

Protocol Title: A Multicentre, Interventional, Post-marketing, Randomised, Double-blind, Crossover Study to Evaluate the Clinical Safety and Efficacy of AbobotulinumtoxinA (Dysport®) in Comparison with OnabotulinumtoxinA (Botox®) when Treating Adults with Upper Limb Spasticity

Protocol Number: CLIN-52120-452

Compounds: USAN: abobotulinumtoxinA; IPN: Dysport®
USAN: onabotulinumtoxinA; IPN: Botox®

Brief Title: A Study to Compare the Safety and Efficacy of Dysport® and Botox® in Adults with Upper Limb Spasticity

Study Phase: Post-marketing

Study Name: DIRECTION

Sponsor Name:

Ipsen Pharma
65, Quai Georges Gorse
92100 Boulogne-Billancourt
France

Regulatory Authority Identifier Number(s):

EU CT number: 2023-509196-16-00

Version number: 6.0

*Persons supplied with this information must understand that it is strictly confidential.
Information contained herein cannot be disclosed, submitted for publication or used for any
purpose other than that contemplated herein without the sponsor's prior written
authorisation.*

Sponsor Signatory:PPD


PPD

Date

Ipsen Pharma
65, Quai Georges Gorse
92100 Boulogne Billancourt
France

PPD


Medical Monitor Name and Contact Information:**Date**PPD


Ipsen Pharma
65, Quai Georges Gorse
92100 Boulogne Billancourt
France
Email: PPD
Tel. PPD



Principal Investigator Signature Page

I have read and agree to Protocol CLIN-52120-452 entitled “A Multicentre, Interventional, Post-marketing, Randomised, Double-blind, Crossover Study to Evaluate the Clinical Safety and Efficacy of AbobotulinumtoxinA (Dysport®) in Comparison with OnabotulinumtoxinA (Botox®) when Treating Adults with Upper Limb Spasticity”. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: PRINCIPAL
INVESTIGATOR

SIGNATURE:

DATE:

OFFICE:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

	DOCUMENT HISTORY		
Document	Version	Date	Status
Amendment 5	6.0	13 January 2025	Effective
Amendment 4	5.0	24 May 2024	Superseded
Amendment 3	4.0	12 April 2023	Superseded
Amendment 2	3.0	02 December 2022	Superseded
Amendment 1	2.0	25 March 2022	Superseded
Original Protocol	1.0	27 April 2021	Superseded

Amendment 5 (13 January 2025)

The protocol was amended to reflect the changes as requested by the French Authority (ANSM).

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 5.0, 24 MAY 2024)	IS (Version 6.0, 13 JANUARY 2025)	Rationale
Synopsis (Overall Design, Number of Participants) & Sections 1.4, 4.1, 9.2	Number of Participants: ~~518~~ participants ~~will be~~ screened to give ~~450~~ eligible participants, who will be randomised in a 1:1 ratio to one of two study intervention sequences (~~225~~ participants per sequence).	Number of Participants: 563 participants were screened to give 464 eligible participants, who will be randomised in a 1:1 ratio to one of two study intervention sequences (232 participants per sequence).	By the end of the study, some sites identified a small group of 14 eligible patients (3.1%); the sponsor decided to include them in the study. As requested by ANSM, this amendment is released to reflect the final number of patients randomized.
Synopsis (Overall Study Duration) & Section 1.4	Recruitment period up to approximately ~~48~~ months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: approximately ~~60~~ months.	Recruitment period up to approximately 45 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: approximately 57 months.	The text is updated to reflect updated timelines.
Synopsis (Statistical Methods) & Section 9.2)	[...] Based on statistical hypotheses associated with the primary study objective and the primary safety endpoint, the required number of participants to be randomised is 450 participants.	[...] Based on statistical hypotheses associated with the primary study objective and the primary safety endpoint, the required number of participants to be randomised is 450 participants. However, by the end of the study, some sites identified a small group of 14 eligible participants (3.1%); the sponsor decided to include them in the study so a total of 464 participants were enrolled.	Text is updated to reflect an increased in the number of participants randomised.
Section 1.2		[Figure 1 to be updated]	Schema is updated to reflect an increased in the number of participants randomised.
Section 1.4	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: approximately ~~March 2026~~ , CSR available: approximately ~~December 2026~~	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: approximately October 2025 , CSR available: approximately April 2026	The text is updated to reflect updated timelines.

Other documents impacted.

Informed consent form	Yes	☒	No	☐
Case report form (CRF)	Yes	☐	No	☒
Statistical analysis plan (SAP)	Yes	☒	No	☐

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES	4
TABLE OF CONTENTS.....	7
LIST OF ABBREVIATIONS.....	11
1 PROTOCOL SUMMARY	14
1.1 Synopsis.....	14
1.2 Schema	19
1.3 Schedule of Activities (SoA).....	20
1.4 Brief Summary	23
2 INTRODUCTION	24
2.1 Background	24
2.2 Study Rationale.....	25
2.3 Benefit/Risk Assessment.....	26
2.3.1 Risk Assessment	26
2.3.2 Benefit Assessment.....	32
2.3.3 Overall Benefit/Risk Conclusion.....	32
3 OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS.....	33
4 STUDY DESIGN.....	34
4.1 Overall Design	34
4.2 Scientific Rationale for Study Design.....	35
4.2.1 Participant Input into Design.....	36
4.3 Justification for Dose	36
4.4 End of Study Definition	36
5 STUDY POPULATION	37
5.1 Inclusion Criteria	37
5.2 Exclusion Criteria	38
5.3 Lifestyle Considerations	39
5.4 Screen Failures	39
5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention	39
6 STUDY INTERVENTION AND CONCOMITANT THERAPY	40
6.1 Study Interventions Administered	40
6.2 Preparation/Handling/Storage/Accountability	41
6.3 Measures to Minimise Bias: Randomisation and Blinding.....	43
6.3.1 Randomisation	43
6.3.2 Maintenance of Blinding.....	43
6.4 Study Intervention Compliance.....	44
6.5 Dose Modification	44
6.5.1 Retreatment Criteria	44
6.6 Continued Access to Study Intervention after the End of the Study	45
6.7 Treatment of Overdose.....	45

6.8	Concomitant Therapy.....	46
6.8.1	<i>Rescue Medicine</i>	46
7	DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	47
7.1	Discontinuation of Study Intervention.....	47
7.1.1	<i>Liver Chemistry Stopping Criteria</i>	47
7.1.2	<i>QTc Stopping Criteria.....</i>	47
7.1.3	<i>Temporary Discontinuation.....</i>	47
7.1.4	<i>Rechallenge.....</i>	47
7.2	Participant Discontinuation/Withdrawal from the Study	47
7.3	Lost to Follow-up	48
8	STUDY ASSESSMENTS AND PROCEDURES	49
8.1	Screening/Baseline Assessments	49
8.1.1	<i>Demographic Data</i>	49
8.1.2	<i>Medical and Surgical History.....</i>	49
8.1.3	<i>Disease History.....</i>	50
8.1.4	<i>Prior BoNT-A Therapy.....</i>	50
8.1.5	<i>Prior and Concomitant Medications/Nondrug Therapy</i>	50
8.1.6	<i>Concomitant Surgery.....</i>	50
8.2	Study BoNT-A Injection Details	50
8.3	Efficacy Assessments	50
8.3.1	<i>Duration of Response.....</i>	50
8.3.2	<i>Modified Ashworth Scale.....</i>	51
8.3.3	<i>Disability Assessment Scale</i>	51
8.3.4	<i>Physician's Global Assessment of the Treatment Response</i>	51
8.3.5	<i>Health-related Quality of Life Assessments.....</i>	51
8.3.5.1	<i>12-Item Short-form Health Survey (SF-12)</i>	51
8.3.5.2	<i>SQoL-6D Questionnaire</i>	52
8.4	Safety Assessments.....	52
8.4.1	<i>Physical Examinations</i>	52
8.4.2	<i>Vital Signs</i>	53
8.4.3	<i>Clinical Safety Laboratory Assessments</i>	53
8.4.4	<i>Pregnancy Testing.....</i>	53
8.5	Adverse Events (AEs) and Serious Adverse Events (SAEs), and Other Safety Reporting	54
8.5.1	<i>Time Period and Frequency for Collecting AE and SAE Information</i>	54
8.5.2	<i>Method of Detecting AEs and SAEs.....</i>	54
8.5.3	<i>Follow-up of AEs and SAEs.....</i>	54
8.5.4	<i>Regulatory Reporting Requirements for SAEs.....</i>	55
8.5.5	<i>Pregnancy.....</i>	55

8.5.6	<i>Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs.....</i>	56
8.5.7	<i>Adverse Events of Special Interest</i>	56
8.5.8	<i>Reporting of Study Intervention Errors Including Misuse/Abuse.....</i>	56
8.6	Pharmacokinetics.....	56
8.7	Genetics and/or Pharmacogenomics	56
8.8	Biomarkers	57
8.9	Immunogenicity Assessments	57
8.10	Medical Resource Utilisation and Health Economics.....	57
9	STATISTICAL CONSIDERATIONS	57
9.1	Statistical Hypotheses	57
9.2	Sample Size Determination	57
9.3	Analysis Sets	58
9.4	Statistical Analyses	58
9.4.1	<i>General Considerations</i>	58
9.4.2	<i>Analysis of Primary Endpoint(s)</i>	59
9.4.3	<i>Analysis of Secondary Endpoint(s)</i>	60
9.4.4	<i>Analysis of Exploratory Endpoint(s).....</i>	61
9.4.5	<i>Safety Analyses.....</i>	61
9.4.6	<i>Subgroup Analyses.....</i>	62
9.5	Interim Analyses	62
10	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	62
10.1	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	62
10.1.1	<i>Regulatory and Ethical Considerations</i>	62
10.1.2	<i>Financial Disclosure.....</i>	63
10.1.3	<i>Informed Consent Process.....</i>	63
10.1.4	<i>Data Protection</i>	64
10.1.5	<i>Committees Structure.....</i>	64
10.1.6	<i>Dissemination of Clinical Study Data.....</i>	64
10.1.7	<i>Data Quality Assurance.....</i>	65
10.1.7.1	<i>Study Monitoring</i>	65
10.1.7.2	<i>Information to Study Personnel</i>	66
10.1.7.3	<i>Investigator's Regulatory Obligations.....</i>	66
10.1.8	<i>Source Documents</i>	66
10.1.8.1	<i>Recording of Study Data.....</i>	67
10.1.8.2	<i>Data Management.....</i>	67
10.1.8.3	<i>Record Archiving and Retention.....</i>	68
10.1.9	<i>Study and Site Start and Closure.....</i>	68
10.1.10	<i>Publication Policy.....</i>	69
10.2	Appendix 2: Clinical Laboratory Tests	69

10.3	Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....	71
10.3.1	<i>Definition of AE.....</i>	71
10.3.2	<i>Definition of SAE.....</i>	72
10.3.3	<i>Recording and Follow-Up of AE and/or SAE</i>	73
10.3.4	<i>Reporting of SAEs.....</i>	74
10.4	Appendix 4: Contraceptive and Barrier Guidance	75
10.4.1	<i>Definitions.....</i>	75
10.4.2	<i>Contraception Guidance.....</i>	76
10.5	Appendix 5: Modified Ashworth Scale	77
10.6	Appendix 6: Disability Assessment Scale.....	77
10.7	Appendix 7: 12-Item Short-form Health Survey Instrument SF-12.....	78
10.8	Appendix 8: Spasticity-related Quality of Life Tool - SQoL-6D (Version 4.0)	78
10.9	Appendix 9: Adverse Events of Special Interest by Function Suggestive of Possible Remote Spread Effect of Toxin.....	81
10.10	Appendix 10: Protocol Amendment History	82
10.10.1	<i>Amendment 1 (25 March 2022).....</i>	83
10.10.2	<i>Amendment 2 (02 December 2022)</i>	93
10.10.3	<i>Amendment 3 (12 April 2023)</i>	101
10.10.4	<i>Amendment 4 (24 May 2024).....</i>	103
11	REFERENCES.....	107

LIST OF TABLES

Table 1	Schedule of Activities	21
Table 2	Summary of Risks and Mitigation Strategy.....	26
Table 3	Objectives and Endpoints/Estimands.....	33
Table 4	Study Interventions Administered During the Study	40
Table 5	AboBoNT-A and OnaBoNT-A Dosing by Muscle	41
Table 6	Protocol-required Safety Laboratory Tests	70

LIST OF FIGURES

Figure 1	Study Schema.....	19
-----------------	--------------------------	-----------

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AboBoNT-A	AbobotulinumtoxinA
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMP	Auxiliary Medicinal Product
BoNT-A	Botulinum toxin type A
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CJD	Creutzfeldt-Jakob disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
CRO	Contract research organisation
CSR	Clinical study report
DAS	Disability Assessment Scale
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
eTMF	Electronic Trial Master File
EW	Early Withdrawal
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HCG	Human chorionic gonadotrophin
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
i.m.	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board
IUD	Intrauterine device

ABBREVIATION	Wording Definition
IUS	Intrauterine hormone-releasing system
IVRS	Interactive voice response system
IWRS	Interactive web response system
LLS	Lower limb spasticity
MAS	Modified Ashworth Scale
MCH	Mean Corpuscular Haemoglobin
MCS	Mental component summary
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NCT	Identification number for ClinicalTrials.gov
NIMP	Non investigational medicinal product
OnaBoNT-A	OnabotulinumtoxinA
PASS	Power Analysis and Sample Size
PCS	Physical component summary
PGA	Physician Global Assessment
PIS	Participant information sheet
PPS-Efficacy	Per Protocol Set for Efficacy
PPS-Safety	Per Protocol Set for Safety
PT	Preferred Term
PTMG	Primary target muscle group
PT/OT	Physiotherapy Treatment and/or Occupational Therapy
PTT	Principal target of treatment
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS[®]	Statistical Analysis System [®]
SD	Standard deviation
SF-12	12-Item Short-form Health Survey
SoA	Schedule of activities
SOC	System Organ Class
SQoL-6D	Spasticity-related Quality of Life Tool
SS	Safety Set
SUSAR	Suspected unexpected serious adverse reaction

ABBREVIATION	Wording Definition
TBI	Traumatic brain injury
TEAE	Treatment-emergent adverse event
ULIS	Upper Limb International Spasticity
ULS	Upper limb spasticity
US(A)	United States (of America)
USAN	United States Adopted Name
USPI	United States Prescribing Information
vCJD	Variant Creutzfeldt-Jakob disease
WBC	White blood cell(s)
WOCBP	Woman of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Multicentre, Interventional, Post-marketing, Randomised, Double-blind, Crossover Study to Evaluate the Clinical Safety and Efficacy of AbobotulinumtoxinA (Dysport®) in Comparison with OnabotulinumtoxinA (Botox®) when Treating Adults with Upper Limb Spasticity

Brief Title:

A Study to Compare the Safety and Efficacy of Dysport® and Botox® in Adults with Upper Limb Spasticity

Rationale:

The safety and efficacy of onabotulinumtoxinA (onaBoNT-A) and abobotulinumtoxinA (aboBoNT-A) have been investigated and demonstrated in phase III trials versus placebo. However, although both products achieved alleviation of clinical symptoms of spasticity compared to placebo, their safety/efficacy has never been compared in a blinded prospective study.

In a recently published International Spasticity Patient Survey, 83% of patients reported recurrence of symptoms prior to their next injection and for the majority this occurred earlier than 3 months [[Jacinto et al 2020](#)]. Early recurrence of clinical symptoms can potentially lead to patient dissatisfaction with BoNT treatment and compliance issues.

In aboBoNT-A phase III trials in adult spasticity, a number of patients were retreated after longer than the minimum 12 weeks permitted by the product label [[Gracies et al 2017](#); [Gracies et al 2018](#)]. This is supported by the results from a phase IV observational study of patients treated with aboBoNT-A or onaBoNT-A which showed encouraging results on retreatment intervals [[Turner-Stokes et al 2019](#)].

Additionally, cost-effectiveness of botulinum toxin type A (BoNT-A) treatment may be impacted by duration of response [[Danchenko et al 2019](#)]. The physician's decision on choice of BoNT-A product will likely be based on a number of factors including the patient's medical needs, the safety profile of the BoNT-A product, the treatment outcome in terms of effectiveness/duration of response and possibly also cost-effectiveness considerations.

Both onaBoNT-A and aboBoNT-A are often underdosed in real-world clinical practice [[De Sainte-Marie and Lysandropoulos 2019](#)], possibly due to clinicians' apprehension, but since the units of each BoNT-A are specific to the preparation and cannot be compared or interconverted, a meaningful comparison of products can only be performed clinically. Therefore, the primary endpoint in the current study will be safety.

There is currently a lack of any multicentre, randomised, double-blind study to compare the clinical safety and efficacy of aboBoNT-A and onaBoNT-A in adult spasticity. This comparative cross-over study will aim to demonstrate the non-inferiority of aboBoNT-A versus onaBoNT-A as a primary safety endpoint, and the superiority of aboBoNT-A over onaBoNT-A with respect to duration of response as the key secondary efficacy endpoint, when used at optimal doses of each product. It will provide robust evidence from the clinical setting to allow informed therapeutic decisions for care optimisation, including use of the optimal dose according to the approved product label (prescribing information).

