmacokinetics

Not applicable for the study.

2.5 Primary population

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

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with international conference on harmonisation (ICH) E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated.

All statistical analyses described in this statistical analysis plan (SAP) will be performed by the Clinical Research Organisation (CRO) Biotrial managed by the sponsor's Biometry Department.

3.1.1 Primary efficacy endpoint

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

The 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.

The definition of a responder is the following: 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).

3.1.2 Secondary efficacy endpoints and exploratory endpoint

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 (based on the composite AROM individual change from baseline to Week 6 after the first injection)
- AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs: mean change from baseline at Week 6, Week 12, re-injection visit and last study visit 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, re-injection visit and last study visit only
- full composite AROM against five UL muscle groups or full composite AROM against five LL muscle groups or overall full composite AROM against ten prespecified muscle groups, regardless of whether the muscle groups were injected or not:
  - mean change from baseline at Week 6, Week 12, re-injection visit and last study visit only
  - the full composite AROM will be calculated as follows:
    (1) full composite X_A UL: X_A full UL = $X_{ASE} + X_{AEF} + X_{AWF} + X_{AFF} + X_{APT}$
    (2) full composite X_A LL: X_A full LL = $X_{ASol} + X_{AGN} + X_{AGM} + X_{AHS} + X_{ARF}$
    (3) overall full composite X_A: X_A full = $X_{ASE} + X_{AEF} + X_{AWF} + X_{AFF} + X_{APT} + X_{ASol} + X_{AGN} + X_{AGM} + X_{AHS} + X_{ARF}$

    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 order of the video recording/visit number for a given subject) at Week 12 after each injection cycle and last study visit.
- active LL function measured using maximal WS barefoot without walking aids or, if absolutely necessary, with a cane, measured using a 10-metre WST: mean change from baseline at Week 12 after each injection cycle and last study visit.
- subject satisfaction with the GSC: at baseline (only for patients who had GSC performed previously), Week 6, Week 12, re-injection visit and last study visit only
- changes in subject's beliefs that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12, re-injection visit and last study visit only

- changes in physiotherapist's belief that the GSC will help to improve functional capacity: change from baseline to Week 6, Week 12, re-injection visit and last study visit only
- subject compliance with the GSC: the percentage of days over study period when GSC therapy was performed (as determined from the subject diary) will be summarized in percentage and in classes (<80% and 80-100%).
- 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 re-injection visit or the last cycle visit
- quality of life changes, measured using the EQ-5D-5L and SF-12 scales:
  - change from baseline to last study visit.
  - the analysed scores for the EQ-5D-5L questionnaire will be:
    (1) the score answered at each question of the questionnaire: Mobility score, Self-care score, Usual activities score, Pain/discomfort score and Anxiety/depression score,
    (2) Index score (for the French centers and the US centers only),
    (3) EQ-5D-5L VAS score.
  - the analysed scores for the SF-12 questionnaire will be the SF-12 physical score and SF-12 mental score.

The exploratory efficacy endpoint is the correlation between full composite AROM and active function (MFS (Local and central review) in UL and WS in LL): Week 12 after each injection cycle and last study visit.

3.1.3 Safety endpoints

The safety endpoints are:

- Treatment Emergent Adverse Events (TEAEs), including information on seriousness, intensity, drug relationship and TEAE associated with premature withdrawal of study medication; Serious Adverse Events (SAEs);
- Clinical safety endpoints: physical examination and vital signs.

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

The statistical analysis of efficacy is only descriptive therefore no formal statistical significance 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. For the 95%CIs of proportions, the Agresti-Coull interval will be used.

3.2 Analysis methods

3.2.1 Efficacy

All efficacy data will be included in the subject data listings for the Enrolled population.

3.2.1.1 Primary efficacy analyses

The analyses of the primary efficacy endpoint will be performed on the mITT population for the primary efficacy analysis, and on the ITT and PP populations for the secondary efficacy analyses in support of the primary efficacy analysis.

3.2.1.1.1 Primary efficacy analysis of the primary efficacy endpoint

A frequency table of the percentage of responder subjects at Week 6 after the second injection will be provided on the mITT population with the two-sided 95% CI.

3.2.1.1.2 Secondary efficacy analyses of the primary efficacy endpoint

A frequency table of the percentage of responder subjects at Week 6 after the second injection will be provided on the ITT population (including the two-sided 95% CI) 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 will be considered nonresponders. The number of imputed data and the number of missing data will be provided.

The time to first response will be defined as the time elapsed from the date of first injection in the study to the date of first response (response as defined in section 3.2.14). For subjects who have a nonresponder status until the last study visit or for dropouts and lost to follow-up subjects, their data will be censored at the time of their last study visit.

The time to first response will be analysed using the Kaplan-Meier (KM) survival analysis method on the ITT population. The median survival time and the 95% CI of the median will be estimated using KM product-limit estimation. The time to first response will also be illustrated graphically using KM's estimates to display the cumulative rate of first response with the number of subjects at risk.

The following SAS® code will be used:

```
PROC LIFETEST data = ADTTE(where = (ittfl="Y")) METHOD=km;
    TIME aval*cnsr(1);
RUN;
```

Additionally, a frequency table of the percentage of responder subjects at Week 6 after the second injection will be provided on the PP population with the two-sided 95% CI.

3.2.1.1.3 Exploratory efficacy analysis of the primary efficacy endpoint

The percentage of responder subjects at Week 6 after the second injection between the upper limb and the lower limb as primary TT will be analysed on the mITT population using a multivariate logistic regression model. The analysis will include the primary TT limb and country as fixed factors and the composite AROM value at

baseline as covariate. The lower limb and the Czech Republic will be defined as reference level for the primary TT limb and the country, respectively. The adjusted odds ratio for the primary TT (UL *versus* LL) and its associated two-sided 95% CI will be presented as well as the adjusted odds ratio for the country (France/Russia/USA *versus* Czech Republic). The p-values of each fixed factor of the model will also be presented.

The following SAS® code will be used:

```
PROC LOGISTIC data = ADFT(where = (paramcd="RESP" AND mittfl="Y"
                                   AND avisitn=6));
    CLASS limb countryc;
    MODEL avalc(event = "Y") = limb countryc carom_b;
RUN;
```

3.2.1.2 Secondary efficacy analyses

The analyses of the secondary efficacy endpoints will be performed on the ITT population.

- **Percentage of responder subjects at Week 6 after the first injection, according to composite AROM in the primary TT limb**

  A frequency table of the percentage of responder subjects at Week 6 after the first injection will be provided with the two-sided 95% CI. Subjects with missing responder status at Week 6 after the first injection will be considered nonresponders. The number of missing data will be provided.

- **AROM against 10 prespecified muscle groups, 5 in upper and 5 in lower limbs**

  Summary statistics (including the two-sided 95% CI) will be presented for raw values and changes from baseline at each relevant visit:

  - Baseline (for raw values only),
  - Week 6 and Week 12 of injection cycle 1,
  - Re-injection cycle visit (Week 12 or Week 16 or Week 20 of injection cycle 1),
  - Week 6 and Week 12 of injection cycle 2,
  - Last study visit (including Early withdrawal visit).

  For AROM against each 10 prespecified muscle group, the change from baseline between the upper limb and the lower limb as primary TT will be analysed using an analysis of covariance (ANCOVA) at each relevant postbaseline timepoint previously listed. The analysis will include the primary TT limb and country as fixed factors and the AROM value at baseline as covariate. The lower limb and the Czech Republic will be defined as reference level for the primary TT limb and the country, respectively. The adjusted mean changes from baseline for each primary TT and its associated two-sided 95% CIs will be presented. The p-values of each fixed factor of the model will also be presented.

The following SAS® code will be used:

```
PROC MIXED data = ADFT(where = (paramcd="ROMxx" AND ittfl="Y"))
                  method=reml;
    BY avisitn;
    CLASS limb countryc;
    MODEL chg = limb countryc base / DDFM=kr;
    LSMEANS limb countryc / ALPHA=0.05 CL;
RUN;
```

In the event of gross violations from the normality assumptions (identified using the shape of the distribution and QQ plots of change from baseline overall) or in case of convergence criterion fails to be reached, a non-parametric analysis will be used instead: the same model will be performed on ranked data using the following SAS® code:

```
PROC RANK data = ADFT(where = (paramcd="ROMxx" AND ittfl="Y"))
          out = RANK;
    BY avisitn;
    VAR chg base;
    RANKS chg_r base_r;
RUN;
PROC MIXED data = RANK method=reml;
    BY avisitn;
    CLASS limb countryc;
    MODEL chg_r = limb countryc base_r / DDFM=kr;
    LSMEANS limb countryc / ALPHA=0.05 CL;
RUN;
```

All the SAS outputs produced during the analyses and the model checking procedures will be included without reworking the data (raw output) in the statistical appendix.

- **Composite AROM against injected muscle groups (any of the 10 prespecified), in upper and lower limbs**

  Summary statistics (including the two-sided 95% CI) will be presented for raw values and changes from baseline at each relevant visit: baseline (for raw values only), Week 6 and Week 12 of injection cycle 1, re-injection cycle visit, Week 6 and Week 12 of injection cycle 2, and last study visit.

  The change from baseline of composite AROM against each injected muscle group between the upper limb and the lower limb as primary TT will be analysed in the same way as AROM against 10 prespecified muscle groups.

- **Full composite AROM against five UL muscle groups or full composite AROM against five LL muscle groups or overall full composite AROM against ten prespecified muscle groups**

  The full composite AROM against five UL muscle groups, the full composite AROM against five LL muscle groups and the overall full composite AROM against ten prespecified muscle groups will be summarised and analysed in the same way as composite AROM against injected muscle groups.

- **Active UL function**

  Summary statistics (including the two-sided 95% CI) will be presented overall and by primary TT limb for raw values of the MFS overall scores, assessed locally and centrally by a reviewer blinded regarding the order of the video recording/visit number for a given subject, at baseline, Week 12 of each injection cycle and last study visit, as well as for the change from baseline at Week 12 of each injection cycle and last study visit.

  For the MFS overall scores, assessed locally and centrally by a reviewer blinded, the change from baseline between the upper limb and the lower limb as primary TT will be analysed at Week 12 of each injection cycle and last study visit using the same model as AROM against 10 prespecified muscle groups.

  The concordance between the results from the local assessment by the investigators and from the central review will be evaluated. For each analysed visit, the Lin's concordance correlation coefficient [9] and the associated two-sided 95% CI will be calculated on the raw data. The Brand-Altman graph will also be presented.

  The Lin's concordance correlation coefficient and the associated two-sided 95% CI will be calculated using the macro mccc.sas (http://bioinformaticstools.mayo.edu/research/mccc/).

- **Active LL function**

  Summary statistics (including the two-sided 95% CI) will be presented overall and by primary TT limb for raw values of the maximal WS barefoot (m/s) at baseline, Week 12 of each injection cycle and last study visit as well as for the changes from baseline at Week 12 of each injection cycle and last study visit.

  For the maximal WS barefoot, the change from baseline between the upper limb and the lower limb as primary TT will be analysed at Week 12 of each injection cycle and last study visit using the same model as AROM against 10 prespecified muscle groups.

- **Subject's satisfaction with the GSC**

  Summary statistics (including the two-sided 95% CI) and frequency tables will be presented for raw scores at each relevant visit:

- Baseline (for non-naïve subjects to GSC only),
- Week 6 and Week 12 of injection cycle 1,
- Re-injection cycle visit,
- Week 6 and Week 12 of injection cycle 2,
- Last study visit.

- **Subject's beliefs that the GSC will help to improve functional capacity**

  Summary statistics (including the two-sided 95% CI) will be presented for raw scores and changes from baseline at each relevant visit: baseline (for raw values only), Week 6 and Week 12 of injection cycle 1, re-injection cycle visit, Week 6 and Week 12 of injection cycle 2, and last study visit.

- **Physiotherapist's belief that the GSC will help to improve functional capacity**

  Summary statistics (including the two-sided 95% CI) will be presented for raw scores and changes from baseline at each relevant visit: baseline (for raw values only), Week 6 and Week 12 of injection cycle 1, re-injection cycle visit, Week 6 and Week 12 of injection cycle 2, and last study visit.

- **Subject compliance with the GSC**

  Summary statistics (including the two-sided 95% CI) will be presented for the percentage of days over study period when GSC therapy was performed in percentage. A frequency table of the percentage of days over study period when GSC therapy was performed in classes will also be provided with the two-sided 95% CI.

- **Global assessment of benefits**

  Summary statistics (including the two-sided 95% CI) and frequency tables for both the investigator and the subject will be presented for raw scores at the re-injection cycle visit and last study visit.

- **Satisfaction with longer interval between 2 injections**

  A frequency table of the satisfaction (including the two-sided 95% CI) with longer interval between 2 injections at the re-injection cycle visit and last cycle will be provided in subjects with an injection planned at Week 16 or 20 of each cycle.

  A shift table comparing the satisfaction with longer interval between 2 injections between the two visits will also be provided in subjects with an injection planned at Week 16 or Week 20 of the two cycles.

- **Quality of life changes, measured using the EQ-5D-5L and SF-12 scales**

  Summary statistics (including the two-sided 95% CI) will be presented for raw scores at baseline and last study visit, as well as for the changes from baseline at last study visit.

For each analysed score from EQ-5D-5L and SF-12 questionnaires, the change from baseline between the upper limb and the lower limb as primary TT will be analysed at last study visit using the same model as AROM against 10 prespecified muscle groups. As the index score is available for the French centers and the US centers only, the country which will be used as reference level in the model to compare the two countries will be the United States.

3.2.1.3 Exploratory efficacy analysis

The correlation between full composite AROM and active function (MFS (Local and central review) in UL and WS in LL) will be evaluated using correlation coefficients and their associated p-values. For each correlation (full composite AROM in UL and MFS (Local) / full composite AROM in UL and MFS (Central review) / full composite AROM in LL and WS), the correlation coefficient will be calculated on the changes from baseline and, at Week 12 of each injection cycle and last study visit. Depending of the normality of the two parameters analysed, the Pearson's correlation coefficient or the Spearman's correlation coefficient will be used.

The following SAS® code will be used:

```
PROC CORR data = table pearson spearman;
    BY avisitn;
    VAR chg_fcXaroms chg_mXXXX;
RUN;
```

The scatter plot of change from baseline of the full composite AROM in upper limb versus the change from baseline of the MFS overall score (Local and central review) will be presented at Week 12 of each injection cycle and last study visit on the same graph.

The scatter plot of change from baseline of the full composite AROM in lower limb versus the change from baseline of the maximal WS barefoot will be presented at Week 12 of each injection cycle and last study visit on the same graph.

3.2.2 Safety

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

3.2.2.1 Adverse events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version in force within Ipsen at the time of first coding.

Listings will be presented and sorted by country, centre, subject ID, start date/time of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study.

Listings of SAEs, AEs leading to withdrawal and listing of deaths will also be presented.

TEAEs will be flagged (*) in the adverse events listing and will be summarised.

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.

An overall summary table of all AEs will be presented.

TEAEs will be summarised with the number and percentage of subjects with adverse events classified by primary system organ class and preferred term. The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for:

- SAEs,
- Non serious TEAEs,
- TEAEs per decreasing frequency,
- TEAEs by maximum intensity,
- TEAEs by most serious causality,
- TEAEs associated with withdrawals,
- TEAEs of special interest by type of adverse events of special interest (AESI) (Hypersensitivity and Remote spread).

The list of MedDRA PTs and/or Standardised MedDRA Queries (SMQs) used to retrieve a list of potential AESIs of each type of specific events is detailed in Appendix 2.