Objectives and Endpoints and/or Estimands:

Objectives	Endpoints and/or Estimands[a]
Primary	
To demonstrate non-inferiority as per safety assessment based on the rate of all TEAEs from injection to 12 weeks	<u>Endpoints:</u> - Rate of TEAEs from injection to 12 weeks[b] <u>Key intercurrent events:</u> - Treatment discontinuation - Prohibited concomitant medication or prohibited concomitant Physiotherapy Treatment and/or Occupational Therapy (PT/OT) interventions on the study limb - No evidence of safety information - Visits delayed or not performed, or AEs due to COVID-19
Secondary	
- To evaluate clinical safety - To assess efficacy	<u>Endpoints:</u> - Rate of ADRs, SAEs and AESIs from injection to 12 weeks - Duration of response based on retreatment criteria - Muscle tone assessed by the MAS for finger, wrist and elbow flexors at 1, 4, 10, 12 ± 16, 20, 24 weeks based on PTMG and MAS total score - Perceived function and pain assessed by the DAS at 1, 4, 10, 12 ± 16, 20, 24 weeks based on PTT and DAS total score - PGA of treatment response at 1, 4, 10, 12 ± 16, 20, 24 weeks - QoL, using the SF-12 perceived health score and SQoL-6D at 4 weeks, 12 weeks and at end of each cycle

AboBoNT-A = abobotulinumtoxinA; AE = adverse event; AESI = adverse event of special interest; ADR = adverse drug reaction; COVID-19 = coronavirus disease 2019 (SARS-CoV-2); DAS = disability assessment scale; MAS = modified Ashworth scale; onaBoNT-A = onabotulinumtoxinA; PGA = physician global assessment; PTMG = primary target muscle group; PTT = principal target of treatment; QoL = quality of life; SAE = serious adverse event; SQoL-6D = Spasticity-related Quality of Life Tool; TEAE = treatment-emergent adverse event.

- a A hierarchical approach will be used for analysis of primary and secondary endpoints. If non-inferiority is demonstrated for the primary endpoint, firstly the superiority of aboBoNT-A over onaBoNT-A will be tested based on the key secondary efficacy endpoint, i.e. duration of response. If superiority of aboBoNT-A over onaBoNT-A is demonstrated, then MAS/DAS/PGA at Week 12 will be tested at the same time. If positive, then the corresponding endpoints at Week 10 will be tested.
- b Including any clinically significant abnormal laboratory test results (see Section 10.3.1).

Overall Design:

This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18-80 years of age inclusive with upper limb spasticity (ULS).

Participants will be recruited from the investigators' clinical practice at approximately 90 study sites in the United States of America (USA), Canada and France (public or private).

A total of approximately 563 participants were screened to give 464 eligible participants, who will be randomised in a 1:1 ratio to one of two study intervention sequences (232 participants per sequence). Assignment to study intervention (randomisation) will be stratified based on the BoNT-A status (BoNT-A previously treated for ULS or naïve).

Before the first study intervention, in addition to confirming study eligibility and performing baseline safety and efficacy assessments, demographic data, medical and surgical history, disease history, prior BoNT-A therapy and prior and concomitant medications (including vaccines) and nondrug therapies will be collected.

The muscles for injection in this study are: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii. In order to maintain the study blinding, a fixed volume of study BoNT-A solution will be injected into each of these muscles.

Randomised participants will receive two cycles of BoNT-A treatment. In each cycle, a volume of 0.5 mL BoNT-A solution will be injected into each of the four wrist/finger flexors (equivalent to 125 U aboBoNT-A or 50 U onaBoNT-A per muscle) and a volume of 1.6 mL BoNT-A solution will be injected into the biceps (equivalent to 400 U aboBoNT-A or 160 U onaBoNT-A), to give a total administration volume of 3.6 mL (equivalent to 900 U aboBoNT-A or 360 U onaBoNT-A).

Sequence 1: participants will receive one cycle of aboBoNT-A (900 Units) followed by one cycle of onaBoNT-A (360 Units) in the selected overactive upper limb muscles using guidance techniques.

Sequence 2: participants will receive one cycle of onaBoNT-A (360 Units) followed by one cycle of aboBoNT-A (900 Units) in the selected overactive upper limb muscles using guidance techniques.

The second BoNT-A injection will be given at Week 12 at the earliest if retreatment criteria are fulfilled. If not, participants will be reassessed every 4 weeks (at Week 16, Week 20 and Week 24) until retreatment criteria are fulfilled, at which point the second injection will be administered. If retreatment criteria are still not fulfilled by Week 24 of Cycle 1, the participant should be withdrawn from the study and "no clinical indication for reinjection" documented as the reason for withdrawal.

Visits for each injection cycle will include the Injection Visit, Week 1, Week 4, Week 10, Week 12 and additional visits at Week 16, Week 20 and Week 24 as required.

Safety will be closely monitored during the study. Type, severity, seriousness, duration, reversibility and outcome of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs), as well as TEAEs leading to withdrawal, will be followed throughout the study. Laboratory safety tests, including full blood counts, international normalised ratio (INR), urea and electrolytes will also be performed at screening and at Week 12 of each cycle.

Efficacy assessments will include modified Ashworth scale (MAS) based on the primary target muscle group (PTMG), disability assessment scale (DAS) based on the principal target of treatment (PTT) and physician global assessment (PGA).

Quality of life assessments will be performed at baseline, at Week 4, at Week 12 and at the end of each cycle (which may be Week 16, Week 20 and Week 24 if these visits are performed).

The End of Treatment (EOT) for each participant will be the date of the Cycle 2 injection. The End of Study (EOS) for each participant will be when the decision is made to retreat or at Week 24 of Cycle 2, whichever occurs first. The participants will be followed up for safety and efficacy, including quality of life (QoL), until their EOS or Early Withdrawal (EW) visit. Participants withdrawing early from the study will not be replaced.

The study will be considered to have started when the first participant has provided signed informed consent and ended when the last participant has completed the last study visit.

All data collected in the study will be recorded in an electronic case report form (eCRF).

An independent Steering Committee will be set up, as described in Section 10.1.5. In addition to involvement in protocol development, the Steering Committee will review the clinical study report (CSR) and oversee any publication of study data.

The maximum duration of the study for each participant is 51 weeks (from screening to Week 24 of Cycle 2).

Condition/Disease:

Upper limb spasticity of any aetiology (US/France) or post-stroke ULS (Canada).

Study Hypothesis:

The study hypotheses are the following:

- Safety profile of both products is comparable: this hypothesis is associated with the primary safety endpoint analysis based on non-inferiority testing regarding the TEAE rate from injection to Week 12. Additional analyses on adverse drug reaction (ADR) rate and detailed analysis of TEAEs and AESIs will also be provided.
- Efficacy profile at peak (Week 4) is similar, but aboBoNT-A has longer duration of effect (Week 10 and beyond): this hypothesis will be associated with secondary efficacy endpoints analyses based on superiority tests.

Statistical hypotheses for the primary analysis have been defined as follows: the anticipated TEAE rate from injection to Week 12 has been set to 44% [[Gracies et al 2015](#)], and it was assumed no difference between the two treatment groups, a non-inferiority margin set to 5% and a nuisance parameter set to 20%. Alpha level was set to 0.1 (one sided), power to 80% and dropout rate to 10%.

Study Duration:

The maximum duration of the study for each participant is 51 weeks (from screening to Week 24 of Cycle 2).

Intervention Duration:

One single administration of BoNT-A on the first day of Cycle 1 and one single administration of BoNT-A on the first day of Cycle 2.

Visit Frequency:

Each cycle: injection visit, Week 1, Week 4, Week 10, Week 12 and if retreatment criteria not fulfilled, Week 16, Week 20 and Week 24 (as required until retreatment). At Week 12 (at the earliest) or Week 16 or Week 20 or Week 24 (at the latest) of Cycle 1, retreatment/entry to Cycle 2 according to retreatment criteria.

Intervention Groups:

Sequence 1: participants will receive one cycle of aboBoNT-A (900 Units) followed by one cycle of onaBoNT-A (360 Units) in the selected overactive upper limb muscles using guidance techniques.

Sequence 2: participants will receive one cycle of onaBoNT-A (360 Units) followed by one cycle of aboBoNT-A (900 Units) in the selected overactive upper limb muscles using guidance techniques.

Overall Study Duration:

Recruitment period up to approximately 45 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: approximately 57 months.

Number of Participants:

Approximately 563 screened to give 464 randomised (232 per study intervention sequence). Assignment to study intervention (randomisation) will be stratified based on the BoNT-A status (BoNT-A previously treated for ULS or naïve).

Statistical Methods:*Sample Size determination*

The sample size was determined with Power Analysis and Sample Size (PASS 15) software using the “Non-Inferiority Tests for the Difference Between Two Correlated Proportions” procedure.

Based on statistical hypotheses associated with the primary study objective and the primary safety endpoint, the required number of participants to be randomised is 450 participants. However, by the end of the study, some sites identified a small group of 14 eligible participants (3.1%); the sponsor decided to include them in the study so a total of 464 participants were enrolled. A blinded sample size reassessment will be performed when at least 100 participants have completed the Week 12 visit of Cycle 2.

Primary Analysis

The primary analysis is evaluation of the safety profile of both products based on TEAEs.

The primary safety endpoint is based on the TEAE incidence rate from injection to Week 12, i.e. TEAEs that occurred during each cycle from injection to 12 weeks after injection.

A generalised linear mixed model approach will be used to estimate the difference in TEAE rate between the two treatment groups while accounting for within-participant correlations arising from the crossover design. The fitted model will include fixed effects for treatment and cycle and a random effect associated with the participant. The treatment by cycle interaction (carryover effect) will be tested: if the associated p-value is more than 0.10 it will be considered as absent or negligible and it will not be included in the final model to provide estimates. The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 80% confidence interval (CI) (or one-sided 90% CI) will be provided: the non-inferiority of aboBoNT-A versus onaBoNT-A in terms of safety profile will be demonstrated if the upper bound of this CI is lower than 5% in the Per Protocol Set for safety analyses.

Secondary Analyses

A hierarchical approach will be used for analysis of primary and secondary endpoints. If non-inferiority is demonstrated for the primary endpoint, firstly the superiority of aboBoNT-A over onaBoNT-A will be tested based on the key secondary efficacy endpoint, i.e. duration of response. If superiority of aboBoNT-A over onaBoNT-A is demonstrated, then

MAS/DAS/PGA at Week 12 will be tested at the same time. If positive, then the corresponding endpoints at Week 10 will be tested.

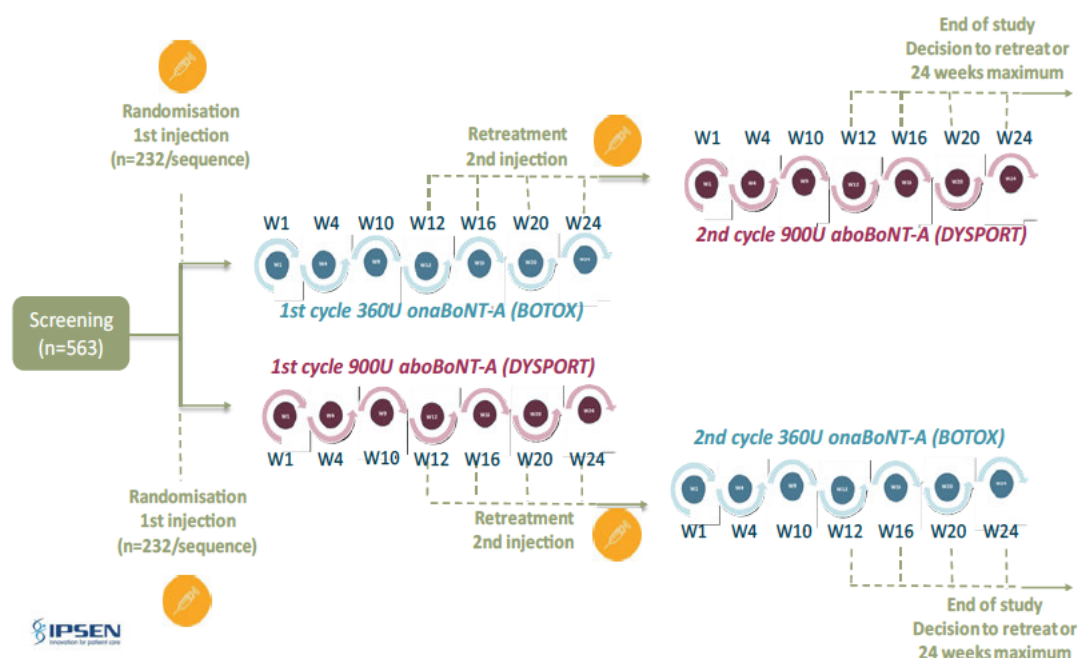
For the secondary safety parameters, the incidence of all reported adverse events (AEs), TEAEs, ADRs, serious adverse events (SAEs), AEs leading to withdrawal and AESIs will be tabulated for the whole cycle duration and from injection to Week 12. Descriptive statistics of other safety endpoints including vital signs will be provided at each timepoint with associated changes or shifts from baseline.

Data Monitoring/Other Committee: Yes; independent Steering Committee.

1.2 Schema

The study schema is provided in Figure 1.

Figure 1 Study Schema



AbBoNT-A = abobotulinumtoxinA; AE = adverse event; D = day; DAS = disability assessment scale; MAS = modified Ashworth scale; labs = laboratory tests; onaBoNT-A = onabotulinumtoxinA; PGA = physician global assessment; QoL = quality of life; SF-12 = 12-Item Short Form Health Survey; SqoL-6D = Spasticity-related Quality of Life Tool; U = units; W = week.

QoL assessments at baseline, Week 4, Week 12 and the end of each cycle include the SF-12 and SqoL-6D questionnaires. Laboratory tests to be conducted at screening and Week 12 of each cycle include full blood count, international normalised ratio, urea and electrolytes.

1.3 Schedule of Activities (SoA)

The schedule of study procedures and assessments is summarised in Table 1.

If the coronavirus disease 2019 (COVID-19) pandemic prevents participants from coming to the site, participants may have their study intervention and/or study visit assessments delayed or even cancelled as judged necessary by the investigator. This must be discussed with the sponsor before being implemented. Of note, as delayed visits deviate from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

In exceptional circumstances, where a scheduled visit cannot be performed (e.g. due to COVID-19), data on AEs and retreatment criteria may be collected by telephone with the prior agreement of the sponsor.

Table 1 Schedule of Activities

Procedure	Screening	Baseline/ Cycle 1 injection D1	Treatment Period														EOS/ EW [a]
			Injection Cycle 1 (12-24 weeks)							Injection Cycle 2 (12-24 weeks)							
			W1	W4	W10	W12	W16 [b]	W20 [b]	W24 [b]	W1	W4	W10	W12 [c]	W16 [b][c]	W20 [b][c]	W24 [b][c]	
Visit number	V1	V2[d]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	
Visit window (days)	D-7 to D-1		±1	±3	±7	+7	±7	±7	±7	±1	±3	±7	+7	±7	±7	±7	
Written informed consent	X																
Eligibility criteria	X	X															
Visit date	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic data	X																
Medical and surgical history	X																
Disease history	X																
Prior BoNT-A therapy	X																
Pregnancy test (WOCBP)	X					X[e]	X[e]	X[e]	X[e]				X[e]	X[e]	X[e]	X[e]	X
Safety laboratory tests	X					X							X				
Physical examination		X				X	X	X	X				X	X	X	X	X
Vital signs		X				X	X	X	X				X	X	X	X	X
Randomisation		X															
Study BoNT-A injection		X[f]				X[g]	X[g]	X[g]	X[g]								
Retreatment criteria					X[h]	X	X	X	X			X[h]	X	X	X	X	X
AE/SAE/SS/AESI collection[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant meds/nondrug therapy[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgery		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MAS [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DAS [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QoL		X		X		X	X[m]	X[m]	X[m]		X		X	X[m]	X[m]	X[m]	X

AE = adverse event; AESI = adverse event of special interest; BoNT-A = botulinum toxin type A; DAS = disability assessment scale; EOS = end of study; EW = early withdrawal; ICF = informed consent form; MAS = modified Ashworth scale; meds = medications; PGA = physician global assessment; PTMG = primary target muscle group; PTT = principal target of treatment; QoL = quality

of life; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SqoL-6D = Spasticity-related Quality of Life Tool; SS = special situation; W = week; WOCBP = women of childbearing potential.

- a For participants who complete the study, the EOS visit will be the visit at which the retreatment criteria (Section 6.5.1) are fulfilled after the Cycle 2 injection, i.e. Week 12 (at the earliest), Week 16, Week 20 or Week 24 (at the latest) of Cycle 2. Note: if the date of the first BoNT-A retreatment after the EOS visit is available, this will be documented.
- B Week 16, Week 20 and Week 24 visits of each cycle only take place if the retreatment criteria (Section 6.5.1) not met at Week 12.
- C From Week 12 of Cycle 2 (at the earliest), decision to retreat/end the study for each participant is made according to the retreatment criteria (Section 6.5.1).
- d In exceptional cases, if all eligibility requirements (including confirmed negative pregnancy test) can be fulfilled and participants have had sufficient time to consider participation in the study and ask questions, V1 and V2 can be combined on the same day (but all screening and baseline assessments must be completed before injection).
- E A negative pregnancy test result must be obtained before each BoNT-A injection. A urine pregnancy test with results available the same day should be confirmed with a serum test if the urine test is positive.
- F Cycle 1 injection must only be performed after all screening and baseline assessments completed.
- G Cycle 2 injection: from Week 12 of Cycle 1, decision to retreat with Cycle 2 is made according to the retreatment criteria (Section 6.5.1). The Cycle 2 injection can therefore be at Week 12 (at the earliest), Week 16, Week 20 or Week 24 (at the latest) of Cycle 1.
- H Retreatment criteria will be assessed from Week 10 in order to assess duration of response, however reinjection cannot take place before Week 12 at the earliest
- i All AEs/SAEs/AESIs will be collected throughout the study from the signing of the ICF until the EOS/EW visit.
- J Prior and concomitant medications (including vaccines) and nondrug therapy will include those for spasticity and spasticity-related pain, as well as those for all other indications.
- K For MAS assessments, the PTMG will be selected by the investigators at screening as the muscle group with the highest MAS score. The PTMG is to remain the same throughout the study.
- L For DAS assessments, the PTT will be defined at screening based on one of the four DAS domains. The PTT is to remain the same throughout the study.
- M QoL is assessed at baseline, Week 4, Week 12 and at the end of each cycle, using SF-12 and SqoL-6D questionnaires.