In the event of multiple reports of the same event being reported by the same subject during the study, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) will be chosen.

3.2.2.2 Laboratory data

Not applicable for the study.

3.2.2.3 Vital signs

Vital signs will be listed at each assessment by country, centre and subject ID. Any unscheduled vital signs will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to IMP administration, i.e. at the Baseline Visit (Cycle 1).

Summary statistics (including the two-sided 95% CI) will be presented at each scheduled assessment for raw values and changes from baseline of blood pressure, heart rate, weight and Body Mass Index (BMI).

3.2.2.4 ECG

Not applicable for the study.

3.2.2.5 Physical examination

A listing with the date of test will be provided by country, centre, subject ID and visit.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

Unless stated otherwise, no missing value will be replaced.

If a value required a retest, the last reliable non-missing value will be taken into account if measured before the administration of IMP; and the first non-missing

reliable value for post-baseline assessments. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values. Any retest or unscheduled assessments performed will be included in the individual subject data listings.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, during the Data Review Meeting.

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used.

For the calculation based on dates of the medical history, medications, non-drug therapies and adverse events, the missing/incomplete dates will not be replaced but the following rules will be applied:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE / concomitant medication is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history will be assumed to have occurred before any study treatment.
- If a partial date and the associated information do not allow the assignation to a group/category, all the possible groups/categories will be considered (i.e. a medication with partial start and stop dates could be considered as prior and concomitant treatment).
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

For the calculation based on the date of ABI or the date of spasticity, the following rules will be applied:

- In the case of completely missing date, it will be estimated by the date of baseline visit.
- If the day and the month are missing:
  - If the year is the same as the year of baseline visit, it will be estimated by the date of baseline visit.
  - If the year is prior to the year of baseline visit, it will be estimated by the 31DECYYYY.
- If only the day is missing:
  - If the month and the year are the same as the month and the year of baseline visit, it will be estimated by the date of baseline visit.
  - If the month and the year are prior to the month and the year of baseline visit, it will be estimated by the last day of the month.

For the calculation based on the date of first BoNT injection before the study, the following rules will be applied:

- In the case of completely missing date, the date will remain missing and it will be assumed to have occurred before any study treatment.
- If the day and the month are missing:
  - If the year is the same as the year of date of last BoNT injection, it will be estimated by the date of last BoNT injection.
  - If the year is prior to the year of date of last BoNT injection, it will be estimated by the 31DECYYYY.
- If only the day is missing:
  - If the month and the year are the same as the month and the year of date of last BoNT injection, it will be estimated by the date of last BoNT injection.
  - If the month and the year are prior to the month and the year of date of last BoNT injection, it will be estimated by the last day of the month.

For the calculation based on the date of last BoNT injection before the study, the following rules will be applied:

- In the case of completely missing date, it will be estimated by the baseline visit.
- If the day and the month are missing:
  - If the year is the same as the year of date of first BoNT injection, it will be estimated by the date of first BoNT injection.
  - If the year is after the year of date of first BoNT injection, it will be estimated by the 01JANYYYY.
- If only the day is missing:
  - If the month and the year are the same as the month and the year of date of first BoNT injection, it will be estimated by the date of first BoNT injection.
  - If the month and the year are after the month and the year of date of first BoNT injection, it will be estimated by the first day of the month.

3.2.3.3 Outliers

Any outlier identified prior to database lock which is impossible / implausible will be excluded from the analysis. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

If any outliers are identified after database lock the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.

A search of outliers by Biotrial should be performed before the database lock and actions with the sponsor should be defined. This will be done for variables used for the primary and secondary analysis: AROM against 10 prespecified muscle groups, MFS overall scores, the maximal WS barefoot, EQ-5D-5L scores (5 scores from the EQ-5D descriptive system and the EQ-5D-5L VAS score) and the answers to the

SF-12 questionnaire. A detection of abnormal values on vital signs data will also be performed.

3.2.4 Subject disposition

The number and percentage of subjects enrolled and included in each population will be tabulated by country and centre. A summary table (including the number of completed subjects defined as all screened subjects who completed his/her Final Visit) and a flow chart will be presented for each subject population and 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 will be tabulated for each population.

A listing of the inclusion and exclusion criteria will be provided and the listings of the inclusion and exclusion criteria not respected will be provided by country, centre, subject ID on all the subjects.

All the protocol deviations, defined prior to database freeze, will be listed by country, centre, subject ID on all the subjects. A frequency table of the number and percentage of subjects with at least one major protocol deviation with the number of major protocol deviations will be provided by protocol deviation class and overall on the ITT population.

The impact of major protocol deviation on the primary efficacy analysis will be investigated by comparing the results of the mITT and PP population analyses.

A listing of subjects screened with the reason for inclusion failure will be presented by country, centre and subject ID for the Enrolled population.

A listing of dates of assessments will be presented by subject ID on all the subjects.

3.2.5 Withdrawals

Discontinued subjects will be listed on all the subjects and a frequency table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented for the Enrolled population.

3.2.6 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by country, centre and subject ID for the Enrolled population.

Summary statistics or frequency tables will be provided for demographic and baseline characteristics for the ITT population. If the ITT population differs from the mITT population by more than 10%, summary statistics for demographic and baseline characteristics will also be presented for the mITT population.

3.2.6.1 Demographic data

The following demographic data will be summarized:

- Age: in years and in classes (<65 years / ≥65 years)
- Sex (Male / Female)
- Race (Asian / Black or African American / White / Native Hawaiian or Other Pacific Islander / American Indian or Alaska Native / Other), except for French centers
- Ethnicity (Hispanic/Latino / Not Hispanic/Latino), except for French centers
- Height (cm)

- Body weight (kg) at baseline
- BMI (kg/m²) at baseline
- Country (France / Czech Republic / Russia / USA)
- Selection of primary TT limb (UL / LL): this variable will be described overall and by country.
- Naïve to BoNT treatment (for UL and/or LL spasticities) (Yes / No)
- Naïve to GSC (Yes / No).

3.2.6.2 Other baseline characteristics

The following other baseline characteristics will be summarized:

- Disease history
  - Type of ABI (Brain trauma / Vascular (infarct or haemorrhage))
  - Duration since the date of ABI: in months and in classes ([12;18[months / [18;24[months / ≥24 months)
  - Time from spasticity onset: in months and in classes ([0;6[months / [6;12[months / [12;18[months / [18;24[months / ≥24 months)
  - Time between spasticity and first BoNT injection (first injection before the study for the non-naïve subjects and first injection in the study for the naïve subjects): in months and in classes ([0;6[months / [6;12[months / [12;18[months / [18;24[months / ≥24 months)
- Previous BoNT injections
  - For UL spasticity and for LL spasticity separately
    - BoNT treatment (naïve / non-naïve)
    - For non-naïve subjects to BoNT treatment: time from the first BoNT injection ([0;6[months / [6;12[months / [12;18[months / [18;24[months / ≥24 months), time from the last BoNT injection ([0;6[months / [6;12[months / [12;18[months / [18;24[months / ≥24 months), brand name at the last injection (AbobotulinumtoxinA - DYSPORT® / OnabotulinumtoxinA - BOTOX® / IncobotulinumtoxinA - XEOMIN® or XEOMEEN® / Other) and, the time from the last BoNT injection and the total dose administered of the last injection (units) by brand
  - For non-naïve subjects previously treated with BoNT for UL and/or LL spasticity: total dose administered of the last injection (units) by brand
- GSC
  - For non-naïve subjects to GSC only: subject satisfaction with GSC at baseline (Completely satisfied / Rather satisfied / Neither satisfied nor dissatisfied / Rather dissatisfied / Completely dissatisfied).
  - Subject's belief that the GSC will help to improve functional capacity at baseline (Very true of what I believe / Somewhat true of what I believe / No opinion/don't know / Somewhat untrue of what I believe / Very untrue of what I believe)

- Physiotherapist's belief that the GSC will help to improve functional capacity of the subject at baseline (Very true of what I believe / Somewhat true of what I believe / No opinion/don't know / Somewhat untrue of what I believe / Very untrue of what I believe)

• The AROM at baseline will be described as follows:

	Muscle group		
	Injected	Not injected	Injected or not
Overall full composite AROM: XA full (ie. sum of ten muscle groups)			X
Full composite AROM - XA full UL (ie. sum of five UL muscle groups) - XA full LL (ie. sum of five LL muscle groups)			X
Composite AROM - composite XA UL (ie. sum of X_{AEF}; X_{AWF}; X_{AFF}) - composite XA LL (ie. sum of X_{ASol}; X_{AGN})			X
Muscle groups - UL: 5 muscle groups - LL: 5 muscle groups	X	X	X

A muscle group will be considered as injected if at least one muscle within the muscle group is injected.