1.4 Brief Summary

The purpose of this study is to compare the clinical safety and efficacy of aboBoNT-A and onaBoNT-A in adults with upper limb spasticity (ULS). The study is designed to address real-world questions of interest about the two BoNT-A marketed products for the first time in a large, multicentre, randomised, double-blind crossover study.

Study details include:

Study Hypothesis:

The safety profile of both products is comparable. The efficacy profile at peak (Week 4) is similar, but aboBoNT-A has a longer duration of effect.

Number of Participants:

Approximately 563 screened to give 464 randomised (232 per study intervention sequence). Assignment to study intervention (randomisation) will be stratified based on the BoNT-A status (BoNT-A previously treated for ULS or naïve).

Study Treatment:

The muscles for injection in this study are: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii.

Randomised participants will receive two cycles of BoNT-A treatment. In each cycle, a volume of 0.5 mL BoNT-A solution will be injected into each of the four wrist/finger flexors (equivalent to 125 U aboBoNT-A or 50 U onaBoNT-A per muscle) and a volume of 1.6 mL BoNT-A solution will be injected into the biceps (equivalent to 400 U aboBoNT-A or 160 U onaBoNT-A), to give a total administration volume of 3.6 mL (equivalent to 900 U aboBoNT-A or 360 U onaBoNT-A).

Cycle 1: Participants will be randomly allocated to one of the two treatment sequences, i.e. to receive aboBoNT-A (900 Units) first or onaBoNT-A (360 Units) first in the selected overactive upper limb muscles using guidance techniques.

Cycle 2: Participants switched to the other BoNT-A product, aboBoNT-A (900 Units) or onaBoNT-A (360 Units).

Treatment Duration:

One single administration of BoNT-A on the first day of Cycle 1 and one single administration of BoNT-A on the first day of Cycle 2.

End of treatment (EOT):

Date of Cycle 2 injection.

End of study (EOS):

Decision to retreat or Week 24 for the Cycle 2 injection, whichever occurs first.

Overall Study Duration:

Recruitment period up to approximately 45 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: approximately 57 months.

Visit Frequency:

Each cycle: injection visit, Week 1, Week 4, Week 10, Week 12 and if retreatment criteria not fulfilled, Week 16, Week 20 and Week 24 (as required until retreatment). At Week 12 (at the earliest) or Week 16 or Week 20 or Week 24 (at the latest) of Cycle 1, retreatment/entry to Cycle 2 according to retreatment criteria.

Timelines:

Expected first participant injected: June 2021, Last Participant's Last Visit: approximately October 2025, CSR available: approximately April 2026.

2 INTRODUCTION

Spasticity is an increase in velocity-dependent stretch reflexes, with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome [[Bakheit 2007](#); [Gracies 2005](#)].

Sanger defined spasticity as hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle [[Sanger et al 2003](#)].

Spasticity is associated with various neurological disorders (for example, multiple sclerosis, cerebral or spinal cord injuries and cerebrovascular disorders), contributing to functional motor disability/impairment, pain and discomfort [[Simpson 2000](#)]. In the upper limbs, increased muscle tone impairs reach, grasp, manipulation and release, leading to restrictions in everyday life and educational activities. The inability to fully use the affected arm(s) for bimanual activities prohibits the development of independent functioning in daily life.

The most effective pharmacological treatment of spasticity is botulinum neurotoxin (BoNT) injections [[Ward 2002](#)]. Treatment with botulinum neurotoxin type A (BoNT-A) in targeted muscles is recognised as an important treatment intervention and is widely used in clinical practice to treat spasticity and to help alleviate symptoms, improve function and delay or prevent the development of contractures or deformities that require surgery. Its use has been included in clinical guidance for the management of spasticity since 2000 [[Graham et al 2000](#)], although its use has been widespread for much longer, and its integral role in the management of focal spasticity is recognised by guidelines from around the world [[Dashtipour et al 2015](#)].

2.1 Background

Botulinum toxin type A is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall strain. It is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps. The neurotoxin complex is composed of the neurotoxin, hemagglutinin proteins and non-toxin non-hemagglutinin protein.

BoNT-A inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalisation of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 leading to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterised by excessive efferent activity in motor nerves.

The primary pharmacodynamic effect of BoNT is due to chemical denervation of the treated muscle resulting in a measurable decrease of the compound muscle action potential, causing a localised reduction of muscle activity. The weakening of voluntary and involuntary muscle contraction can be used to therapeutic advantage in the treatment of focal dystonias, muscle spasms and muscle spasticity.

Recovery of transmission occurs gradually as the neuromuscular junction recovers from SNAP25 cleavage and as new nerve endings are formed.

Potential medical applications of BoNT-A were recognised in the early 1980s and it was approved by the Food and Drug Administration in 1989 for ophthalmologic and neurologic use in strabismus, blepharospasm and hemifacial spasm.

BoNT-A has since been approved and used in other conditions related to excessive muscle activity, including the treatment of ULS. The use of BoNT-A to treat spasticity is now widely recommended in clinical practice and supported by controlled clinical studies [[Royal College of Physicians 2018](#)].

At least three different BoNT-A preparations are currently commercially available: Dysport® (Ipsen), Botox® (Allergan) and Xeomin® (Merz). The two BoNT-A products to be investigated in the current study are abobotulinumtoxinA (aboBoNT-A; Dysport®) and onabotulinumtoxinA (onaBoNT-A; Botox®). Both BoNT-A marketed products are widely considered as established, well-characterised and effective treatments for ULS.

A more detailed description of the study intervention products, administration procedures, nonclinical studies and clinical studies in all indications are provided in Section 6.1 and the approved local label for each product in the participating countries.

2.2 Study Rationale

The safety and efficacy of onaBoNT-A and aboBoNT-A have been investigated and demonstrated in phase III trials versus placebo. However, although both products achieved alleviation of clinical symptoms of spasticity compared to placebo, their safety/efficacy has never been compared in a blinded prospective study.

In a recently published International Spasticity Patient Survey, 83% of patients reported recurrence of symptoms prior to their next injection and for the majority this occurred earlier than 3 months [[Jacinto et al 2020](#)]. Early recurrence of clinical symptoms can potentially lead to patient dissatisfaction with BoNT treatment and compliance issues.

In aboBoNT-A phase III trials in adult spasticity, a number of patients were retreated after longer than the minimum 12 weeks permitted by the product label [[Gracies et al 2017](#); [Gracies et al 2018](#)]. This is supported by the results from a phase IV observational study of patients treated with aboBoNT-A or onaBoNT-A which showed encouraging results on retreatment intervals [[Turner-Stokes et al 2019](#)].

Additionally, cost-effectiveness of BoNT-A treatment may be impacted by duration of response [[Danchenko et al 2019](#)]. The physician's decision on choice of BoNT-A product will likely be based on a number of factors including the patient's medical needs, the safety profile of the BoNT-A product, the treatment outcome in terms of effectiveness/duration of response and possibly also cost-effectiveness considerations.

Both onaBoNT-A and aboBoNT-A are often underdosed in real-world clinical practice [[De Sainte-Marie and Lysandropoulos 2019](#)], possibly due to clinicians' apprehension, but since the units of each BoNT-A are specific to the preparation and cannot be compared or interconverted, a meaningful comparison of products can only be performed clinically. Therefore, the primary endpoint in the current study will be safety.

There is currently a lack of any multicentre, randomised, double-blind study to compare the clinical safety and efficacy of aboBoNT-A and onaBoNT-A in adult spasticity. This study will aim to demonstrate the non-inferiority of aboBoNT-A versus onaBoNT-A as a primary safety endpoint, and the superiority of aboBoNT-A over onaBoNT-A with respect to duration of response as the key secondary efficacy endpoint, when used at optimal doses of each product. It will provide robust evidence from the clinical setting to allow informed therapeutic decisions for care optimisation, including use of the optimal dose according to the approved product label (prescribing information).

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

The key risks of clinical significance for the study interventions aboBoNT-A and onaBoNT-A are summarised in Table 2 based on the United States Prescribing Information (USPI) of the two products. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of aboBoNT-A and onaBoNT-A may be found in the approved local label for each product, which are the safety reference documents for this study.

Table 2 Summary of Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
BoNT-A Contraindications (Sections 4, 5 and 6 of USPI[a])		
Hypersensitivity to BoNT or to any of the components in the formulations	Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea. If such a reaction occurs, further injection of BoNT-A should be discontinued and appropriate medical therapy immediately instituted.	Participant selection: Participants known to be hypersensitive to any BoNT product or excipients will be excluded from the study (Section 5.2). Participant monitoring: During the study, there will be close monitoring for signs of hypersensitivity and any cases will be recorded as AESIs (Section 8.5.7). Withdrawal criteria: Participants who experience serious hypersensitivity/allergic reactions will be withdrawn from study intervention (Section 7.1).
Hypersensitivity to cow's milk protein	The BoNT-A products may contain trace amounts of cow's milk protein. Participants known to be hypersensitive to cow's milk protein should not be treated with BoNT-A.	Participant selection: Participants known to be hypersensitive to cow's milk protein will be excluded from the study (Section 5.2). Participant monitoring: During the study, there will be close monitoring for signs of hypersensitivity and any cases will be recorded as AESIs (Section 8.5.7). Withdrawal criteria: Participants who experience serious hypersensitivity/allergic reactions will be withdrawn from study intervention (Section 7.1).
Infection at the proposed injection site(s)	As with any intramuscular injection, BoNT-A should only be used where strictly necessary in patients with infection/inflammation at the proposed site(s) of injection.	Participant selection: Participants with infection at the proposed injection site(s) will be excluded from the study (Section 5.2). Participant monitoring: During the study, there will be close

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		monitoring for signs of infection at the injection site(s) and any cases will be recorded as AEs (Section 8.5). Withdrawal criteria: Participants who exhibit signs of infection at the injection site(s) will be withdrawn from study intervention (Section 7.1).
BoNT-A Warnings and Precautions/Serious Adverse Reactions (Sections 5 and 6 of USPI[a])		
Spread of toxin effects	Post marketing safety data from BoNTs suggest that effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of BoNT and may include asthenia, generalised muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat spasticity. <i>Distant (remote) spread of toxin effect is a boxed warning in the USPI[a].</i>	Participant selection: Participants with any underlying conditions that would predispose them to this risk (e.g. pre-existing swallowing or breathing difficulties/compromised respiratory function) will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of these risks in the PIS/ICF and directed to call the investigator or get medical help immediately if they have any respiratory, speech or swallowing difficulties. Participants will also be warned that if loss of strength, muscle weakness, blurred vision, dizziness or drooping eyelids occur, they should avoid driving a car, operating machinery or engaging in other potentially hazardous activities. During the study, there will be close monitoring for signs of spread of toxin and any cases will be recorded as AESIs (Section 8.5.7). Withdrawal criteria: Participants who experience serious remote spread of toxin effects will be withdrawn from study intervention (Section 7.1).
Pre-existing neuromuscular disorders	Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given BoNT. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalised muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory	Participant selection: Participants with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders will be excluded from the study as these disorders may exacerbate clinical effects of treatment (Section 5.2). Participant monitoring: Participants will be informed of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	compromise from typical/therapeutic doses of BoNT-A.	these risks in the PIS/ICF [b] and closely monitored during the study. Withdrawal criteria: Participants who experience moderate-severe swallowing or breathing difficulties will be withdrawn from study intervention (Section 7.1).
Human albumin and transmission of viral diseases	BoNT-A contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.	Participant selection: N/A Participant monitoring: Participants will be closely monitored and AEs will be collected during the study Withdrawal criteria: In the unlikely event of transmission of viral disease or CJD, the participant would be withdrawn from study intervention (Section 7.1).
Bronchitis and URT infections	Bronchitis was reported more frequently as an adverse reaction in adult patients treated for ULS with BoNT (3%), compared to placebo (1%). In adult patients with reduced lung function treated for ULS, URT infections were also reported more frequently as adverse reactions in patients treated with BoNT (8-11%) compared to placebo (6%).	Participant selection: Participants with compromised respiratory function will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of these risks in the PIS/ICF [b] and closely monitored during the study, and any cases will be recorded as AEs (Section 8.5). Withdrawal criteria: N/A
BoNT-A Adverse Reactions/Clinical Trials/Postmarketing Experience (Section 6 of USPI[a])		
Clinical risks/adverse reactions	Injection site reactions (e.g. pain, bruising, haemorrhage, erythema/haematoma, etc.) have occurred following administration of BoNT-A. Adverse reactions in $\geq 2\%$ of patients treated with BoNT-A and more frequent than in placebo-treated patients in double-blind trials of adult patients with ULS were: AboBoNT-A: muscular weakness, fall, depression, influenza, infection, pain in extremity, back pain, headache, convulsion, syncope, hypoaesthesia, partial seizures, fatigue, asthenia, injury, contusion, diarrhoea, constipation, blood triglycerides increased, cough and hypertension. OnaBoNT-A: nausea, fatigue, bronchitis, pain in extremity and muscular weakness. Other adverse reactions for aboBoNT-A and onaBoNT-A are detailed in the USPI.	Participant selection: Participants with any medical condition that may increase, in the opinion of the investigator, the likelihood of AEs related to BoNT-A treatment will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of these risks in the PIS/ICF [b] and closely monitored during the study, and any cases will be recorded as AEs (Section 8.5). Withdrawal criteria: N/A

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	The following adverse reactions have been identified during post-approval use: AboBoNT-A: vertigo, photophobia, influenza-like illness, amyotrophy, muscle atrophy, burning sensation, facial paresis, hypoesthesia, erythema, dry eye and excessive granulation tissue. Hypersensitivity reactions including anaphylaxis have been reported. OnaBoNT-A: abdominal pain, alopecia including madarosis, anorexia, brachial plexopathy, denervation/muscle atrophy, diarrhoea; dry eye, eyelid oedema (following periocular injection), hyperhidrosis, hypoacusis, hypoaesthesia, localised muscle twitching, malaise, mephisto sign, paresthesia, peripheral neuropathy, radiculopathy, erythema multiforme, dermatitis psoriasiform and psoriasiform eruption, strabismus, tinnitus, and visual disturbances. There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with BoNT. There have also been reports of AEs involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the BoNT injection has not been established. New onset or recurrent seizures have also been reported.	
Immunogenicity	As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading. In ULS, from 230 subjects treated with aboBoNT-A and tested for the presence of binding antibodies, 5 subjects were positive at baseline and 17 developed antibodies after treatment. Among those 17 subjects, 10 subjects developed neutralising antibodies. An additional 51 subjects from a separate repeat-dose study were tested for the presence of neutralising antibodies only. None of the subjects tested positive. In total, from the 281 subjects treated in the long-term studies and tested for the presence of	Participant selection: Participants with prior history of non-responsiveness to BoNT-A treatment will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of the risk of immunogenicity in the PIS/ICF [b]. Withdrawal criteria: N/A

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	neutralising antibodies, 3.6% developed neutralising antibodies after treatment. Two patients among the 380 adult ULS patients (0.5%) treated with onaBoNT-A with analysed specimens developed the presence of neutralising antibodies. Formation of neutralising antibodies to BoNT-A may reduce the effectiveness of treatment by inactivating the biological activity of the toxin. In the presence of binding and neutralising antibodies to aboBoNT-A some patients continued to experience clinical benefit.	
BoNT-A Drug Interactions (Section 7 of USPI[a])		
Aminoglycosides and other agents interfering with neuromuscular transmission	Co-administration of BoNT-A and aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents), or muscle relaxants, should be performed with caution and observed closely because the effect of BoNT-A may be potentiated. Excessive weakness may be exaggerated by administration of a muscle relaxant before or after administration of BoNT-A.	Participant selection: Participants receiving aminoglycosides and other agents interfering with neuromuscular transmission will be excluded from the study (Section 5.2). Participants receiving oral antispasticity medication will be required to have a stable treatment with these agents for at least three months prior to study entry, and this treatment must be likely to remain stable throughout the study. Participant monitoring: Participants will be informed of these risks in the PIS/ICF and closely monitored during the study, and any AEs will be recorded (Section 8.5). Aminoglycosides and other agents interfering with neuromuscular transmission are prohibited medications (Section 6.8) Withdrawal criteria: N/A
Anticholinergic drugs	The use of anticholinergic drugs after administration of BoNT-A may potentiate systemic anticholinergic effects such as blurred vision.	Participant selection: Participants receiving anticholinergic medication will be required to have a stable treatment with these agents for at least three months prior to study entry, and this treatment must be likely to remain stable throughout the study. Participant monitoring: Participants will be informed of these risks in the PIS/ICF and closely monitored during the study, and any AEs will be recorded (Section 8.5).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withdrawal criteria: N/A.
Other BoNT products	The effect of administering different BoNT products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another BoNT prior to the resolution of the effects of a previously administered BoNT.	Participant selection: Participants treated with BoNT of any type for any indication (e.g. bladder injection) within the previous 12 weeks or planned/likely to be treated during the course of the study will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of the risks of excessive neuromuscular weakness in the PIS/ICF and closely monitored during the study, and any AEs will be recorded (Section 8.5). Withdrawal criteria: N/A
BoNT-A in Specific Populations (Section 8 of USPI[a])		
Pregnancy	Based on animal data, BoNT-A may cause foetal harm. There are no adequate data on the developmental risk associated with use of BoNT-A in pregnant women.	Participant selection: Participants with a current pregnancy or a positive pregnancy test at screening will be excluded from the study (Section 5.2). Participant monitoring: Participants will be informed of the risk to the foetus of BoNT treatment during pregnancy in the PIS/ICF. Additional pregnancy tests will be performed during the study and any pregnancies will be reported (Section 8.5.5). Withdrawal criteria: Participants who become pregnant during the study will be withdrawn from study intervention (Section 7.1)
Lactation	There are no data on the presence of BoNT-A in human or animal milk, the effects on the breastfed infant, or the effects on milk production.	Participant selection: Lactating women will be excluded from the study (Section 5.2). Participant monitoring: N/A. Withdrawal criteria: N/A.
Females and males of reproductive potential – impairment of fertility	In rats, BoNT-A produced adverse effects on mating behaviour and fertility.	Participant selection: Male and female participants must be using contraceptives consistent with local regulations regarding the methods of contraception for those participating in clinical studies (Section 5.1). Participant monitoring: Participants will be informed of the risk of possible effects of BoNT-A treatment on fertility in the PIS/ICF.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Withdrawal criteria: N/A.
Other drug therapy in elderly patients	BoNT-A must be administered with care in elderly patients, reflecting the greater frequency of concomitant disease and other drug therapy.	Participant selection: The upper age limit for participants is 80 years of age (Section 5.1). Participant monitoring: N/A. Withdrawal criteria: N/A.
BoNT-A Overdosage (Section 10 of USPI[a])		
Overdosage	Excessive doses of BoNT may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis	Participant selection: N/A Participant monitoring: There will be close monitoring for signs of overdose and detailed instructions given for action to be taken (Section 6.7). Withdrawal criteria: In case of overdose, participants will be withdrawn from study intervention (Section 7.1).

AboBoNT-A = abobotulinumtoxinA; AE = adverse event; AESI = adverse event of special interest; CJD = Creutzfeldt-Jakob disease; BoNT = botulinum toxin; BoNT-A = botulinum toxin type A; FVC = forced vital capacity; ICF = informed consent form; i.m. = intramuscular; MRHD = maximum recommended human dose; N/A = not applicable; PIS = participant information sheet; ULS = upper limb spasticity; URT = upper respiratory tract; USPI = United States Prescribing Information; UTI = urinary tract infection; vCJD = variant Creutzfeldt-Jakob disease.

a [Dysport® USPI](#) and [Botox® USPI](#).

b Participants will be informed of the more common and most serious ADRs in the PIS/ICF.

2.3.2 Benefit Assessment

The two BoNT-A preparations being investigated in this study are both indicated for the treatment of ULS in adults and are widely acknowledged as effective for patients with this condition.

It is expected that the two BoNT-A marketed products will have similar safety profiles. However, it is possible that differences in the safety and/or clinical effectiveness and duration of response could lead to differences in the benefit/risk profiles of the two products.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimise risk to participants, the potential risks identified in association with aboBoNT-A and onaBoNT-A are justified by the anticipated benefits that may be afforded to participants with ULS.

3 OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

Table 3 displays the objectives, corresponding endpoints and key intercurrent events for this study. Other attributes of an estimand are described in other sections: the study population in Section 5, study interventions in Section 6, prohibited medications in Section 6.8, analysis sets are defined in Section 9.3 and estimands are described in further detail in Section 9.4 including handling of key intercurrent events.

Table 3 Objectives and Endpoints/Estimands

Objectives	Endpoints and/or Estimands[a]
Primary	
To demonstrate non-inferiority as per safety assessment based on the rate of all TEAEs from injection to 12 weeks	<u>Endpoints:</u> - Rate of TEAEs from injection to 12 weeks[b] <u>Key intercurrent events:</u> - Treatment discontinuation - Prohibited concomitant medication or prohibited concomitant PT/OT interventions on the study limb - No evidence of safety information - Visits delayed or not performed, or AEs due to COVID-19
Secondary	
- To evaluate clinical safety - To assess efficacy	<u>Endpoints:</u> - Rate of ADRs, SAEs and AESIs from injection to 12 weeks - Duration of response based on retreatment criteria - Muscle tone assessed by the MAS for finger, wrist and elbow flexors at 1, 4, 10, 12 ± 16, 20, 24 weeks based on PTMG and MAS total score - Perceived function and pain assessed by the DAS at 1, 4, 10, 12 ± 16, 20, 24 weeks based on PTT and DAS total score - PGA of treatment response at 1, 4, 10, 12 ± 16, 20, 24 weeks - QoL, using the SF-12 perceived health score and SQoL-6D at 4 weeks, 12 weeks and at end of each cycle

AboBoNT-A = abobotulinumtoxinA; AE = adverse event; AESI = adverse event of special interest; ADR = adverse drug reaction; COVID-19 = coronavirus disease 2019 (SARS-CoV-2); DAS = disability assessment scale; MAS = modified Ashworth scale; onaBoNT-A = onabotulinumtoxinA; PGA = physician global assessment; PTMG = primary target muscle group; PTT = principal target of treatment; QoL = quality of life; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SQoL-6D = Spasticity-related Quality of Life Tool; TEAE = treatment-emergent adverse event.

a A hierarchical approach will be used for analysis of primary and secondary endpoints. If non-inferiority is demonstrated for the primary endpoint, firstly the superiority of aboBoNT-A over onaBoNT-A will be tested based on the key secondary efficacy endpoint, i.e. duration of response. If superiority of aboBoNT-A over onaBoNT-A is demonstrated, then MAS/DAS/PGA at Week 12 will be tested at the same time. If positive, then the corresponding endpoints at Week 10 will be tested (see Section 9.4.3).

b Including any clinically significant abnormal laboratory test results (see Section 10.3.1).

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18-80 years of age inclusive with ULS.

Participants will be recruited from the investigators' clinical practice at approximately 90 study sites in the United States of America (USA), Canada and France (public or private).

A total of approximately 563 participants were screened to give 464 eligible participants, who will be randomised in a 1:1 ratio to one of two study intervention sequences (232 participants per sequence). Assignment to study intervention (randomisation) will be stratified based on the BoNT-A status (BoNT-A previously treated for ULS or naïve).

Before the first study intervention, in addition to confirming study eligibility and performing baseline safety and efficacy assessments, demographic data, medical and surgical history, disease history, prior BoNT-A therapy and prior and concomitant medications (including vaccines) and nondrug therapies will be collected.

The muscles for injection in this study are: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii. In order to maintain the study blinding, a fixed volume of study BoNT-A solution will be injected into each of these muscles.

Randomised participants will receive two cycles of BoNT-A treatment. In each cycle, a volume of 0.5 mL BoNT-A solution will be injected into each of the four wrist/finger flexors (equivalent to 125 U aboBoNT-A or 50 U onaBoNT-A per muscle) and a volume of 1.6 mL BoNT-A solution will be injected into the biceps (equivalent to 400 U aboBoNT-A or 160 U onaBoNT-A), to give a total administration volume of 3.6 mL (equivalent to 900 U aboBoNT-A or 360 U onaBoNT-A).

Sequence 1: participants will receive one cycle of aboBoNT-A (900 Units) followed by one cycle of onaBoNT-A (360 Units) in the selected overactive upper limb muscles using guidance techniques.

Sequence 2: participants will receive one cycle of onaBoNT-A (360 Units) followed by one cycle of aboBoNT-A (900 Units) in the selected overactive upper limb muscles using guidance techniques.

The second BoNT-A injection will be given at Week 12 at the earliest if retreatment criteria are fulfilled. If not, participants will be reassessed every 4 weeks (at Week 16, Week 20 and Week 24) until retreatment criteria are fulfilled, at which point the second injection will be administered. If retreatment criteria are still not fulfilled by Week 24 of Cycle 1, the participant should be withdrawn from the study and "no clinical indication for reinjection" documented as the reason for withdrawal.

Visits for each injection cycle will include the Injection Visit, Week 1, Week 4, Week 10, Week 12 and additional visits at Week 16, Week 20 and Week 24 as required.

Safety will be closely monitored during the study. Type, severity, seriousness, duration, reversibility and outcome of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs), as well as TEAEs leading to withdrawal, will be followed throughout the study. Laboratory safety tests, including full blood counts, international normalised ratio (INR), urea and electrolytes will also be performed at screening and at Week 12 of each cycle.

Efficacy assessments will include modified Ashworth scale (MAS) based on the primary target muscle group (PTMG), disability assessment scale (DAS) based on the principal target of treatment (PTT) and physician global assessment (PGA).

Quality of life assessments will be performed at baseline, at Week 4, at Week 12 and at the end of each cycle (which may be Week 16, Week 20 and Week 24 if these visits are performed).

The End of Treatment (EOT) for each participant will be the date of the Cycle 2 injection. The End of Study (EOS) for each participant will be when the decision is made to retreat or at Week 24 of Cycle 2, whichever occurs first. The participants will be followed up for safety and efficacy, including quality of life (QoL), until their EOS or Early Withdrawal (EW) visit. Participants withdrawing early from the study will not be replaced.

The study will be considered to have started when the first participant has provided signed informed consent and ended when the last participant has completed the last study visit.

All data collected in the study will be recorded in an electronic case report form (eCRF).

An independent Steering Committee will be set up, as described in Section 10.1.5. In addition to involvement in protocol development, the Steering Committee will review the CSR and oversee any publication of study data.

The maximum duration of the study for each participant is 51 weeks (from screening to Week 24 of Cycle 2).

The study design is illustrated in Figure 1.

4.2 Scientific Rationale for Study Design

The current study will be the first randomised blinded study in which safety profiles, time to retreatment and other efficacy endpoints (MAS, DAS, PGA and QoL measures) will be compared directly for the two BoNT-A marketed products, using the same muscles and same dilution of BoNT-A to achieve a blinded comparison.

Standard safety assessments are included in the study and AESIs have been defined based on known risks from the approved USPI (prescribing information) of the two BoNT-A marketed products.

Available evidence suggests that many patients on BoNT-A treatment experience recurrence of symptoms at around 9-10 weeks but cannot be retreated until 12 weeks according to the USPI. This may affect adherence to treatment with toxins. The Upper Limb International Spasticity (ULIS) III study, an international, multicentre, observational, prospective, longitudinal cohort study to assess the impact of integrated ULS management including the use of BoNT-A injections on patient-centred goal attainment in real life practice (Ipsen Study ^{CCI} ClinicalTrials.gov code ^{CCI}), showed longer retreatment intervals for aboBoNT-A than onaBoNT-A but this has never been investigated in a blinded comparison.

It is expected that the two BoNT-A marketed products will have similar safety profiles. However, it is possible that differences in the safety and/or clinical effectiveness and duration of response could lead to differences in the benefit/risk profiles of the two products.

In addition to study visits every 4 weeks after each BoNT-A injection, a visit at Week 1 is scheduled, as clinical improvement may be expected as early as one week after administration of BoNT-A and it will be important to capture this information. A visit at Week 10 after administration of BoNT-A is also scheduled to capture information on the earliest recurrence of symptoms. Visits at Week 12 and beyond are designed to further define the duration of effect of the two BoNT-As, and will serve to determine when the next injection is appropriate for each participant.

The efficacy assessments scheduled in the study are widely used in ULS.

The Spasticity-related Quality of Life Tool (SQoL-6D) is a health utility measure that specifically assesses aspects of QoL that are likely to be affected by spasticity. It was developed to fulfil the need for a health-related quality of life measure that would be sensitive to the disease burden and changes following focal treatment for ULS and that could in future be used in economic evaluation of treatments for ULS. Although the SQoL-6D has not been fully validated, it addresses areas that have been poorly documented in previous studies and for which the currently available tools are deficient. This tool will be applied alongside the 12-Item Short Form Health Survey (SF-12), a well-researched, frequently used self-reported measure of health, responsive to changes.

The participant population and BoNT-A doses will be consistent with the approved local label in the participating countries to ensure that the results are applicable to the wider population of patients receiving marketed product Dysport® and/or Botox®.

4.2.1 Participant Input into Design

None.

4.3 Justification for Dose

The doses of BoNT-A chosen for this study (900 Units for aboBoNT-A and 360 Units for onaBoNT-A) are consistent with the approved recommended doses for the indication adult ULS in the USPI/local labels for Dysport® and Botox® respectively in the participating countries, taking into account the common muscles to be injected according to the USPIs/local labels of both products and the maximum dose recommended for each muscle, and total dose recommended for treatment of ULS.

It should be noted that the potency units of BoNTs are specific to the preparation and assay method utilised for the particular BoNT-A marketed product and are not interchangeable. Units of biological activity for aboBoNT-A and onaBoNT-A cannot be compared or interconverted.

4.4 End of Study Definition

The End of the Study (EOS) is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial in any country.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

Criteria for study intervention discontinuation and participant discontinuation/withdrawal from the study are described in Section 7.1 and Section 7.2, respectively. Loss to follow-up is described in Section 7.3.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent;

Type of Participant and Disease Characteristics

2. 2a. [US/France] Participants with stable ULS for at least 3 months, in whom treatment of only one upper limb is necessary for the duration of the study;
2b. [Canada] Participants with stable post-stroke ULS for at least 3 months, in whom treatment of only one upper limb is necessary for the duration of the study;
3. Participants who are either naïve to BoNT-A for ULS or who have been previously treated with BoNT-A for ULS;
4. Participants with MAS score of at least 2 in two muscle groups (one of these two muscle groups should be the PTMG) and at least 1 in the remaining muscle group;
5. Participants with DAS score of at least 2 on the PTT (one of four functional domains: dressing, hygiene, limb position and pain);
6. Participants who require BoNT-A injection in all of the following muscles: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii;
7. Participants for whom injection of a total dose of 900 Units aboBoNT-A or 360 Units onaBoNT-A is considered by the investigator to be clinically appropriate;
8. Participants who have been stable for at least 3 months prior to study entry in terms of oral antispasticity, anticoagulant and/or anticholinergic medication, if treated, and are considered by the investigator likely to remain stable for the duration of the study;

Sex

9. Male and female participants

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

Male participants must agree that, if their partner is at risk of becoming pregnant, they will use an effective method of contraception. The participants must agree to use the contraception during the whole period of the study.

b. Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential, defined as postmenopausal for at least 1 year; surgical sterilisation at least 3 months before entering the study; or hysterectomy.
or
- Is a woman of childbearing potential (WOCBP) and using an acceptable contraceptive method as described in Section 10.4.2, Appendix 4: Contraceptive

and Barrier Guidance during the entire study period. The investigator should evaluate the potential for contraceptive method failure (e.g. noncompliance, recently initiated) in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive pregnancy test at screening (urine or serum) as required by local regulations.

- If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Randomisation in the study and injection with BoNT-A must not take place until a negative pregnancy test result is obtained. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.5.5.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Major limitations in the passive range of motion in the paretic upper limb;
2. Major neurological impairment (other than limb paresis) that could negatively affect functional performance;
3. Participants clinically requiring injection into any upper limb muscles other than the five muscles of one arm listed in Section 5.1, or requiring injection into both arms or any lower limb within the timeframe of the study;
4. Hypersensitivity to any BoNT product or excipients;
5. Hypersensitivity to cow's milk protein (casein);
6. Infection at the proposed injection site(s);
7. Known peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome);
8. Any medical condition (including dysphagia or breathing difficulties/compromised respiratory function) that, in the opinion of the investigator, might jeopardize the participant's safety;
9. Abnormal screening/baseline findings or any other medical condition(s) that, in the opinion of the investigator, might jeopardize the participant's safety;
10. Women who are pregnant or lactating (see Section 5.1);
11. In the clinical judgement of the investigator, BoNT treatment is inappropriate;
20. BoNT naïve participants with a history of facial neurogenic disorder (facial paralysis, polyradiculoneuropathy) (only for France);

Prior/concomitant therapy

12. Participants treated with BoNT of any type for any indication (e.g. bladder injection, headache or cosmetic) within the previous 12 weeks or planned/likely to be treated during the course of the study;
13. Prior history of non-responsiveness to BoNT treatment;
14. Previous surgery or administration of alcohol or phenol in the study limb within the 6 months prior to study enrolment or planned/likely to be treated in the study limb during the course of the study;
15. Participants treated with intrathecal baclofen (except if treatment has reached a stable dose for >4 weeks and is likely to remain stable throughout the study), aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents) within the 4 weeks prior to study enrolment or planned/likely to be treated during the course of the study;
21. Participants receiving concomitant treatment with the following PT/OT interventions on the study limb: new splinting/orthotics/casting, serial casting, shockwave therapy, dry needling and needle tenotomies. *However, PT/OT interventions not intended to reduce study limb spasticity (e.g. functional training exercises) or with a transient (<1 day) reduction of study limb spasticity (e.g. stretching, weight bearing) are allowed.*

Other exclusions

17. Participants previously randomised for this study;
18. Participants unwilling or unable to understand the nature, scope and possible consequences of the study and to comply with study procedures and requirements;
19. Participants currently enrolled in any other clinical study or have participated in one within the 12 weeks (or 5 half-lives of the investigational product of that study, whichever is longer) prior to enrolment/inclusion visit, or are scheduled to receive a new investigational drug while the study is ongoing.