• MFS overall scores, assessed locally and centrally by a reviewer blinded regarding the order of the video recording/visit number for a given subject, at baseline: these variables will be described overall and by primary TT limb.

• WST at baseline

- Ability of the patient to walk 10 metres in 5 min or less (Yes / No)
- Maximal WS barefoot (m/s): this variable will be described overall and by primary TT limb.

• EQ-5D-5L questionnaire at baseline

- Answer to the 5 questions
  - Mobility (I have no problems walking / I have slight problems walking / I have moderate problems walking / I have severe problems walking / I am unable to walk)
  - Self-care (I have no problems washing or dressing myself / I have slight problems washing or dressing myself / I have moderate problems washing or dressing myself / I have severe problems washing or dressing myself / I am unable to wash or dress myself)
  - Usual activities (I have no problems doing my usual activities / I have slight problems doing my usual activities / I have moderate problems doing my usual activities / I have severe problems doing my usual activities / I am unable to do my usual activities)
  - Pain/discomfort (I have no pain or discomfort / I have slight pain or discomfort / I have moderate pain or discomfort / I have severe pain or discomfort / I have extreme pain or discomfort)
  - Anxiety/depression (I am not anxious or depressed / I am slightly anxious or depressed / I am moderately anxious or depressed / I am severely anxious or depressed / I am extremely anxious or depressed)

- Index score (for the French centers and the US centers only)
- EQ-5D-5L VAS score.

- SF-12 questionnaire at baseline: SF-12 physical score and SF-12 mental score.
- Urine pregnancy test: positive results will be listed.
- Vital signs at baseline:
  - Supine systolic blood pressure (mmHg)
  - Supine diastolic blood pressure (mmHg)
  - Supine heart rate (BEATS/min).
- Physical examination at baseline: the dates of physical examination will be listed only.

3.2.7 Medical and surgical history

Medical and surgical history will be coded using MedDRA Version in force within Ipsen at the first time of first coding.

A listing will present the primary system organ class, the preferred term and the reported term for the Enrolled population. The listing of medical history will be sorted by country, centre, subject ID, primary system organ class, preferred term and reported term.

A frequency table of the number and percentage of subjects will be provided by primary system organ class and preferred term on the ITT population for:

- prior significant medical and surgical history not related to UL or LL spasticity,
- ongoing significant medical and surgical history not related to UL or LL spasticity.

3.2.8 Subject compliance

3.2.8.1 Subject compliance to study drug

Listings will be presented for the drug administration date, the technique used to target injection with the side injected and details of injections (muscle group injected, site of administration injected, number of injection sites, dose administered by muscle and total doses administered for each limb and for both limbs) by country, centre, subject ID, cycle, limb, muscle group and site of administration for the Enrolled population.

The study exposure (weeks) will be summarized on the safety population.

Compliance to study drug will be calculated in percentage as the total dose administered based on the expected total units to be injected (1500 U per cycle) and will be categorized as <80%, 80-120% and >120%. The overall compliance to study drug and the compliance to study drug for each cycle will be summarized in percentage and in classes, on the safety population. Compliance to study drug will also be listed by country, centre, subject ID and cycle.

A frequency table of the number and percentage of subjects with less than 750 units for the target limb and the number and the percentage of subjects injected in only one limb will be provided on the safety population.

Summary statistics of the dose administered (units) will be presented on the safety population by:

- Muscle: overall and by primary TT limb only for the muscles which are injected in at least 20% of the safety population.
- Muscle group
  - for UL limb: shoulder extensors, elbow flexors, wrist flexors, extrinsic finger flexors, pronator teres and other.
  - for LL limb: soleus, gastrocnemius, gluteus maximus, hamstrings, rectus femoris muscle, tibialis posterior, hallux flexors, adductors, gracilis and other.
- Limb (for each limb and for both limbs)
- Primary TT limb: Upper limb and Lower limb.

The technique used (ES, ultrasound and both) and the laterality will also be presented on the safety population.

Summary statistics of the time to re-injection (days) will be presented. A frequency table of the percentage of subjects re-injected will also be provided by visit during the cycle 1.

3.2.8.2 Subject compliance to GSC

Compliance to GSC will be calculated in percentage based on the number of days when GSC therapy was not performed (as determined from the subject diary) and will be categorized as <80% and 80-100%. The overall compliance to GSC and the compliance to GSC for each cycle will be summarized in percentage and in classes, on the safety population. Compliance to GSC will also be listed by country, centre, subject ID and cycle.

3.2.8.3 Global compliance to study drug and/or GSC

The global compliance to study drug and/or GSC will be derived in classes (Compliance to both study drug and GSC / Compliance to at least one (study drug or GSC) / No compliance) and described on the safety population.

3.2.9 Prior and concomitant medications

3.2.9.1 Prior and concomitant medications (excluding UL or LL spasticity)

Prior and concomitant medications (excluding UL or LL spasticity) will be coded using World Health Organisation (WHO) Drug Dictionary. The WHO Drug Dictionary version in force within Ipsen at the first time of first coding will be used. The therapeutic class will correspond to the second level of anatomic therapeutic class (ATC) code, that is, corresponding to the first 3 figures.

A listing will present the therapeutic class, the preferred name and the reported name. The listing of general medications (excluding UL or LL spasticity) will be sorted by country, centre, subject ID, chronological start date, therapeutic class, preferred name and reported name on the Enrolled population.

A frequency table of the number and percentage of subjects will be provided for general prior medications (excluding UL or LL spasticity) by therapeutic class and preferred name on the ITT population. The same table will be provided for general concomitant medications (excluding UL or LL spasticity).

3.2.9.2 Concomitant medications for UL or LL spasticity

The concomitant medications for UL or LL spasticity will be coded, listed and summarised in the same way as for the general prior and concomitant medications (excluding UL or LL spasticity) previously detailed.

3.2.10 Prior and concomitant non-drug therapies

Prior and concomitant non-drug therapies will be coded using MedDRA Version in force within Ipsen at the first time of first coding.

A listing will present the primary system organ class, the preferred term and the reported term. The listing of non-drug therapies will be sorted by country, centre, subject ID, primary system organ class, preferred term and reported term on the Enrolled population.

A frequency table of the number and percentage of subjects will be provided by primary system organ class and preferred term on the ITT population for:

- Prior non-drug therapies for UL or LL spasticity,
- Prior non-drug therapies for other indication,
- Concomitant non-drug therapies for UL or LL spasticity,
- Concomitant non-drug therapies for other indication.

3.2.11 Concomitant surgical procedures

Concomitant surgical procedures will be coded using MedDRA Version in force within Ipsen at the first time of first coding.

A listing will present the primary system organ class, the preferred term and the reported term. The listing of concomitant surgical procedures will be sorted by country, centre, subject ID, primary system organ class, preferred term and reported term on the Enrolled population.

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by therapeutic class and preferred name on the ITT population.

3.2.12 Pharmacokinetics & antibodies (if applicable)

Not applicable for the study.