5.3 Lifestyle Considerations

No lifestyle restrictions are required in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent, demography, reason for screen failure, eligibility criteria and any AE/serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number and will have to sign a new ICF if the rescreening occurs more than 7 days after the initial screening. The informed consent process is described in Section 10.1.3. All screening assessments need to be repeated for the rescreened participant.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention

In case of suspected or confirmed COVID-19 infection, enrolment, randomisation or administration of study intervention will be temporarily delayed depending on the participant's

clinical presentation. If a participant tests positive for COVID-19, it is recommended that they be retested before study procedures performed on site are resumed. In addition to a negative COVID-19 test result, a stable clinical presentation with COVID-19 symptoms resolved (excluding ageusia and anosmia) must be demonstrated, in the opinion of the investigator, before allowing the participant to continue in the study.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

Table 4 Study Interventions Administered During the Study

Sequence Name	Sequence 1: Cycle 1 aboBoNT-A (900 Units) followed by Cycle 2 onaBoNT-A (360 Units) in the selected overactive upper limb muscles Sequence 2: Cycle 1 onaBoNT-A (360 Units) followed by Cycle 2 aboBoNT-A (900 Units) in the selected overactive upper limb muscles Both sequences receive both study interventions.	
Intervention name	AboBoNT-A Dysport®	OnaBoNT-A Botox®
Type	Biologic	Biologic
Description	AbobotulinumtoxinA for injection: 500 Unit vial	OnabotulinumtoxinA for injection: 200 Unit vial
Dose formulation	Lyophilised powder in a sterile single-dose vial for reconstitution with preservative-free 0.9% Sodium Chloride Injection, USP	Vacuum-dried powder in a sterile single-dose vial for reconstitution with preservative-free 0.9% Sodium Chloride Injection, USP
Unit dose strength(s)/ dilution	500 Units Dilution with 2 mL diluent (0.9% Sodium Chloride) to give 25 Units per 0.1 mL	200 Units Dilution with 2 mL diluent (0.9% Sodium Chloride) to give 10 Units per 0.1 mL
Dosage Level(s)	900 Units (3.6 mL)	360 Units (3.6 mL)
Regimen/treatment Period	Single administration of study intervention in each cycle	Single administration of study intervention in each cycle
Route of administration	i.m. injection	i.m. injection
Use	Active study intervention	Active study intervention
IMP and AMP/NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study intervention will be provided in a vial (as marketed product). Each vial will be labelled as required per country requirement	Study intervention will be provided in a vial (as marketed product). Each vial will be labelled as required per country requirement
Storage requirements	Unopened vials must be stored at 2° to 8°C and protected from light. Once reconstituted, to be stored at 2° to 8°C protected from light and used within 24 hours. Use immediately after reconstitution in the syringe. Do not freeze after reconstitution.	Unopened vials must be stored at 2° to 8°C and protected from light. Once reconstituted, to be stored at 2° to 8°C protected from light and used within 24 hours. Use immediately after reconstitution in the syringe. Do not freeze after reconstitution.

AboBoNT-A = abobotulinumtoxinA; AMP = auxiliary medicinal product; i.m. = intramuscular; IMP = investigational medicinal product; NIMP = non investigational medicinal product; OnaBoNT-A = onabotulinumtoxinA; U = unit(s).

Study participants will be treated in accordance with the approved local labels of aboBoNT-A and onaBoNT-A, which contain further details of the products, as well as the requirements of the protocol.

Physicians administering aboBoNT-A and onaBoNT-A must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

The muscles for injection in this study are: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii.

In each treatment cycle, study intervention will be injected locally into the five specified upper limb muscles. The injector will be blinded to BoNT-A type **and should be the same person for both cycles**. The injection volume for each muscle and the number of injection sites are shown in Table 5. For the biceps, the total 1.6 mL injection volume can be split between the two biceps brachii injection sites according to the investigator's clinical judgement but no more than 1 mL should be injected into a single site. Dosing syringes will be labelled "wrist/finger flexors" (2.0 mL total volume) or "biceps" (1.6 mL total volume).

The full blinded injection volume of 3.6 mL must be administered as specified in order to achieve a total dose of 900 Units of aboBoNT-A or 360 Units of onaBoNT-A.

Table 5 AboBoNT-A and OnaBoNT-A Dosing by Muscle

Syringe Label	Muscle Injected	Volume/ Muscle (mL)	Injection Sites	AboBoNT-A Dose (U) Total 900 U	OnaBoNT-A Dose (U) Total 360 U
Wrist/finger flexors	Flexor carpi radialis	0.5	1	125	50
	Flexor carpi ulnaris	0.5	1	125	50
	Flexor digitorum profundus	0.5	1	125	50
	Flexor digitorum superficialis	0.5	1	125	50
Biceps	Biceps brachii	1.6[a]	2	400	160

AboBoNT-A = abobotulinumtoxinA; OnaBoNT-A = onabotulinumtoxinA; U = unit(s).

a No more than 1 mL to be administered at any injection site.

The use of injection guidance techniques to target the injection sites is mandatory in this study. Guidance techniques should be electromyography (EMG), electrostimulation (ES), or ultrasound (US) or combination at each treatment cycle. The same guidance technique must be used in both cycles.

Because of the possibility of site injection stiffness and pain, any intramuscular vaccination to the shoulder (e.g. COVID-19) should be administered in the arm contralateral to the study medication.

6.2 Preparation/Handling/Storage/Accountability

Study interventions must be reconstituted and dispensed by suitably qualified staff members, following the instructions in the USPI/approved local label. The pharmacist or qualified preparer performing reconstitution and dispensing of the study intervention syringes will be unblinded to the study interventions.

Two vials of study intervention per participant will be required for each injection cycle. Each vial of study intervention will be reconstituted with 2 mL diluent (sterile, preservative-free 0.9% Sodium Chloride Injection USP). Using an appropriately sized sterile syringe, needle and aseptic technique, the diluent of should be drawn up.

The needle should be inserted into the BoNT-A vial. The partial vacuum will begin to pull the saline into the vial. The specified volume of saline should be introduced into the vial. The vial should not be used if a vacuum is absent. The vial contents should be gently swirled to dissolve. Parenteral drug products should be inspected visually for particulate matter and discoloration

prior to administration. Reconstituted BoNT-A should be a clear, colourless solution, free of particulate matter; otherwise it should not be injected.

Any air bubbles in the syringe barrel should be expelled. The needle used to reconstitute the product should be removed and an appropriately sized new sterile needle attached.

For both study interventions, a fixed volume of 3.6 mL is required per cycle. A volume of 1.8 mL will be taken from vial 1 and a volume of 0.2 mL from vial 2 to give a total volume of 2.0 mL for administration to the flexors. A volume of 1.6 mL will be taken from vial 2 for administration to the biceps.

The two syringes dispensed to the investigator/study team will be blinded but will be labelled “Dysport or Botox” and the labelling “wrist/finger flexors” or “biceps” will be added manually by the pharmacist or qualified preparer. Treatment number, participant number and date/hour of reconstitution will also be added manually to the syringe labels by the pharmacist or qualified preparer.

The vial and needle should be discarded in accordance with local regulations.

Further guidance and information for the receipt, preparation, management and disposal/return of the study interventions are provided in the “Investigational Medicinal Product Handling Manual”.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants screened in the study and who meet the eligibility criteria may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- The sponsor will provide guidance on the destruction of unused study intervention. If destruction is authorised to take place at the investigational site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented. For on-site destruction, a certificate of destruction must be provided to the sponsor.

At each dispensation, two treatment numbers (one per vial of BoNT-A) will be assigned by an Interactive Web Response System (IWRS). The IWRS will also manage all logistical aspects of the study treatment (e.g. replacement, drug supplies and expiry dates) and the recording of drug accountability/destruction. This service provides the investigator, investigational site coordinators and project team members with a service that is available 24 hours a day, 7 days a week. Additional details may be found in the IWRS reference manual provided to each investigational site. In case of technical or dispensation queries, a 24-hour helpline is available. If a participant discontinues the study before any intake of study treatment, his/her assigned treatment number(s) will not be reused.

In addition to the information provided in the IWRS, drug accountability paper records will be maintained by the investigator.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Randomisation

The sponsor's randomisation manager who is a statistician independent from the study will prepare:

- A list of randomisation numbers (List A). It will be produced in blocks, on a balanced 1:1 ratio study intervention sequence 1 (Cycle 1: Dysport[®]/Cycle 2: Botox[®]): study intervention sequence 2 (Cycle 1: Botox[®]/Cycle 2: Dysport[®]) and will be stratified according to BoNT-A status (BoNT-A previously treated for ULS or naïve).
- A list of intervention numbers/intervention which will be dispatched to the sites (List B). It will be produced in blocks, on a balanced 1:1 ratio Botox[®]: Dysport[®].

The randomisation and the intervention number(s) assignment at dispensation, will be managed by IWRS. After eligibility is confirmed, at baseline, participants will be assigned a randomisation number and to the associated treatment sequence, in sequential order within each centre (and within each level of strata).

An intervention number will be also allocated by IWRS each time intervention is dispensed (at the beginning of Cycles 1 and 2) according to the allocated intervention sequence. The IWRS will also manage all the logistical aspects of intervention (e.g. supplies, replacement of lost, damaged, quarantined, expiring and expired kits).

This service provides investigators, site coordinators and project team members with a 24-hour per day, 7-day per week service (additional details may be found in the IWRS reference manual provided to each site). In case of medical or technical randomisation or dispensation queries, a 24-hour helpline is available – see supporting information in the investigator site file. Recruitment will stop once approximately 450 evaluable participants have been randomised.

Randomised participants who terminate their study participation for any reason before administration of the first dose of randomised intervention will retain their randomisation and intervention numbers (i.e. these numbers will not be reused). The next participant will be assigned another randomisation number and another intervention number, even if he/she should receive the same treatment. Randomised participants who discontinue the study early will not be replaced.

The sponsor's randomisation manager will keep the master lists. A copy of the list of intervention numbers (List B) will be confidentially supplied to the Global Clinical Supply Chain (Ipsen PharmSciences, rue d'Ethé Virton, 28100 Dreux, France), and Service Provider in charge of IWRS. Similarly, a copy of the list of randomisation numbers (List A) will be also confidentially supplied to the Service Provider in charge of IWRS. The master lists and the copies supplied to the Global Clinical Supply Chain and/or Service Provider in charge of IWRS will be kept confidential in a secure location. Access to the randomisation lists must be restricted until authorisation is given to release them for final analysis.

6.3.2 Maintenance of Blinding

Both the boxes of study intervention (aboBoNT-A and onaBoNT-A) and their contents will be different in appearance. Consequently, to maintain the blinding between aboBoNT-A and onaBoNT-A, an unblinded pharmacist/qualified preparer, independent of the investigator/injector/assessor and blinded study site team, appointed by the investigator, will receive, reconstitute and dispense the study intervention. This person will be fully trained in the method of preparing the study intervention and the importance of their role in maintaining the blind for the participant, the investigator and the rest of the study team.

Reconstitution will occur in indistinguishable syringes following a specific reconstitution process and according to the dose and volume to be considered.

Once reconstituted and prepared in identical ready-to-administer syringes with identical volumes of diluent, the study interventions will be similar in colour and appearance allowing the blinded conditions of the study to be maintained for the study intervention administration by the investigator.

Participants and investigators administering the study intervention injections and performing assessments will remain blinded to intervention assignment during the study. The study intervention injector may also be the assessor and perform safety and efficacy assessments for the participant he/she has injected.

Each participant should have the same injector for both cycles and the same assessor for all their assessments throughout the study.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomisation/dispensing has been done accurately.

The IWRS, and a backup Interactive Voice Response System (IVRS), will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor will be immediately notified, but not unblinded, via the IWRS/IVRS. If code break was performed using IWRS/IVRS, the investigator must store the email notification revealing unblinded intervention in a sealed envelope. The investigator will then sign, date and provide reason for the code break on the emergency code break form and on the sealed envelope. The date and reason for identifying the intervention group will be recorded in the eCRF.

In addition, sponsor pharmacovigilance will also have direct and immediate access to breaking the treatment code through the IWRS/IVRS.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision, at the study site and therefore participant compliance with study intervention is not expected to be an issue. The date and time of each dose administered in the site will be recorded in the source documents and in the eCRF. The volume of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

Not applicable. No dose modifications are permitted in the study.

6.5.1 Retreatment Criteria

All participants entered into the study will be treated on the first day of Cycle 1, which is also the randomisation day. A participant may receive Cycle 2 of study interventions if he/she meets retreatment criteria as determined by the investigator. Throughout the study, study intervention will be blinded.

After the first injection cycle, the participant must meet all of the following criteria to be eligible for retreatment with Cycle 2:

- Decided per the investigator's clinical judgement (the same person will have to do all assessments for a given participant for the full study duration);
- No decrease from baseline (Day 1; before Cycle 1 injection) of at least one grade in the MAS score in the PTMG;
- No unacceptable safety risk for the participant to receive the next treatment cycle, based on the investigator's judgement;

Retreatment with Cycle 2, based on when the effect of a previous injection has diminished and clinical symptoms return (according to the above criteria), may be at Week 12 (earliest retreatment timepoint), Week 16, Week 20 or Week 24 (latest retreatment timepoint). However, retreatment criteria will also be assessed at Week 10 even though reinjection cannot take place until Week 12 at the earliest.

6.6 Continued Access to Study Intervention after the End of the Study

The participants will not receive any additional study intervention following the end of the study. Any further BoNT-A treatment after the end of the study will be at the investigator's discretion with marketed product according to the approved local label.

6.7 Treatment of Overdose

For this study, any dose of aboBoNT-A or onaBoNT-A greater than those specified in Section 6.1 will be considered an overdose.

Excessive doses of BoNT-A may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the participant should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the study participant should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis, which could be local, or distant (remote) from the site of injection. For further details, refer to the approved local label of the BoNT-A marketed products. These participants should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalisation.

If the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of an overdose, the investigator/treating physician should follow the instructions in the approved local label and should also:

- Contact the sponsor's medical monitor immediately (email: PPD or tel. PPD);
- Discontinue the study intervention (see Section 7.1);
- Closely monitor the participant for signs and/or symptoms of excessive muscle weakness or muscle paralysis as detailed above and any other AEs, SAEs, AESIs and laboratory abnormalities;

- Document the quantity of the excess dose as well as the duration of symptoms (see Section 10.3.1 for reporting requirements concerning overdose).

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, COVID-19 vaccine, recreational drugs, vitamins, and/or herbal supplements), nondrug therapy or other specific categories of interest that the participant has received within 30 days of enrolment, is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prohibited Medications due to Drug Interactions

Prior/concomitant therapy that would exclude participants from enrolment in the study are detailed in Section 5.2.

The following concomitant medications are prohibited during this study:

- Any form of BoNT (other than the specific study interventions) for administration into any site of the body;
- Intrathecal baclofen (except if ongoing treatment dose is stable and there are no dose adjustments planned), aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents);
- Any experimental new drug or device.

Concomitant medications for other purposes are allowed at the investigator's discretion. It is recommended that the dosage for these medications is kept constant throughout the study. Where medically appropriate, all concomitant medications being taken by a participant at entry into the study should continue at the same dose.

Physiotherapy Treatment and/or Occupational Therapy (PT/OT)

PT/OT interventions not intended to reduce study limb spasticity (e.g. functional training exercises) or with a *transient* (<1 day) reduction of study limb spasticity (e.g. stretching, weight bearing) are permitted as concomitant therapy as long as the interventions are consistent across both study treatment cycles.

Due to potential for durable reduction of spasticity, the following PT/OT interventions on the study limb are prohibited: new splinting/orthotics/casting, serial casting, shockwave therapy, dry needling and needle tenotomies.

PT/OT interventions must be standard of care as they will not be compensated for in the study. Any deviations or additional care that the participant receives must be documented.

6.8.1 Rescue Medicine

Not applicable in this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. In this study, there will be only two single-injection treatment cycles, thus discontinuation of the study intervention is only possible after the Cycle 1 injection.

If a participant is randomised but does not receive any study intervention, the participant will not remain in the study and the EOS/EW assessments will not be performed.

If study intervention is permanently discontinued after the Cycle 1 injection, the participant will remain in the study as far as possible to be evaluated for safety and efficacy until the retreatment criteria are fulfilled or Week 24, and as a minimum up to Week 12 (see Section 8.5.3 for follow-up of AEs and SAEs). See the SoA in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Study intervention must be discontinued immediately in the event of:

- Serious hypersensitivity/allergic reactions (these should also be reported as AESIs; see Section 8.5.7);
- Infection at injection site(s);
- Remote spread of toxin effects including dysphagia, dysarthria or breathing difficulties (these should also be reported as AESIs; see Section 8.5.7);
- Evidence of transmission of viral disease or Creutzfeldt-Jakob disease (CJD);
- Pregnancy (this should also be reported as an SAE; see Section 8.5.5);
- Overdosage (refer to Section 10.3.1 regarding overdose reporting requirements).

7.1.1 Liver Chemistry Stopping Criteria

Not applicable in this study.

7.1.2 QTc Stopping Criteria

Not applicable in this study.

7.1.3 Temporary Discontinuation

In case of suspected or confirmed COVID-19 infection, the intervention administration will be temporarily discontinued depending on the participant's clinical presentation. If a participant tests positive for COVID-19, it is recommended that they be retested before the intervention administration is resumed. In addition to a negative COVID-19 test result, a stable clinical presentation with COVID-19 symptoms resolved (excluding ageusia and anosmia) must be demonstrated, in the opinion of the investigator, before allowing the participant to be retreated in the study.

7.1.4 Rechallenge

Not applicable in this study.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the

time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The reason for discontinuation will be recorded in the eCRF.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If the participant withdraws consent, it should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up. This information must be entered in the eCRF.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

In case of premature discontinuation of a site or those who completed the study, depending on the reason(s) for the discontinuation, the sponsor will notify the investigator(s) affected in writing as to whether the ongoing participants should continue receiving the study intervention administration.

A participant may discontinue participation in the study at any time for any reason (e.g. lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a participant from the study at any time for any reason (e.g. protocol violation or deviation, noncompliance with the protocol conditions or AEs). All cases of discontinuation will be discussed between the investigator and the sponsor.

If a participant decides to withdraw from the study after administration of study intervention, or should the investigator decide to withdraw the participant, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the participant's withdrawal should be made and an explanation given of why the participant is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded in the eCRF. If a participant withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the participant is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study intervention or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the participant receives study intervention, or as soon as possible thereafter.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls

and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1, Appendix 1.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers and exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 30 mL.
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.

8.1 Screening/Baseline Assessments

In addition to the screening/baseline efficacy assessments of MAS, DAS and QoL (see Section 8.3) and screening/baseline safety assessments including physical examination, pregnancy test for WOCBP, safety laboratory tests, vital signs and AE/SAE/AESI collection (See Section 8.4 and Section 8.5) shown in the SoA in Section 1.3, the following data will be collected.

8.1.1 Demographic Data

Demographic data such as sex, year of birth and race/ethnicity (only in USA) will be recorded.

8.1.2 Medical and Surgical History

Details of any significant medical and surgical history will be recorded.

8.1.3 Disease History

All available history of spasticity will be collected, including diagnosis of neurological condition leading to spasticity (acquired brain injury from stroke, trauma or other cause, spinal cord injury, progressive neurological condition, congenital (e.g. cerebral palsy) or other), primary aetiology of spasticity (trauma, vascular (infarct or haemorrhage), hypoxic, inflammatory/infective, tumour, degenerative or other), date of onset of the event leading to spasticity, pattern of paresis (unilateral or bilateral), affected upper limb (left, right or both) and presence of lower limb spasticity (LLS) if applicable.

8.1.4 Prior BoNT-A Therapy

Details will be recorded on whether participants are BoNT-A naïve for ULS or previously treated with BoNT-A for ULS. Treatment history will be collected for previously BoNT-A treated participants, including number of previous injection cycles, details of most recent BoNT-A injection for ULS prior to study enrolment (i.e. date, product/brand injected, total dose injected in upper limb) and whether the participant has received BoNT-A for indications other than ULS. If yes, the dose and product/brand for each indication (LLS, cervical dystonia, other dystonia, bladder overactivity, sialorrhea, or other) will be collected.

8.1.5 Prior and Concomitant Medications/Nondrug Therapy

Prior and concomitant medications (including vaccines) and nondrug therapies, including those for spasticity and spasticity-related pain, will be recorded at screening/baseline and throughout the study.

Medications for spasticity and spasticity-related pain to be collected include systemic antispasticity medications (e.g. baclofen, tizanidine, dantrolene), pain medications for simple pain relief (e.g. paracetamol, non-steroidal anti-inflammatory drugs), pain medications for neuropathic pain and spasticity (e.g. gabapentin, pregabalin, amitriptyline), opioids, phenol or alcohol (except if in accordance with exclusion criterion #14, Section 5.2) or other neurolytic agents. If baclofen has been administered (please refer to Section 5.2, exclusion criterion #15), route of administration will be recorded.

Nondrug therapies for spasticity and spasticity-related pain to be collected include specific interventions by therapists such as professional occupational therapy or physiotherapy, soft tissue stretching techniques (i.e. casting, splinting, bracing or others) or other intervention types, intensive occupational therapy (i.e. at least 2.5 hours a day for at least 2 weeks) and place of therapy (i.e. rehabilitation centre, school, home and/or other). The investigator should collect the name and details of the techniques used.

8.1.6 Concomitant Surgery

Details of concomitant surgery will be recorded from baseline until the end of the study.

8.2 Study BoNT-A Injection Details

Details of study BoNT-A injections will be collected including date of study drug administration, total volume injected, muscles injected, volume injected into each muscle and type of injection guidance technique used for each muscle (electromyography (EMG), electrostimulation (ES), or ultrasound (US) or combination at each treatment cycle).

8.3 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

Efficacy assessments will be performed by the same assessor in Cycle 1 and Cycle 2.

8.3.1 Duration of Response

Duration of response will be assessed based on retreatment criteria.

Note: if the date of the first BoNT-A retreatment after the EOS visit is available, this will be documented.

8.3.2 Modified Ashworth Scale

The MAS is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e. improvement in spasticity). This tool assesses muscle tone using a six-point scale (with available scores of 0, 1, 1+, 2, 3 and 4) which reports changes in muscle tone during muscle flexion or extension [[Bohannon and Smith 1987](#)], depending on the muscle being assessed.

MAS score for joints in the affected upper limb

Finger flexor muscle tone, wrist flexor muscle tone and elbow flexor muscle tone will be assessed with the MAS tool using a scale which is categorised for each of the three joints as follows: no change (0), slight increase (1 or 1+), marked increase (2), considerable increase (3) or affected/rigid region (4).

The primary target muscle group (PTMG; finger, wrist or elbow flexors) will be selected by the investigators at screening as the muscle group with the highest MAS score. If several muscle groups have the highest MAS score at screening, the investigator will select the PTMG among those muscle groups based on clinical judgement. The PTMG is to remain the same throughout the study.

MAS total score

The MAS total score is used as a reflection of spasticity severity and is calculated as the sum of the scores for all three joints analysed (finger, wrist and elbow), ranging between 0 and 12. Further details are provided in Section 10.5, Appendix 5.

8.3.3 Disability Assessment Scale

The disability assessment scale (DAS) [[Macfarlane et al 2002](#)] will be used at each visit to determine the extent of functional impairment in four domains: hygiene, dressing, limb position and pain. Impairment will be assessed on a four-point scale (range 0 to 3, where 0 indicates no disability and 3 indicates severe disability). The four domain ratings will be added to give an overall score between 0 and 12.

The PTT will be defined at screening based on one of the four DAS domains. The PTT is to remain the same throughout the study.

Further details are provided in Section 10.6, Appendix 6.

8.3.4 Physician's Global Assessment of the Treatment Response

The PGA of treatment response will be assessed by asking the investigator the following question:

‘how would you rate the response to treatment in the participant's upper limb since the last injection?’

Answers will be made on a nine-point rating scale (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved and +4: markedly improved).

8.3.5 Health-related Quality of Life Assessments

8.3.5.1 12-Item Short-form Health Survey (SF-12)

Participants will be asked to complete the SF-12 health survey (QualityMetric) [[Ware et al 1998](#)] to assess their general health and wellbeing. The SF-12 is a generic, multipurpose short-form survey consisting of 12 questions. The acute, or 1-week recall, survey form will be

used. It asks the respondent to answer the SF-12v2 questions as they pertain to the way he or she felt or acted during the past week.

The SF-12 covers eight domains/dimensions of health, including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, and two summary measures of physical and mental health: the physical component summary (PCS-12) and mental component summary (MCS-12), scored using norm-based methods.

The SF-12 summary score is between 0 and 100, with higher scores indicating better self-reported health.

Validated country-specific versions of the SF-12 will be used for all participating countries and are available in the electronic Trial Master File (eTMF).

Further details are provided in Section 10.7, Appendix 7.

8.3.5.2 *SQoL-6D Questionnaire*

Participants will be asked to complete the SQoL-6D questionnaire. This is a brief questionnaire in six domains (pain/discomfort, involuntary movements or spasms, restricted range of movement, caring for the affected limb, using the affected limb and mobility/balance) designed to assess QoL in relation to spasticity that affects the upper limb, which includes the arm, shoulder or hand. Each dimension is assessed by asking participants about symptoms within the last 7 days, using a five-level scale ranging from 0 to 4, with higher scores meaning worse condition. A total score between 0 and 100 will be calculated from the individual dimension scores, with a higher score indicating better QoL.

Further details are provided in Section 10.8, Appendix 8.

8.4 **Safety Assessments**

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.4.1 *Physical Examinations*

Physical examination should be focused on looking for the signs and symptoms of local and distant (remote) spread of toxin including (but not limited to):

- Examination of the face – looking for abnormalities related to vision (blurry vision, diplopia, inability to accommodate near vision), eyelid position, eyebrow position, inability to accommodate near vision, expressionless faces;
- Examination of cranial nerves – looking to identify cranial nerve paralysis as symptoms of botulism (i.e. symmetrical cranial nerve palsies, dysphagia, regurgitations, dysarthria);
- Examination of voluntary muscles in a descending manner: neck, shoulder, upper and lower limb looking for signs suggesting symmetrical descending flaccid paralysis of voluntary muscles, progressive disappearance of deep tendon reflexes and loss of muscle tone. These are as follows:
 - (a) General physical examination to evaluate potential distant (remote) spread;
 - (b) Examination of respiratory function searching for signs of paralysis of the diaphragm and accessory breathing muscles that may result in respiratory compromise or arrest;
 - (c) Examination of digestive function searching for eventual constipation;
 - (d) Looking for autonomic symptoms including anhidrosis with severe dry mouth and throat and postural hypotension.
- In addition, investigators should pay special attention to clinical signs related to previous serious illnesses.

- The investigator may choose to investigate any other sign that he/she observes during the physical examination. Abnormalities noted pre-injection, i.e. at the screening/baseline visits, should be recorded as medical history and any subsequent abnormalities noted should be recorded as AEs if clinically significant.
- Any clinically significant physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4.2 Vital Signs

- Temperature, pulse rate and systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with the participant in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded in the eCRF.

8.4.3 Clinical Safety Laboratory Assessments

All clinical safety laboratory tests will be performed locally at the study sites.

- See Section 10.2, Appendix 2 for the list of protocol-required clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Of note, all laboratory results should not be recorded in the eCRF (only the ones related to the clinically significant changes reported as AEs should be recorded in the corresponding AE page).
- Abnormal laboratory findings associated with the underlying disease, are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
 - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified through the AE form.
 - If laboratory values from non-protocol specified laboratory tests performed at the study site laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the eCRF.
 - Details of the methodology and reference ranges will be filed in the eTMF.

8.4.4 Pregnancy Testing

- Refer to the inclusion criteria (Section 5.1) for pregnancy testing entry criteria.
- Pregnancy testing (beta human chorionic gonadotrophin (HCG)) (urine or serum as required by local regulations) must be performed for all WOCBP as specified in the SoA

(Section 1.3): at screening/baseline, before each study intervention and at the end of relevant systemic exposure.

- A positive urine pregnancy test at any visit will be followed up by a serum beta-HCG test.
- A negative pregnancy test result must be obtained before each BoNT-A injection.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Any participant becoming pregnant during the study will be withdrawn.
- All pregnancies that occur during the study are to be reported as described in Section 8.5.5.

8.5 Adverse Events (AEs) and Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3, Appendix 3. Treatment-emergent adverse events (TEAEs) are defined in Section 9.4.2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the EOS/EW visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the case report form.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of awareness of the event, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation of the participant. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.5.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs (including AESIs, as defined in

Section 8.5.7) will be followed until resolution, stabilisation, the event is otherwise explained or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3, Appendix 3.

8.5.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ independent ethics committee (IECs) and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the package insert and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days.

8.5.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected from the signing of the ICF and until the end of the study.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate forms (AE form ticked serious in the eCRF and Drug Exposure Form – paper form) and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an additional AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.5.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.5.6 *Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs*

Not applicable in this study.

8.5.7 *Adverse Events of Special Interest*

Based on the risk assessment summarised in Section 2.3.1, the AESIs for this study are:

- Hypersensitivity;
- Remote spread of toxin.

Events that suggest a possible remote spread of toxin include the events presented by function in Section 10.9 (Appendix 9). These symptoms could be related to toxin spread and in case of occurrence they should be reported and monitored carefully until resolution.

AEs suggestive of hypersensitivity reaction are also of special interest and will be analysed using the Medical Dictionary for Regulatory Activities (MedDRA) Hypersensitivity standardised MedDRA queries (SMQ) (narrow).

All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs.

In rare cases, events such as these can be fatal and therefore participants should be advised to contact the investigator immediately if they develop any of these or any other unusual symptoms.

Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties.

Full details of these events must be collected in the eCRF.

Study intervention must be discontinued immediately in the event of serious hypersensitivity or remote spread of toxin (see Section 7.1). If the AESI meets the seriousness criteria, it should also be reported as an SAE (see Section 10.3, Appendix 3).

8.5.8 *Reporting of Study Intervention Errors Including Misuse/Abuse*

- Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a study intervention (medicinal product) while under the control of a healthcare professional, participant or consumer (European Medicines Agency definition).
- Misuse refers to situations where the study intervention is intentionally and inappropriately used not in accordance with the protocol.
- Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- Study intervention errors and uses outside of what is foreseen in the protocol will be recorded in the eCRF irrespective of whether associated with an AE/SAE or not. It will be documented in the AE section of the eCRF. It will be reported in the safety database only if associated with an SAE.
- Misuse or abuse will be collected and reported in the safety database, whether associated or not with an AE/SAE, within 24 hours of investigator's awareness.

8.6 *Pharmacokinetics*

Pharmacokinetic parameters are not evaluated in this study.

8.7 *Genetics and/or Pharmacogenomics*

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The study hypotheses are the following:

- Safety profile of both products is comparable: this hypothesis is associated with the primary safety endpoint analysis based on non-inferiority testing regarding the TEAE rate from injection to Week 12. Additional analyses on adverse drug reaction (ADR) rate and detailed analysis of TEAEs and AESIs will also be provided.
- Efficacy profile at peak (Week 4) is similar, but aboBoNT-A has longer duration of effect (Week 10 and beyond): this hypothesis will be associated with secondary efficacy endpoints analyses based on superiority tests.

Statistical hypotheses for the primary analysis have been defined as follows: the anticipated TEAE rate from injection to Week 12 has been set to 44% [[Gracies et al 2015](#)], and it was assumed no difference between the two treatment groups, a non-inferiority margin set to 5% and a nuisance parameter set to 22%. Alpha level was set to 0.1 (one sided), power to 80% and dropout rate to 10%.

9.2 Sample Size Determination

The sample size was determined with Power Analysis and Sample Size (PASS 15) software using the “Non-Inferiority Tests for the Difference Between Two Correlated Proportions” procedure.

Based on statistical hypotheses associated with the primary study objective and the primary safety endpoint as reported in Section 9.1, the required number of participants to be randomised is 450 participants. However, by the end of the study, some sites identified a small group of 14 eligible participants (3.1%); the sponsor decided to include them in the study so a total of 464 participants were enrolled. A blinded sample size reassessment was performed when at least 100 participants have completed the Week 12 visit of Cycle 2 (see Section 9.5).

Approximately 563 participants were screened to achieve 464 randomised to one of the two intervention sequences using a 1:1 randomisation ratio. A stratified randomisation based on the previous ULS treatment (BoNT-A non-naïve versus naïve) will be performed.

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Screened Population	All participants who signed the ICF.
Randomised Population	A participant will be considered as randomised if a sequence has been assigned by the IWRS/IVRS. For analyses and displays, participants will be classified according to randomised sequence.
Safety Set (SS) / Full Analysis Set (FAS)	All randomised participants who received at least 1 dose of either aboBoNT-A or onaBoNT-A. If there is any doubt whether a participant was treated or not, they will be assumed treated for the purposes of analysis. Efficacy analyses (FAS) will be based on allocated sequence, whereas participants will be analysed according to the sequence they actually received for safety analyses (SS).
Per Protocol Set for Safety (PPS-Safety)	The PPS-Safety analyses will contain all participants from the SS who received 1 dose of aboBoNT-A and 1 dose of onaBoNT-A and who completed the 12-week period for both cycles without any major protocol deviation that may interfere with safety evaluation.
Per Protocol Set for Efficacy (PPS-Efficacy)	The PPS-Efficacy analyses will contain all participants from the FAS who completed the 12-week period for both cycles and who did not experience any major protocol deviation that may interfere with efficacy evaluation.

Protocol deviations will be described and their impact on inclusion in each analysis population will be assessed. The final list of protocol deviations impacting the safety and efficacy populations will be reviewed prior to database lock.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised prior to database lock. It will include a more technical and detailed description of the statistical analyses of the data collected in this study as well as shells for tables, figures and listings.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Other endpoints as well as demographics, baseline characteristics and disposition will be detailed in the SAP.

The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.4.1 General Considerations

The statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the sponsor's Biometry Department.

The Statistical Analysis System (SAS)[®] software (version 9.4 or higher) will be used.

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

- For quantitative variables: mean, standard deviation (SD), median, lower quartile, upper quartile and range;
- For categorical variables: counts and percentages for each category.

Unless otherwise specified, no imputation of missing data will be done.

Summary statistics associated with demographics/baseline characteristics and disposition of participants will be presented by sequence and overall. Efficacy and safety analyses will be presented by treatment, and also by cycle (overall and by treatment by cycle) for primary and key secondary endpoints.

For each parameter, the baseline value will be defined as the last value collected before study intervention. The second baseline measurement corresponding to the end of the first cycle will not be considered in the analysis.

Multiplicity adjustment to control the overall type I error rate at 2-sided 0.20 (or one-sided 0.1) is detailed in Section 9.4.3 for key secondary endpoints. No multiplicity adjustment will be made for other secondary and sensitivity analyses: they will be assessed using a nominal alpha level of 2-sided 0.20.