3.2.13 Pharmacodynamics (if applicable)

Not applicable for the study.

3.2.14 Derived data

The derived data are variables which are calculated from the raw data in the eCRF and not included in the database. The list of derived data is available in Appendix 1.

3.2.15 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-

treatment assessments the closest non-missing result to the scheduled visit should be used. Both the scheduled visits and the analysed visits will be listed, if applicable.

Study phase	Scheduled visit	Time interval (days)
Active phase	Cycle 1 Baseline	less than 21 days (excluded) after the first injection
	Cycle 1 Week 6	21 to 63 days after the first injection
	Cycle 1 Week 12	64 to 98 days after the first injection
	Cycle 1 Week 16	99 to 126 days after the first injection
	Cycle 1 Week 20	127 to 161 days after the first injection
	Cycle 2 Week 6	21 to 63 days after the second injection
	Cycle 2 Week 12	64 to 98 days after the second injection
	Cycle 2 Week 16	99 to 126 days after the second injection
	Cycle 2 Week 20	127 to 161 days after the second injection

3.2.16 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics of continuous data, the following will be presented n, number of missing values, arithmetic mean, standard deviation, median, first quartile and third quartile (Q1 and Q3), and the range (minimum, maximum). The 95% CIs will also be presented for the efficacy endpoints only.

For summary statistics of categorical nominal data, the following will be presented n, number of missing values and percentage of subjects for each category. The 95% CIs will also be presented for the efficacy endpoints only.

For summary statistics of categorical ordinal data, both presentations as described above will be presented.

Mean, median, Q1, Q3, standard deviation and 95% CIs for means values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects with available data in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary. Missing values will not be accounted for in denominator.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as ‘<0.0001’.

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format [yyyy-mm-dd] and times in the format [hh:mm].

3.2.17 Pooling of Centres

Descriptive analysis of the AROM (degrees) against each muscle group (separately for injected muscle groups, not injected muscles groups and injected or not muscle groups), the composite AROM, the full composite AROM and the overall full composite AROM at baseline and the primary efficacy endpoint will be performed by country.

3.2.18 Interim analysis

An interim analysis was performed after subject enrolment has been completed in order to describe baseline data and more specifically injection details (previous injections and the first injection in the study).

The first version of SAP (dated on 22 November 2017) focused on the baseline data interim analysis.

3.2.19 Role of independent data monitoring committee (DMC)/interim data review committee [if applicable]

No independent data monitoring committee/interim data review committee will be used in this study.

3.2.20 Covariates and analysis of subgroups

The following subgroup variables will be used for the description of the AROM per muscle group, the composite AROM, the full composite AROM and the overall full composite AROM at baseline:

- Country
  - France
  - Czech Republic
  - Russia
  - USA
- Primary TT limb
  - UL
  - LL
- Naïve to BoNT treatment for UL and LL spasticities
  - Yes
  - No
- Naïve to BoNT treatment for UL spasticity
  - Yes
  - No
- Naïve to BoNT treatment for LL spasticity
  - Yes
  - No
- Naïve to GSC
  - Yes
  - No

The following subgroup variables will be used for the description of the primary efficacy endpoint on the mITT population only:

- Sex
  - Male
  - Female
- Age
  - <65 years
  - ≥65 years
- Country
  - France
  - Czech Republic
  - Russia
  - USA
- Primary TT limb
  - UL
  - LL
- Naïve to BoNT treatment for UL and LL spasticities
  - Yes
  - No
- Naïve to BoNT treatment for UL spasticity
  - Yes
  - No
- Naïve to BoNT treatment for LL spasticity
  - Yes
  - No
- Naïve to GSC
  - Yes
  - No

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Microsoft Windows 7 Enterprise.

4.2 Software

All tables, listings and figures will be produced and statistical analysis performed using Statistical Analysis System (SAS) version 9.4 or higher. All outputs will be in Microsoft Word Format and compiled in bookmarked .pdf files as per ICH section (e.g. 14.1, 14.2 …).

4.3 Validation programs

The CRO Biotrial will provide a Validation Plan to Ipsen identifying the methods of validation.

The validation report with all relevant documents as detailed in the validation plan will be submitted to the sponsor to support the validation.

The Program Reviewer is responsible for reviewing each project program and output associated with the deliverable product. Program logs are reviewed for logical, syntax and fatal errors. The review in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The Reviewing/Quality control (QC) Statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g., SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the statistical and analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further changes are required to produce the deliverable, the Program Reviewer and Reviewing/QC Statistician need to complete and sign the CRO's Validation Checklist/Sign-off Sheet, to indicate that they have successfully performed all of their responsibilities.

Copies of the internal QC forms produced for the validation process and the CRO's sign-off forms will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs (including Macros and analysis datasets) producing the tables, listings and statistical outputs along with associated logs should be given to the sponsor when the tables, listings, figures and statistical analysis are finalised.

5 CHANGES FROM PROTOCOL

- The screened population defined in the protocol will be replaced by "Enrolled population" with the same definition.
- Protocol stated that the ITT population will be identical to the safety population. However, two ITT populations will be defined: one for the interim analysis, which corresponds to the safety population, and one for the final analysis.
- The description of the AROM (degrees) against each muscle group (separately for injected muscle groups, not injected muscles groups and injected or not muscle groups), the composite AROM and the full composite AROM at baseline will be described by the following subgroups: country, primary TT limb, naïve or non-naïve to BoNT treatment and naïve or non-naïve to GSC.

- Protocol stated that the variable for the subject satisfaction with longer interval between 2 injections will be a Likert scale score. However, the possible answer to this question is: Yes / No / No opinion.
- Protocol stated that subgroup analyses will be provided for the primary efficacy endpoint by race (Asian / Black or African American / White / Native Hawaiian or Other Pacific Islander / American Indian or Alaska Native / Other) and ethnicity (Hispanic/Latino / Not Hispanic/Latino). As more than 90% of the subjects are represented in a single category for each variable, these subgroup analyses will not be performed.
- The analysis of the overall full composite AROM will be added.
- The analysis of concordance of the MFS between the local assessment by the investigators and the central review will be added.
- The analysis of the time to first response will be added.
- The analyses of the re-injection will be added: time to re-injection and moment of the re-injection in cycle 1.
- The analysis of the TEAEs of special interest will be added.

6 REFERENCES

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7 APPENDICES TO THE SAP

Appendix 1 Derived Data

The following derived data will be calculated and included in the listings:

(1) **Study day**

Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist).

(2) **Baseline**

Baseline will be derived as the last available (and reliable if applicable) assessment before IMP administration (at Baseline Visit).

(3) **Change from baseline**

Change from baseline will be calculated as the difference from baseline (e.g. assessment at the visit – assessment at baseline).

(4) **Composite AROMs**

The composite AROM for the upper limb (Composite AROM UL (degrees)) will be calculated as $X_{AEF} + X_{AWF} + X_{AFF}$ where X_A = AROM, EF = elbow flexors, WF = wrist flexors and FF = extrinsic finger flexors.

The composite AROM for the lower limb (Composite AROM LL (degrees)) will be calculated as $X_{ASol} + X_{AGN}$ where X_A = AROM, Sol = soleus muscle and GN = gastrocnemius.

(5) **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).

(6) **Re-injection visit and last study visit**

The re-injection cycle visit is defined as the visit when the subject is re-injected. It corresponds to Week 12 or Week 16 or Week 20 of injection cycle 1.

The last study visit is defined as the last post-baseline visit performed by the subject including the Early withdrawal visit.

(7) **Full composite AROMs**

The full composite AROM for the upper limb (Full composite AROM UL (degrees)) will be calculated as $X_{ASE} + X_{AEF} + X_{AWF} + X_{AFF} + X_{APT}$ where X_A = AROM, SE = shoulder extensors, EF = elbow flexors, WF = wrist flexors, FF = extrinsic finger flexors and PT = pronator teres.

The full composite AROM for the lower limb (Full composite AROM LL (degrees)) will be calculated as $X_{ASol} + X_{AGN} + X_{AGM} + X_{AHS} + X_{ARF}$ where X_A = AROM, Sol = soleus muscle, GN = gastrocnemius, GM = gluteus maximus, HS = hamstrings and RF = rectus femoris.

The overall full composite AROM (Overall full composite AROM (degrees)) will be calculated as $X_{ASE} + X_{AEF} + X_{AWF} + X_{AFF} + X_{APT} + X_{ASol} + X_{AGN} + X_{AGM} + X_{AHS} + X_{ARF}$ where X_A = AROM, SE = shoulder extensors, EF = elbow flexors, WF = wrist flexors, FF = extrinsic finger flexors, PT = pronator teres, Sol = soleus muscle, GN = gastrocnemius, GM = gluteus maximus, HS = hamstrings and RF = rectus femoris.

(8) **Maximal WS barefoot**

The maximal WS barefoot (m/s) will be calculated as the distance walked (m) / duration of the walk (s). If the distance walked is equal to 0 m and the duration of the walk is equal to 0 s, the maximal WS barefoot will be derived to 0 m/s.

(9) **Percentage of days over study period when GSC therapy was performed**

The percentage of days over study period when GSC therapy was performed will be calculated as follows:

$$\%\ \text{days GSC therapy performed} = \frac{\text{Total number of study days} - \text{Total number of days when GSC therapy was not performed}}{\text{Total number of study days}} * 100$$

where,

- the total number of study days will be calculated as (date of last assessment for GSC compliance – date of baseline visit).

- the total number of days when GSC therapy was not performed will be calculated as the sum of the number of days when GSC therapy was not performed since the last visit recorded at each visit and according to the following rules (worst case).

NUMBER OF DAYS WHEN GSC THERAPY WAS NOT PERFORMED SINCE THE LAST VISIT	
Recorded data	**Imputed data for the calculation of compliance with the GSC**
Exact Number (Days)	Exact Number (Days), if not missing.
Ranges	
1 to 5 Days	5 Days
6 to 10 days	10 Days
11 to 15 days	15 Days
>15 days	Number of days between the previous visit and the visit divided by 2 if this number is superior to 15, 16 otherwise
Missing days	Adjusted on the overall percentage of days over study period when GSC therapy was performed, estimated without taking into account the period with missing days.

(10) **Index score of EQ-5D-5L**

The index score will be derived from the EQ-5D-5L value sets. For the interim analysis and the final analysis, these EQ-5D-5L value sets are not yet available but the ones which have been estimated with the crosswalk methodology based on the EQ-5D-3L value sets will be used [10]. These value sets have been calculated for France and USA only, the index score will not be calculated for the patients from Czech Republic and Russia. The value sets are available in the following Excel file which comes from the EuroQol website (https://euroqol.org/).

If the EQ-5D-5L value sets are available at the time of the final analysis, they will be used.

(11) **SF-12 scores**

The SF-12 physical score and the SF-12 mental score will be derived using the SF scoring software which can be downloaded here: https://www.amihealthy.com/download/SFScoringSoftwareV5Setup.msi.

From SAS, an Excel file (in CSV format) containing the variables required by the software to calculate the SF-12 scores will be generated and imported into the software. Once the calculated SF-12 scores will be available in the software, they will be exported in Excel file (in CSV format) and will be integrated in the ADQS.

(12) **Time to first response**

The time to first response will be calculated as (date of first response or date of last study visit - date of first injection) + 1. For subjects who have a responder status, the date of first response will be used. For subjects who have a nonresponder status until the last study visit or for dropouts and lost to follow-up subjects, the date of last study visit will be used.

(13) **BMI (specified VS table)**

BMI (kg/m²) will be derived as Weight (kg)/[Height(cm)/100]² and rounded to the nearest decimal.

(14) **Naïve or non-naïve to BoNT treatment**

A subject will be considered as non-naïve to BoNT treatment if he/she has been previously treated with BoNT for UL and/or LL spasticities. He/she will be considered as naïve to BoNT treatment otherwise.

(15) **Naïve or non-naïve to GSC**

A subject will be considered as non-naïve to GSC if he/she has followed GSC within the last 4 months prior to study entry. He/she will be considered as naïve to GSC otherwise.

(16) **Duration since the date of ABI**

The duration since the date of ABI will be calculated as ((baseline visit date – date of ABI) + 1)/30.4375 and presented in months.

(17) **Time from spasticity onset**

The time from spasticity onset will be calculated as ((baseline visit date – onset date of spasticity) + 1)/30.4375 and presented in months.

(18) **Time between spasticity and first BoNT injection**

The time between spasticity and first BoNT injection will be calculated as ((date of first BoNT injection – onset date of spasticity) + 1)/30.4375 and presented in months. The date of first BoNT injection will be the date of first BoNT injection before the study for the non-naïve subjects and the date of first BoNT injection in the study for the naïve subjects.

(19) **Time from the first/last BoNT injection**

The time from the first/last BoNT injection will be calculated only for non-naïve subjects to BoNT treatment as ((baseline visit date – date of first/last BoNT injection) + 1)/30.4375 and presented in months.

(20) **Ability of the patient to walk 10 metres in 5 min or less**

A subject will be considered as to be able to walk 10 metres in 5 min or less if the time to complete 10 meter walk is filled. He/she will be considered as not to be able to walk 10 metres in 5 min or less if the distance walked and the duration of the walk are filled.

(21) **Study exposure**

The study exposure (weeks) will be calculated as (Date of last study visit – Date of inform consent + 1)/7.

(22) **Compliance to study drug**

For a given cycle, the compliance to study drug in percentage will be calculated as (Total dose administered / Expected dose) x 100.

(23) **Overall compliance to study drug**

The overall compliance to study drug in percentage will be calculated as (Total dose administered during all cycles / Expected dose during all cycles) x 100.

(24) **Time to re-injection**

The time to re-injection will be calculated as (date of re-injection - date of first injection) + 1. The date of re-injection corresponds to the date when the subject was injected a second time, at the beginning of the cycle 2.

(25) **Compliance to GSC**

For a given cycle, the compliance to GSC in percentage will be calculated as follows:

$$\text{Compliance to GSC}_i\ (\%) = \frac{\begin{array}{c}\text{Total number of study days during the ith cycle} - \\ \text{Total number of days when GSC therapy} \\ \text{was not performed during the ith cycle}\end{array}}{\text{Total number of study days during the ith cycle}} * 100$$

where,

- the total number of study days during the i^{th} cycle will be calculated as (date of last assessment for GSC compliance in the i^{th} cycle (at Week 12 or Week 16 or Week 20 of injection cycle or Early withdrawal visit (if the Early withdrawal visit occurs after the baseline visit without re-injection for the cycle 1 or after the re-injection cycle visit for the cycle 2) – date of baseline visit).

- the total number of days when GSC therapy was not performed during the i^{th} cycle will be calculated as the sum of the number of days when GSC therapy was not performed since the last visit recorded at each visit of the i^{th} cycle and according to the rules previously detailed ((9)).

(26) **Overall compliance to GSC**

The overall compliance to GSC corresponds to the percentage of days over study period when GSC therapy was performed previously detailed ((9)).

(27) **Global compliance to study drug and/or GSC**

A subject will be considered as having a global compliance to both study drug and GSC if he/she has got an overall compliance to study drug between 80% and 120% and an overall compliance to GSC between 80% and 100%. A subject will be considered as having a global compliance to at least one (study drug or GSC) if he/she has got an overall compliance to study drug between 80% and 120% or a overall compliance to GSC between 80% and 100%. He/she will be considered as having no compliance otherwise.

(28) **Dose administered by muscle group**

For a given muscle group, the dose administered will be derived as the sum of the doses administered in each muscle of the muscle group.

(29) **Dose administered by limb**

For a given limb, the dose administered will be derived as the sum of the doses administered in each muscle of the limb.