9.4.2 Analysis of Primary Endpoint(s)

Evaluation of the safety profile of both products will be based on TEAEs. A TEAE is defined for each treatment cycle (*) as any AE that occurs during the cycle if:

- it was not present prior to treatment injection, or
- it was present prior to treatment injection but the intensity increased during the cycle.

(*) Cycle 1 covers the period between first injection and second injection or EOS if the participant did not receive the second injection. Cycle 2 covers the period between second injection and EOS.

The primary safety endpoint is based on the TEAE incidence rate from injection to Week 12, i.e. TEAEs that occurred during each cycle from injection to 12 weeks after injection.

A generalised linear mixed model approach will be used to estimate the difference in TEAE rate between the two treatment groups while accounting for within-participant correlations arising from the crossover design. The fitted model will include fixed effects for treatment and cycle and a random effect associated with the participant. The treatment by cycle interaction (carryover effect) will be tested: if the associated p-value is more than 0.10 it will be considered as absent or negligible and it will not be included in the final model to provide estimates. The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 80% confidence interval (CI) (or one-sided 90% CI) will be provided: the non-inferiority of aboBoNT-A versus onaBoNT-A in terms of safety profile will be demonstrated if the upper bound of this CI is lower than 5% in the PPS-Safety analyses.

Estimand approach and sensitivity analyses

Estimand framework is addressed in this study only for the analysis of the primary endpoint. The variable and associated population-level summary are defined above. As the primary analysis is based on non-inferiority testing for a safety criterion, the primary population will be the PPS-Safety. The non-inferiority should be confirmed in the Safety Set for a robust interpretation.

Intercurrent events listed in Section 3 will be handled mainly using a treatment policy strategy. Study discontinuations with associated reasons and timepoints will be investigated and detailed. Participants who do not receive the Cycle 2 injection will not be part of the PPS-Safety; they will be analysed in the Safety Set with Cycle 1 data only as part of robustness analyses. The number of study discontinuations before Week 12 of Cycle 1 or Cycle 2 (i.e. participants who would receive an injection but could not be followed up for the next 12 weeks) is assumed to be negligible, thus no specific strategy is deemed necessary to take into account such cases. A listing including all participants who had a cycle where no safety information was recorded, either the subject discontinued before the end of the cycle, or there was no evidence of safety recording (no safety related page filled in: neither physical examination, nor vital signs nor concomitant medications nor AEs) will be provided. The intake of prohibited medications or prohibited concomitant PT/OT interventions on the study limb will be ignored: all TEAEs reported in the 12-week period after injection will be considered for the primary endpoint. Analyses on specific TEAE categories such as related TEAEs are described in Section 9.4.5.

The potential impact of the COVID-19 pandemic on the TEAE rate will be explored through a supplementary analysis in which TEAEs identified as COVID-19 TEAEs will not be considered for the calculation of the incidence rate.

In addition to the model-based estimate, a sensitivity analysis will be performed in the PPS-Safety analyses: the estimated overall difference and the estimated SD of the paired differences will be calculated using the paired differences of (aboBoNT-A – onaBoNT-A) for each participant within each sequence and the associated two-sided 80% (or one-sided 90%) Wald CI will be derived.

9.4.3 Analysis of Secondary Endpoint(s)

This section covers secondary endpoints associated with efficacy assessments. Secondary endpoints associated with safety assessments are described in Section 9.4.5.

The duration of response will be defined as follows:

- For Cycle 1: time between Cycle 1 injection and the first Cycle 1 visit when retreatment criteria are met (from Week 10 visit), or time between Cycle 1 injection and study withdrawal if the participant discontinues from the study before Cycle 2 injection without meeting retreatment criteria.
- For Cycle 2: time between Cycle 2 injection and the first Cycle 2 visit when retreatment criteria are met (from Week 10 visit), or time between Cycle 2 injection and EOS if the participant completes the study or discontinues from the study after Cycle 2 injection without meeting retreatment criteria.

The main assessment of MAS will be based on the PTMG. MAS total score (finger, wrist and elbow flexors) will also be calculated. A numeric score of 1.5 will be associated with the '1+' value.

The main assessment of DAS will be based on the PTT. DAS total score (hygiene, dressing, limb position and pain) will also be calculated.

Multiplicity Adjustment

In order to preserve an overall type I error rate of 0.1 (one-sided) for the primary key and secondary endpoints, a multiplicity adjustment involving Bonferroni adjustment and serial gatekeeping procedure with pre-specified hierarchical order will be performed.

Each hypothesis (or hypotheses family) will be formally tested only if the previous hypothesis in the pre-specified hierarchical order is tested significantly. If a test is not significant, the serial gatekeeping procedure will stop (the result of the test as well as the next tests of the sequence cannot be claimed significant).

The statistical testing sequence of key secondary endpoints will be the following:

- (1) If the analysis of the primary safety criterion (TEAE rate from injection to Week 12) demonstrates the non-inferiority of aboBoNT-A versus onaBoNT-A, then the superiority test comparing the duration of response (aboBoNT-A versus onaBoNT-A) will be performed (hypothesis 1).
- (2) If hypothesis 1 is tested significantly, alpha will propagate to the next step: a Bonferroni split will then be used where $\alpha/3$ is allocated to test family related to PGA, test family related to DAS score (for the PTT) and test family related to MAS score (for the PTMG). Within each family, the superiority test of aboBoNT-A versus onaBoNT-A for the score will be performed at Week 12 (at $\alpha/3$ level), then at Week 10 only if the test at Week 12 is significant (same alpha levels as for tests at Week 12).

Statistical analysis

Analyses and summary tables for efficacy endpoints will be based mainly on the FAS. Analyses in the PPS-Efficacy will be performed additionally.

The duration of response will be described and compared between treatment groups using a mixed effects model with cycle and treatment as fixed effects and participant as random effect. The within-participant variance covariance matrix will be assumed to be unstructured. The p-value associated with cycle and treatment effects will be provided, and the estimate of the difference between treatment groups and associated two-sided 80% (or one-sided 90%) CI will be provided. Descriptive statistics of the number and percentage of participants retreated from 12 weeks (Week 12, Week 16, Week 20, Week 24) will also be provided.

Sensitivity analyses will be performed in participants having available values for both treatments: the difference between treatments will be tested using non-parametric tests based on ranks (Wilcoxon signed-rank test), the median and associated CI will be provided.

PGA of treatment response will be described qualitatively and quantitatively at each timepoint (Week 1, 4, 10, 12 ± 16, 20, 24) and at the end of the cycle. MAS score for the PTMG, MAS total score, DAS score for the PTT and DAS total score will be described qualitatively and quantitatively at each timepoint (baseline, Week 1, 4, 10, 12 ± 16, 20, 24) and at the end of the cycle.

PGA, DAS (PTT) and MAS (PTMG) scores at Week 10 and Week 12 will be compared between treatment groups in the same way as the duration of response using a mixed effects model and non-parametric sensitivity analyses.

9.4.4 Analysis of Exploratory Endpoint(s)

Quality of Life assessments will be described at each timepoint (baseline, Week 4, Week 12 and the end of each cycle):

- SF-12 scores for eight health concepts (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) and PCS-12 and MCS-12 scores;
- SQoL-6D scores associated with each of the six dimensions and total SQoL-6D score.

9.4.5 Safety Analyses

Analyses and summary tables for safety endpoints will be based on the safety set.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term (PT) and system organ class (SOC).

An ADR is defined for each treatment cycle as any TEAE that was assessed by the investigator as related to the study treatment. A TEAE will be considered as an ADR in case of missing causality assessment.

The incidence of all reported AEs, TEAEs, ADRs, SAEs, AEs leading to withdrawal and AESIs will be tabulated overall and by primary SOC and PT, for the whole cycle duration and from injection to Week 12.

An overview of TEAEs will display the number of TEAE occurrences along with the number and percentage of participants with at least one TEAE according to time to onset, seriousness and seriousness criteria, severity, investigator causality assessment, outcome and action taken. Individual data listings will be provided.

Descriptive statistics of other safety endpoints including vital signs will be provided at each timepoint with associated changes or shifts from baseline.

9.4.6 Subgroup Analyses

Descriptive statistics will be provided for the primary and key secondary endpoints within each category of the following variables if sample size allows:

- Sex (Male, Female)
- Age (< 65 years, ≥ 65 years)
- Country (USA, Canada, France)
- BoNT-A status for ULS (naïve, non-naïve)

Additional subgroup analyses may be planned in the SAP according to clinical interest.

9.5 Interim Analyses

No interim analysis is planned other than the blinded sample size reassessment.

The reassessment procedure was performed after at least 100 participants have completed the Week 12 visit of Cycle 2. The TEAE rate from injection to Week 12 in each cycle was estimated as well as the percentage of discordant pairs (participants with TEAE in Cycle 1 but not in Cycle 2 or conversely). Only blinded data was used. It was to provide an estimate of the nuisance parameter in order to update the sample size for the trial based on this estimate.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations such as Regulation EU 536/2014
- The protocol, protocol amendments, ICF and other relevant documents (e.g. any participant recruitment materials) must be approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The protocol and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to applicable local regulations, ICH guidelines and the IRB/IEC requirements/procedures.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

- The ICF and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws. They must be approved prior to use as described in Section 10.1.1, Appendix 1.
- The ICF used during the informed consent process and any participant recruitment materials must be approved by the IRB/IEC before use, and available for audit and inspection.
- Prior to study entry, the investigator or his/her authorised representative will explain to the participant (or their legally authorised representative and impartial witness, when applicable) the nature and objectives of the study and possible risks associated with the participation. They will answer all questions raised by the participant regarding the study and allow sufficient time for discussion.
- Participants (or their legally authorised representative and impartial witness, when applicable) must be informed that their participation is voluntary.
- The investigator or his/her authorised representative will obtain written informed consent from each participant (or their legally authorised representative and impartial witness, when applicable) before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant (or their legally authorised representative and impartial witness, when applicable).
- The medical record must include a statement that written informed consent was obtained before the participant was included in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- The ICF will contain a separate section that addresses the use of all data and remaining material after analysis from mandatory samples and any extra samples for optional future research. These data and biosamples may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study and the storage period. A specific consent will be required to document a participant's agreement to allow any data and remaining specimens to be used for future research.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 7 days from the previous ICF signature date.
- Participants who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

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

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- All local data protection/patient privacy laws and regulations will be complied with.
- The sponsor will ensure that appropriate organisational and technical arrangements are implemented to comply with the applicable rules on the protection of personal data. In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: ^{PPD} [REDACTED]

10.1.5 Committees Structure

Steering Committee

- A Steering Committee will be appointed for the study. In addition to involvement in protocol development, the Steering Committee will review the CSR and oversee any publications.
- The Steering Committee will be composed of three expert neurologists with extensive experience in the use of BoNT-A.

10.1.6 Dissemination of Clinical Study Data

- The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.
- Protocol and result summary will be made publicly available on the US Clinical Trials Registry (ClinicalTrials.gov) and if the study is conducted in the EU/EEA on the EU Clinical Trials Portal (<https://euclinicaltrials.eu/home>). Where applicable, the sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.
- A lay protocol synopsis and a summary of the study results will be made available on the EU Clinical Trials Portal (<https://euclinicaltrials.eu/home>) and Sponsor website.
- A CSR will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. The CSR may be disclosed according to regulatory requirements.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections, make all documents available for audit and inspection and provide direct access to source data documents.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals, e.g. CROs.
- Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Reasons should be given on the relevant eCRF for any missing data. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

10.1.7.1 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of participants are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP guidelines and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all participants) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF and will assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator. The investigator or an approved representative (e.g. pharmacist) will ensure that all study interventions are reconstituted and dispensed by unblinded qualified staff who will document the participant allocated treatment number and the number of vials used/not used. A sponsor-assigned unblinded monitor will be responsible for study intervention accountability. Participants and investigators will remain blinded to treatment assignment during the study.

The site must complete the eCRFs on an ongoing basis in 5 working days to allow regular review by the study monitor, both remotely by the internet and during site visits.

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

10.1.7.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRF and all study procedures. The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of participant management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

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

10.1.7.3 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP guidelines. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor or inspected by regulatory bodies. The investigator must adhere to ICH GCP guidelines in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study participants. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

This clinical trial will be conducted in compliance with all international laws and regulations and national laws and regulations of the countries in which the clinical trial is performed, as well as any applicable guidelines.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation that supports the information entered in the eCRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that

the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. When permitted by local regulation and guidance, study monitors may access source documents/data remotely to conduct source data verification, while maintaining appropriate security measures and ensuring the protection of the data. This will be described in the monitoring plan or equivalent.

10.1.8.1 Recording of Study Data

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

The investigator must record all data relating to protocol procedures, study intervention administration, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the study centre authorisation form, may formally designate authority to complete eCRFs to appropriately qualified staff (having certified user access to the eCRF).

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

10.1.8.2 Data Management

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

Data management will be conducted by a CRO, directed by the sponsor's Data Management Group Leader. All data management procedures will be completed in accordance with the sponsor and/or the contracted CRO standard operating procedures. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigator site, (see Section 10.1.7.1). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive or will be given the possibility to extract their data from the clinical study in an electronic format (PDF files) which will be an exact copy of the eCRF and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted CRO. It is the CRO's study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa) up to the point of database lock, after which additional late information may be provided to pharmacovigilance, e.g. regarding outcome.

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by the contracted CRO, directed by the sponsor's data management department and reviewed and approved by the sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary and AEs/medical history terms will be coded using MedDRA.

Only data from screened participants will be reported in the eCRFs and collected in the sponsor's database.

For screen failure participants, at least the Unique Participant Identifier, the date of informed consent signature, demographic and eligibility criteria data, the reason why the participant failed screening and any AEs/SAEs which occurred during the screening phase will be reported in the eCRFs and collected in the sponsor's database.

10.1.8.3 Record Archiving and Retention

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

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 25 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

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

10.1.9 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement and the Steering Committee will oversee publication plans.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory at the visits indicated in the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Tests

Parameters	Screening	Intervention Period	EOS/EW
Haematology			
Platelet count	X	X	
RBC count	X	X	
Haemoglobin	X	X	
Haematocrit	X	X	
RBC indices: MCV, MCH, % reticulocytes	X	X	
WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	X	X	
International normalised ratio	X	X	
Clinical Chemistry[a]			
Blood urea nitrogen	X	X	
Creatinine	X	X	
Glucose (nonfasting)	X	X	
Potassium	X	X	
Sodium	X	X	
Calcium	X	X	
AST/SGOT	X	X	
ALT/SGPT	X	X	
Alkaline phosphatase[b]	X	X	
Total and direct bilirubin	X	X	
Total protein	X	X	
Pregnancy Testing			
Highly sensitive urine hCG pregnancy test (as needed for WOCBP)[c]	X	X	X

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOS = end of study; EW = early withdrawal; hCG = human chorionic gonadotropin; IEC = independent ethics committee; INR = international normalised ratio; IRB = institutional review board; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential.

- a All events of ALT [or AST] $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin) or ALT [or AST] $\geq 3 \times$ ULN and INR >1.5, (if INR measured) which may indicate severe liver injury (possible Hy's Law), must be reported to the sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
- b If alkaline phosphatase is elevated, consider fractionating.
- c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. A negative result must be obtained before the participant is randomised and before the Cycle 2 injection.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

g. Is a suspected transmission of any infectious agent via an authorised medicinal product

10.3.3 Recording and Follow-Up of AE and/or SAE**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required forms.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information on a new SAE form.

10.3.4 Reporting of SAEs

SAE Reporting to sponsor via paper

- The site will email the paper SAE form or fax the cover sheet and SAE form to the sponsor within 24 hours of awareness of event.
- Contacts for SAE reporting can be found on the SAE form.
- A new SAE form is required if follow-up data becomes available.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
 2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhoea, confirmation with more than one FSH measurement is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
 - Permanent sterilisation methods (for the purpose of this study) include:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy
 - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g. amenorrhoea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods [b] That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) [b] • Bilateral tubal occlusion • Azoospermic partner (vasectomised or due to a medical cause) <i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.)</i>
Highly Effective Methods [b] That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i>
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation [c] – oral – injectable
Sexual abstinence <i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</i>
Effective Methods [d] That Are Not Considered Highly Effective <i>Failure rate of $\geq 1\%$ per year when used consistently and correctly.</i>
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide [e] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) [c]

- Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
- Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
- If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
- Considered effective, but not highly effective – failure rate of $\geq 1\%$ per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.
- Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Modified Ashworth Scale

The muscles for injection in this study are: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis and biceps brachii.

A primary target muscle group will be defined for assessment.

Finger flexor muscle tone, wrist flexor muscle tone and elbow flexor muscle tone will be assessed.

Muscle tone will be scored as follows for each joint:

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

The MAS total score is used as a reflection of spasticity severity and is calculated as the sum of the scores for all three joints analysed (finger, wrist and elbow), ranging between 0 and 12.

10.6 Appendix 6: Disability Assessment Scale

A principal target of treatment will be defined for assessment.

The rater should interview the participant to determine the extent of functional impairment for each of the following domains:

Hygiene

The rater assesses:

- Extent of maceration, ulceration, and/or palmar infection;
- Palm and hand cleanliness;
- Ease of cleanliness;
- Ease of nail trimming;
- Degree of interference caused by hygiene-related disability in the participant's daily life.

Dressing

The rater assesses:

- Difficulty or ease with which the participant could put on clothing (e.g. shirts, jackets, gloves);
- Degree of interference caused by dressing-related disability in the participant's daily life.

Limb position

The rater assesses:

- Amount of abnormal position of the upper limb.