(30) **Prior and concomitant flags**

The date of the baseline visit will be used as the cut-off date for the definition of prior and concomitant medications/non-drug therapies. A medication/non-drug therapy that started before baseline visit and is continuing at time of baseline visit will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be coded as P, C and PC respectively.

(31) **Duration for medical and surgical history**

The duration of medical and surgical history will be calculated as (end date – start date) + 1. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (screening visit date – start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as a superior inequality "≥ xx"day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

(32) **Duration for medications, non-drug therapies and adverse events**

If times are available, the duration of medications or non-drug therapies etc. will be calculated as (end date/time - start date/time). If at least one time is missing, the duration will be calculated as (end date - start date) +1. If the recorded end date is CONT. (for continuing) then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e.: ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

Appendix 2 List of codes used to identify each adverse event of special interest

- The following list of MedDRA 20.0 PTs terms will be used to identify AE reports of possible remote spread of effects of botulinum toxin.
- Hypersensitivity reactions will be identified using the MedDRA SMQ for Hypersensitivity reactions (Narrow search query).

The following tables specify the MedDRA 20.0 PTs terms to use for the programming of AESI.

Possible remote spread of effects of botulinum toxin:

Remote Spread PTs	
Accommodation disorder	10000389
Areflexia	10003084
Aspiration	10003504
Botulism	10006041
Bradycardia	10006093
Bulbar palsy	10006542
Constipation	10010774
Cranial nerve palsies multiple	10011314
Cranial nerve paralysis	10061908
Diaphragmatic paralysis	10012725
Diplopia	10013036
Dry mouth	10013781
Dysarthria	10013887
Dysphagia	10013950
Dysphonia	10013952
Dyspnoea	10013968
Extraocular muscle paresis	10015829
Eyelid function disorder	10061145
Eyelid ptosis	10015995
VIIth nerve paralysis	10050040
Facial paresis	10051267
Hemiparesis	10019465
Hypoglossal nerve paresis	10067129
Hyporeflexia	10021089
Hypotonia	10021118
IIIrd nerve paresis	10054202
Ileus paralytic	10021333
IVth nerve paresis	10054201
Monoparesis	10027925
Muscular weakness	10028372
Paralysis	10033799
Paralysis flaccid	10033809
Paraparesis	10033885
Paresis	10033985
Paresis cranial nerve	10061911
Pelvic floor muscle weakness	10064026
Peripheral nerve palsy	10058530
Peripheral paralysis	10054808
Pneumonia aspiration	10035669
Pupillary reflex impaired	10037532
Quadriparesis	10049680
Respiratory arrest	10038669
Respiratory depression	10038678
Respiratory failure	10038695

Remote Spread PTs	
Speech disorder	10041466
Trigeminal nerve paresis	10068008
Urinary retention	10046555
Vision blurred	10047513
Vocal cord paralysis	10047674
Vocal cord paresis	10049234
Neuromuscular toxicity	10062284
Paralysis recurrent laryngeal nerve	10033830
Respiratory distress	10038687
Respiratory paralysis	10038708

Potential hypersensitivity reactions:

Hypersensitivity Narrow SMQ	
Acute generalised exanthematous pustulosis	10048799
Administration site dermatitis	10075096
Administration site eczema	10075099
Administration site hypersensitivity	10075102
Administration site rash	10071156
Administration site recall reaction	10075964
Administration site urticaria	10075109
Administration site vasculitis	10075969
Allergic bronchitis	10052613
Allergic colitis	10059447
Allergic cough	10053779
Allergic cystitis	10051394
Allergic eosinophilia	10075185
Allergic gastroenteritis	10075308
Allergic hepatitis	10071198
Allergic keratitis	10057380
Allergic myocarditis	10001715
Allergic oedema	10060934
Allergic otitis externa	10075072
Allergic otitis media	10061557
Allergic pharyngitis	10050639
Allergic respiratory disease	10063532
Allergic respiratory symptom	10063527
Allergic sinusitis	10049153
Allergic transfusion reaction	10066173
Allergy alert test positive	10075479
Allergy test positive	10056352
Allergy to immunoglobulin therapy	10074079
Allergy to surgical sutures	10077279
Allergy to vaccine	10055048
Alveolitis allergic	10001890
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113
Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Anaphylaxis treatment	10002222
Angioedema	10002424
Antiallergic therapy	10064059
Antiendomysial antibody positive	10065514
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894

Hypersensitivity Narrow SMQ	
Application site dermatitis	10003036
Application site eczema	10050099
Application site hypersensitivity	10063683
Application site rash	10003054
Application site recall reaction	10076024
Application site urticaria	10050104
Application site vasculitis	10076027
Arthritis allergic	10061430
Aspirin-exacerbated respiratory disease	10075084
Atopy	10003645
Blepharitis allergic	10005149
Blood immunoglobulin E abnormal	10005589
Blood immunoglobulin E increased	10005591
Bromoderma	10006404
Bronchospasm	10006482
Catheter site dermatitis	10073992
Catheter site eczema	10073995
Catheter site hypersensitivity	10073998
Catheter site rash	10052271
Catheter site urticaria	10052272
Catheter site vasculitis	10074014
Chronic eosinophilic rhinosinusitis	10071399
Chronic hyperplastic eosinophilic sinusitis	10071380
Circulatory collapse	10009192
Circumoral oedema	10052250
Conjunctival oedema	10010726
Conjunctivitis allergic	10010744
Contact stomatitis	10067510
Contrast media allergy	10066973
Contrast media reaction	10010836
Corneal oedema	10011033
Cutaneous vasculitis	10011686
Dennie-Morgan fold	10062918
Dermatitis	10012431
Dermatitis acneiform	10012432
Dermatitis allergic	10012434
Dermatitis atopic	10012438
Dermatitis bullous	10012441
Dermatitis contact	10012442
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Dermatitis herpetiformis	10012468
Dermatitis infected	10012470
Dermatitis psoriasiform	10058675
Device allergy	10072867
Dialysis membrane reaction	10076665
Distributive shock	10070559
Documented hypersensitivity to administered product	10076470
Drug cross-reactivity	10076743
Drug eruption	10013687
Drug hypersensitivity	10013700
Drug provocation test	10074350
Drug reaction with eosinophilia and systemic symptoms	10073508
Eczema	10014184
Eczema infantile	10014198

Hypersensitivity Narrow SMQ	
Eczema nummular	10014201
Eczema vaccinatum	10066042
Eczema vesicular	10058681
Eczema weeping	10055182
Encephalitis allergic	10056387
Encephalopathy allergic	10014627
Eosinophilic granulomatosis with polyangiitis	10078117
Epidermal necrosis	10059284
Epidermolysis	10053177
Epidermolysis bullosa	10014989
Epiglottic oedema	10015029
Erythema multiforme	10015218
Erythema nodosum	10015226
Exfoliative rash	10064579
Eye allergy	10015907
Eye oedema	10052139
Eye swelling	10015967
Eyelid oedema	10015993
Face oedema	10016029
Fixed drug eruption	10016740
Giant papillary conjunctivitis	10018258
Gingival oedema	10049305
Gingival swelling	10018291
Gleich's syndrome	10066837
Haemorrhagic urticaria	10059499
Hand dermatitis	10058898
Henoch-Schonlein purpura	10019617
Henoch-Schonlein purpura nephritis	10069440
Heparin-induced thrombocytopenia	10062506
Hereditary angioedema	10019860
Hypersensitivity	10020751
Hypersensitivity vasculitis	10020764
Idiopathic urticaria	10021247
Immediate post-injection reaction	10067142
Immune thrombocytopenic purpura	10074667
Immune tolerance induction	10070581
Immune-mediated adverse reaction	10077665
Implant site dermatitis	10063855
Implant site hypersensitivity	10063858
Implant site rash	10063786
Implant site urticaria	10063787
Incision site dermatitis	10073168
Incision site rash	10073411
Infusion site dermatitis	10065458
Infusion site eczema	10074850
Infusion site hypersensitivity	10065471
Infusion site rash	10059830
Infusion site recall reaction	10076085
Infusion site urticaria	10065490
Infusion site vasculitis	10074851
Injection site dermatitis	10022056
Injection site eczema	10066221
Injection site hypersensitivity	10022071
Injection site rash	10022094
Injection site recall reaction	10066797

Hypersensitivity Narrow SMQ	
Injection site urticaria	10022107
Injection site vasculitis	10067995
Instillation site hypersensitivity	10073612
Instillation site rash	10073622
Instillation site urticaria	10073627
Interstitial granulomatous dermatitis	10067972
Intestinal angioedema	10076229
Iodine allergy	10052098
Kaposi's varicelliform eruption	10051891
Kounis syndrome	10069167
Laryngeal oedema	10023845
Laryngitis allergic	10064866
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Limbal swelling	10070492
Lip oedema	10024558
Lip swelling	10024570
Mast cell degranulation present	10076606
Medical device site dermatitis	10075572
Medical device site eczema	10075575
Medical device site hypersensitivity	10075579
Medical device site rash	10075585
Medical device site recall reaction	10076140
Medical device site urticaria	10075588
Mouth swelling	10075203
Mucocutaneous rash	10056671
Multiple allergies	10028164
Nephritis allergic	10029120
Nikolsky's sign	10029415
Nodular rash	10075807
Oculomucocutaneous syndrome	10030081
Oculorespiratory syndrome	10067317
Oedema mouth	10030110
Oral allergy syndrome	10068355
Oropharyngeal blistering	10067950
Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Palatal oedema	10056998
Palatal swelling	10074403
Palisaded neutrophilic granulomatous dermatitis	10068809
Palpable purpura	10056872
Pathergy reaction	10074332
Periorbital oedema	10034545
Pharyngeal oedema	10034829
Pruritus allergic	10063438
Radioallergosorbent test positive	10037789
Rash	10037844
Rash erythematous	10037855
Rash follicular	10037857
Rash generalised	10037858
Rash macular	10037867
Rash maculo-papular	10037868
Rash maculovesicular	10050004
Rash morbilliform	10037870
Rash neonatal	10037871

Hypersensitivity Narrow SMQ	
Rash papulosquamous	10037879
Rash pruritic	10037884
Rash pustular	10037888
Rash rubelliform	10057984
Rash scarlatiniform	10037890
Rash vesicular	10037898
Reaction to azo-dyes	10037973
Reaction to colouring	10037974
Reaction to drug excipients	10064787
Reaction to preservatives	10064788
Red man syndrome	10038192
Rhinitis allergic	10039085
Scleral oedema	10057431
Scleritis allergic	10051126
Scrotal oedema	10039755
Serum sickness	10040400
Serum sickness-like reaction	10040402
Shock	10040560
Shock symptom	10040581
Skin necrosis	10040893
Skin reaction	10040914
Skin test positive	10040934
Solar urticaria	10041307
Solvent sensitivity	10041316
Stevens-Johnson syndrome	10042033
Stoma site hypersensitivity	10074509
Stoma site rash	10059071
Swelling face	10042682
Swollen tongue	10042727
Symmetrical drug-related intertriginous and flexural exanthema	10078325
Tongue oedema	10043967
Toxic epidermal necrolysis	10044223
Toxic skin eruption	10057970
Tracheal oedema	10044296
Type I hypersensitivity	10045240
Type II hypersensitivity	10054000
Type III immune complex mediated reaction	10053614
Type IV hypersensitivity reaction	10053613
Urticaria	10046735
Urticaria cholinergic	10046740
Urticaria chronic	10052568
Urticaria contact	10046742
Urticaria papular	10046750
Urticaria physical	10046751
Urticaria pigmentosa	10046752
Urticaria vesiculosa	10046755
Urticarial vasculitis	10048820
Vaccination site dermatitis	10069477
Vaccination site eczema	10076161
Vaccination site exfoliation	10069489
Vaccination site hypersensitivity	10068880
Vaccination site rash	10069482
Vaccination site recall reaction	10076188
Vaccination site urticaria	10069622
Vaccination site vasculitis	10076191

Hypersensitivity Narrow SMQ	
Vaccination site vesicles	10069623
Vaginal exfoliation	10064483
Vaginal ulceration	10046943
Vasculitic rash	10047111
Vessel puncture site rash	10077117
Vessel puncture site vesicles	10077813
Vulval ulceration	10047768
Vulvovaginal rash	10071588
Vulvovaginal ulceration	10050181

Appendix 3 List of TFLs

7.1 Listings Index

16.1.7 Randomisation Scheme and Codes

Not applicable for the study.

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects

Listing 16.2.1.1: Subject Disposition and Population - All subjects
Listing 16.2.1.2: Subject Disposition - Study Withdrawals - All subjects
Listing 16.2.1.3/1: Inclusion Criteria Assessments
Listing 16.2.1.3/2: Inclusion Criteria Not Respected - All subjects
Listing 16.2.1.4/1: Exclusion Criteria Assessments
Listing 16.2.1.4/2: Exclusion Criteria Not Respected - All subjects
Listing 16.2.1.5: Inclusion Failures - Enrolled Population
Listing 16.2.1.6: Assessment Dates - All subjects

16.2.2 Protocol deviations

Listing 16.2.2.1: Subject Eligibility for the Study - All subjects
Listing 16.2.2.2: Protocol Deviations - All subjects

16.2.3 Subjects excluded from the efficacy analysis

Listing 16.2.3.1: Subjects Excluded from the Efficacy Analysis - Enrolled Population

16.2.4 Demographic data

Listing 16.2.4.1: Demographic Data - Enrolled Population
Listing 16.2.4.2: Disease History - Enrolled Population
Listing 16.2.4.3: Previous BoNT Injections - Enrolled Population
Listing 16.2.4.4: Urine Pregnancy Test - Enrolled Population
Listing 16.2.4.5.1: Significant Medical and Surgical History Not Related to UL or LL Spasticity - Reported Terms and Associated MedDRA Terms - Enrolled Population
Listing 16.2.4.5.2: Significant Medical and Surgical History Not Related to UL or LL Spasticity - Enrolled Population
Listing 16.2.4.6.1.1: General Prior and Concomitant Medications Not Related to UL or LL Spasticity - Reported Terms and Associated WHO-DD Names - Enrolled Population
Listing 16.2.4.6.1.2: General Prior and Concomitant Medications Not Related to UL or LL Spasticity - Enrolled Population
Listing 16.2.4.6.2.1: General Concomitant Medications for UL or LL Spasticity - Reported Terms and Associated WHO-DD Names - Enrolled Population
Listing 16.2.4.6.2.2: General Concomitant Medications for UL or LL Spasticity - Enrolled Population
Listing 16.2.4.7.1: Prior and Concomitant Non-Drug Therapies - Reported Terms and Associated MedDRA Terms - Enrolled Population

7.2 Tables Index

In case of analysis should be performed on mITT population (if more than 10% of the subjects in the ITT population are excluded from the mITT population), the same tables for demographic and baseline characteristics as planned above (from Table 14.1.5.1 to Table 14.1.10) will be performed and numbered adding one level in the numbering 1 for ITT population and 2 for mITT population)

14.2 EFFICACY DATA

Listing 14.3.2.1: Deaths - Safety Population

Listing 14.3.2.2: Serious Adverse Events - Safety Population

14.3.3 Narratives of deaths, other serious and certain other significant adverse events

Not applicable for the study.

14.3.4 Abnormal laboratory value listing

Not applicable for the study.

14.3.5 Laboratory measurements

Not applicable for the study.

14.3.6 Other safety data

Table 14.3.6.1: Vital Signs - Summary Statistics on Raw Data with Changes from Baseline - Safety Population