Pain

The rater assesses:

- Intensity of pain or discomfort related to ULS.

Rating

- 0: No disability.
- 1: Mild disability (noticeable but does not interfere significantly with normal activities).
- 2: Moderate disability (normal activities require increased effort and/or assistance).
- 3: Severe disability (normal activities limited).

Total score calculation

The four domain ratings will be added to give an overall score between 0 and 12.

10.7 Appendix 7: 12-Item Short-form Health Survey Instrument SF-12

The SF-12 yields scale scores for each of the eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) and two summary measures of physical and mental health: the physical component summary (PCS-12) and mental component summary (MCS-12).

The PCS-12 and MCS-12 scales are scored using norm-based methods. Physical and mental regression weights and a constant for both measures come from the general US population. The SF-12 summary score is between 0 and 100, with higher scores indicating better self-reported health.

Further details on how to score the SF-12 physical and mental health summary scales are available in [Ware et al 1998](#).

10.8 Appendix 8: Spasticity-related Quality of Life Tool - SQoL-6D (Version 4.0)**The spasticity-related quality of life tool (SQoL-6D)****Background:**

Spasticity is a condition in which certain muscles are continuously contracted.

- The resulting stiffness and tightness of muscles may affect your ability to move one or more of your limbs.
- Sometimes spasticity is so severe that it gets in the way of daily activities, sleep patterns, and caregiving.

Common unwanted effects of spasticity are:

- Pain
- Spasms or involuntary movements
- Contracture and deformity
- Decreased ability to use the arm/hand in active movements, such as reaching for, grasping, holding and releasing objects
- Difficulties with caring for the arm and hand (eg keeping it clean and dressed),
- Reduced balance and mobility

The SQoL-6D is a brief questionnaire in six domains, designed to assess quality of life in relation to spasticity that affects the upper limb, which includes the arm, shoulder or hand.

Please answer the following questions about how you have felt in the last 7 days, in relation to symptoms related to spasticity in your affected upper limb(s)

The spasticity-related quality of life tool (SQoL-6D)

Within the last 7 days:

1. Pain / discomfort:	
To what extent have you experienced pain or discomfort due to spasticity in your arm, shoulder or hand that interferes with activities or sleep?	
<i>(eg stiffness or a cramp-like sensation in the muscles, the joints being pulled into uncomfortable positions, or the finger-nails digging into the palm, that can sometimes interfere with activities or sleep)</i>	
☐	I have no pain or discomfort in my affected upper limb(s)
☐	I have mild pain or discomfort in my affected upper limb(s) which does not interfere with my activities or sleep
☐	I have moderate pain or discomfort in my affected upper limb(s), which only occasionally interferes with my activities or sleep
☐	I have severe pain or discomfort in my affected upper limb(s) which sometimes interferes with my activities or sleep
☐	I have extremely severe pain or discomfort in my affected upper limb(s) which frequently interferes with my activities or sleep

2. Involuntary movements or spasms:	
To what extent have you experienced involuntary movements or spasms in your arm shoulder or hand that interfere with normal activities?	
<i>(eg movements or abnormal limb postures that you can't control such as sudden spasms; or the arm pulling up or the hand clenching into a fist when you use another part of your body, which may affect normal activities such as your ability to move around)</i>	
☐	I have not experienced any involuntary movements or spasms in my affected upper limb(s)
☐	I have mild involuntary movements or spasms in my affected upper limb(s) which do not interfere with normal activities
☐	I have moderate involuntary movements or spasms in my affected upper limb(s) which interfere minimally with normal activities
☐	I have severe involuntary movements or spasms in my affected upper limb(s) which interfere significantly with normal activities
☐	I have extremely severe involuntary movements or spasms in my affected upper limb(s) which interfere severely with normal activities

3. Restricted range of movement:	
To what extent has spasticity restricted the range of movement in the joints of your arm, shoulder or hand?	
<i>(eg inability to straighten or bend the limb fully due to shortening of muscles or stiffness in joints)</i>	
☐	I have no restriction of movement in my affected upper limb(s)
☐	I have mild restriction in range of movement in my affected upper limb(s) but I am able to stretch my joints out fully with assistance
☐	I have moderate restriction in range of movement in my affected upper limb(s) or restriction affecting just a few joints
☐	I have severe restriction in range of movement in my affected upper limb(s) or restriction affecting many of my joints
☐	I have extremely severe restriction in range of movement in my affected upper limb(s) so that I can barely move my affected limb at all

4. Caring for the affected limb

To what extent has spasticity limited the ability (of you or your carer) to care for your arm shoulder or hand?

(Eg to keep the palm or armpit clean and odour-free, to cut the finger-nails or dress the limb (eg getting the arm through a sleeve or the hand in a glove))?

☐	I have no problems with caring for my affected upper limb(s)
☐	I have mild problems caring for my affected upper limb(s) for example it takes some extra time or effort to care for my limb
☐	I have moderate problems caring for my affected upper limb(s) for example it takes me a long time or I need help from someone else to care for the limb
☐	I have severe problems caring for my affected upper limb(s) for example despite assistance my limb is sometimes smelly or left undressed
☐	I am unable to care for my affected limb(s) and am unable to keep my limb clean and dressed

5. Using the affected limb

To what extent has spasticity limited active use of your arm shoulder or hand?

(Eg reaching for, grasping, holding and releasing objects or fine finger movements)

☐	I have no problems using my affected limb(s)
☐	I have slight problems using my affected limb(s), which limit tasks requiring a high level of dexterity
☐	I have moderate problems using my affected limb(s), but am able to use it actively in some tasks
☐	I have severe problems using my affected limb(s), but am able to use it as a 'prop' to hold or steady an object
☐	I am unable to use my affected limb(s) for any useful purpose

6. Mobility / Balance:

To what extent have involuntary movements or tightness of your arm, shoulder or hand interfered with your mobility or balance?

☐	I have no problems with mobility or balance
☐	I have mild problems with mobility or balance, but I can get around independently
☐	I have moderate problems with mobility or balance, which limit my ability to get round independently outdoors
☐	I have severe problems with mobility or balance, which limit my ability to get around independently, outdoors and indoors
☐	I have extremely severe problems with mobility or balance, and need help from another person to get around

10.9 Appendix 9: Adverse Events of Special Interest by Function Suggestive of Possible Remote Spread Effect of Toxin

Function	Adverse Event of Special Interest
Related to eye function	Accommodation disorder, vision blurred, diplopia, extraocular muscle paresis, IIIrd nerve paresis, IVth nerve paresis, pupillary reflex impaired, eyelid function disorder, eyelid ptosis
Related to chewing/tongue	Bulbar palsy, hypoglossal nerve paresis, trigeminal nerve paresis
Related to voice	Dysphonia, bulbar palsy, dysarthria, hypoglossal nerve paresis, speech disorder, vocal cord paralysis, vocal cord paresis
Related to mouth/throat/bowel	Dysphagia, dry mouth, constipation, paralytic ileus, bulbar palsy
Related to heart function	Bradycardia
Related to lung function	Dyspnoea, diaphragmatic paralysis, respiratory arrest, aspiration, pneumonia aspiration, respiratory depression, respiratory failure
Related to bladder function	Pelvic floor muscle weakness, urinary retention
Related to muscle function/strength	Cranial nerve palsies multiple, cranial nerve paralysis, paresis cranial nerve, trigeminal nerve paresis, monoparesis, muscular weakness, paralysis, paralysis flaccid, paresis, peripheral nerve palsy, peripheral paralysis, facial palsy, facial paresis, areflexia, botulism, hyporeflexia, hypotonia, quadriparesis, hemiparesis, paraparesis

10.10 Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

:

10.10.1 Amendment 1 (25 March 2022)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for the Amendment:

The protocol was amended to reflect the changes as requested by the French Authority (ANSM). In addition, clarifications were made to the protocol as detailed in the Table below, including correction to reflect that the sample size was performed using a one-sided non-inferiority test, the alignment of the injection guidance techniques with the Botox USPI update.

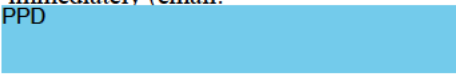
Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
Sponsor signature page	PPD  ~~Ipsen Pharma~~ ~~65, Quai Georges Gorse~~ ~~92100 Boulogne Billancourt~~ ~~France~~ PPD 	PPD  Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France PPD 	Update of the signature page to modify the Medical Monitor's name and contact details.
Synopsis & 1.4	<u>Study Duration:</u> Recruitment period ~~of 13~~ months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum 25 months.	<u>Study Duration:</u> Recruitment period up to 22 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum 34 months .	Extension of the recruitment period to manage operational delays.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
Synopsis & 9.1	Alpha level was set to ~~0.025~~ (one sided), power to 80% and dropout rate to 10%.	Alpha level was set to 0.05 (one sided), power to 80% and dropout rate to 10%.	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.
Synopsis – Statistical Methods & 9.4.2	The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided ~~95%~~ confidence interval (CI) (or one-sided ~~97.5%~~ CI) will be provided: the non-inferiority of aboBoNT-A versus onaBoNT-A in terms of safety profile will be demonstrated if the upper bound of this CI is lower than 5% in the Per Protocol Set for safety analyses.	The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 90% confidence interval (CI) (or one-sided 95% CI) will be provided: the non-inferiority of aboBoNT-A versus onaBoNT-A in terms of safety profile will be demonstrated if the upper bound of this CI is lower than 5% in the Per Protocol Set for safety analyses.	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.
1.4	<u>Timelines:</u> Expected first participant injected: June 2021, Last Participant's Last Visit: ~~July 2023~~ , CSR available December ~~2023~~ .	<u>Timelines:</u> Expected first participant injected: June 2021, Last Participant's Last Visit: April 2024 , CSR available December 2024 .	Corrected to extend the recruitment period.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
2.3.1 Table 2 (Human albumin and transmission of viral diseases)	Participant selection: N/A Participant monitoring: ~~Participants will be informed of these risks in the PIS/ICF and closely monitored during the study.~~ Withdrawal criteria: In the unlikely event of transmission of viral disease or CJD, the participant would be withdrawn from study intervention (Section 7.1).	Participant selection: N/A Participant monitoring: Participants will be closely monitored and AEs will be collected during the study. Withdrawal criteria: In the unlikely event of transmission of viral disease or CJD, the participant would be withdrawn from study intervention (Section 7.1).	Corrected to reflect the actual PIS/ICF. This risk is not mentioned in the actual PIS/ICF because this is extremely rare and a theoretical risk.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
2.3.1 Table 2 (Aminoglycosides and other agents interfering with neuromuscular transmission)	Participant selection: Participants receiving aminoglycosides, other agents interfering with neuromuscular transmission ~~or muscle relaxants~~ will be excluded from the study (Section 5.2).	Participant selection: Participants receiving aminoglycosides and other agents interfering with neuromuscular transmission will be excluded from the study (Section 5.2). Participants receiving oral antispasticity medication will be required to have a stable treatment with these agents for at least three months prior to study entry, and this treatment must be likely to remain stable throughout the study.	Updated as requested by the French Authority ANSM to ensure consistency with exclusion criteria.
2.3.1 Table 2 (Anticholinergic drugs)	Participant selection: Participants receiving anticholinergic drugs will be ~~excluded from the study (Section 5.2).~~	Participant selection: Participants receiving anticholinergic medication will be required to have a stable treatment with these agents for at least three months prior to study entry, and this treatment must be likely to remain stable throughout the study.	Updated as requested by the French Authority ANSM to ensure consistency with exclusion criteria.
2.3.1 Table 2 (Lactation)	Participant selection: Lactating women will be excluded from the study (Section 5.2). Participant monitoring: ~~Participants will be informed of the risk to the infant of BoNT-A treatment during lactation in the PIS/ICF.~~ Withdrawal criteria: N/A.	Participant selection: Lactating women will be excluded from the study (Section 5.2). Participant monitoring: N/A. Withdrawal criteria: N/A.	Corrected to reflect the actual protocol inclusion/exclusion criteria (i.e., lactating and pregnant women are excluded from the study).

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
2.3.1 Table 2 (Pre-existing neuromuscular disorders) (Bronchitis and URT infections) (Clinical risks/adverse reactions) (Immunogenicity)	Participant monitoring: Participants will be informed of these risks in the PIS/ICF and closely monitored during the study.	Participant monitoring: Participants will be informed of these risks in the PIS/ICF [b] and closely monitored during the study. <i>Footnote added</i> Participants will be informed of the more common and most serious ADRs in the PIS/ICF.	Footnote added to provide clarification.
5.2		20. BoNT naïve participants with a history of facial neurogenic disorder (facial paralysis, polyradiculoneuropathy) (only for France);	Addition of an exclusion criterion. Added as requested by the French Authority ANSM. In France, both Dysport and Botox SmPCs indicate that, in these patients, the dose should be reduced to a quarter of the recommended dose for the first administration, which is not possible to achieve in this study (fixed dose of 900 U and 360 U respectively, with dose modifications that are not permitted).
5.2	14. Previous surgery, or administration of alcohol or phenol in the study limb 6 months ~~or earlier from~~ study enrolment or planned/likely to be treated during the course of the study;	14. Previous surgery or administration of alcohol or phenol in the study limb within the 6 months prior to study enrolment or planned/likely to be treated in the study limb during the course of the study;	Clarification of existing exclusion criterion.
5.2	15. Participants treated with intrathecal baclofen, aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents) within the ~~previous~~ 4 weeks or planned/likely to be treated during the course of the study;	15. Participants treated with intrathecal baclofen (except if treatment has reached a stable dose for >4 weeks and is likely to remain stable throughout the study) , aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents) within the 4 weeks prior to study enrolment or planned/likely to be treated during the course of the study;	Clarification of existing exclusion criterion.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
5.2	19. Participants currently enrolled in any other clinical study or have participated in one within the 12 weeks prior to enrolment/inclusion visit, or are scheduled to receive a new investigational drug while the study is ongoing.	19. Participants currently enrolled in any other clinical study or have participated in one within the 12 weeks (or 5 half-lives of the investigational product of that study, whichever is longer) prior to enrolment/inclusion visit, or are scheduled to receive a new investigational drug while the study is ongoing.	Added as requested by the French Authority ANSM to take into account the commonly admitted period of washout for medicinal products (5 half-lives).
6.1 & 8.2	The use of injection guidance techniques to target the injection sites is mandatory in this study. Guidance techniques should be ~~electromyography and/or electrical stimulation, with additional ultrasound if needed.~~	The use of injection guidance techniques to target the injection sites is mandatory in this study. Guidance techniques should be electromyography (EMG), electrostimulation (ES), or ultrasound (US) or combination at each treatment cycle.	Updated to align with Botox USPI update.
6.2	For both study interventions, a fixed volume of 3.6 mL is required per cycle. ~~Dosing syringes of 2.0 mL will be used for the study.~~	For both study interventions, a fixed volume of 3.6 mL is required per cycle.	Removed to reflect the SmPC.
6.7	Contact the sponsor's medical monitor immediately (email:  PPD)	Contact the sponsor's medical monitor immediately (email:  PPD)	Updated to reflect the change in the Medical Monitor's name and contact details.
6.8	The following concomitant medications are prohibited during this study: - Any form of BoNT (other than the specific study interventions) for administration into any site of the body; - Intrathecal baclofen, aminoglycosides or other agents interfering with neuromuscular transmission (e.g. curare-like agents);	The following concomitant medications are prohibited during this study: - Any form of BoNT (other than the specific study interventions) for administration into any site of the body; - Intrathecal baclofen (except if ongoing treatment dose is stable and there are no dose adjustments planned), aminoglycosides or other	Corrected to clarify that intrathecal baclofen will not be prohibited if the current treatment dose is stable and there are no dose adjustments planned.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
	Any experimental new drug or device.	agents interfering with neuromuscular transmission (e.g. curare-like agents); Any experimental new drug or device.	
8.1.5	Medications for spasticity and spasticity-related pain to be collected include systemic antispasticity medications (e.g. baclofen, tizanidine, dantrolene), pain medications for simple pain relief (e.g. paracetamol, non-steroidal anti-inflammatory drugs), pain medications for neuropathic pain and spasticity (e.g. gabapentin, pregabalin, amitriptyline), opioids, ~~and phenol, alcohol~~ or other neurolytic agents. If baclofen has been administered, route of administration will be recorded.	Medications for spasticity and spasticity-related pain to be collected include systemic antispasticity medications (e.g. baclofen, tizanidine, dantrolene), pain medications for simple pain relief (e.g. paracetamol, non-steroidal anti-inflammatory drugs), pain medications for neuropathic pain and spasticity (e.g. gabapentin, pregabalin, amitriptyline), opioids, phenol or alcohol (except if in accordance with exclusion criterion #14, Section 5.2) or other neurolytic agents. If baclofen has been administered (please refer to Section 5.2, exclusion criterion #15), the route of administration will be recorded.	Cross-reference to Section 5.2 was added as a reminder that treatment with alcohol, phenol and intrathecal baclofen will only be allowed if treatment follows the conditions specified in the exclusion criteria #14 and #15.
9.2	Approximately 650 participants will be screened to achieve 564 randomised to ~~study intervention~~ using a 1:1 randomisation ratio.	Approximately 650 participants will be screened to achieve 564 randomised to one of the 2 intervention sequences using a 1:1 randomisation ratio.	Corrected to reflect the cross-over design of the study.
9.4.1	Multiplicity adjustment to control the overall type I error rate at 2-sided ~~0.05~~ (or one-sided ~~0.025~~) is detailed in Section 9.4.3 for key secondary endpoints. No multiplicity adjustment will be made for other secondary ~~and exploratory endpoints~~ and for sensitivity analyses: they will be assessed using a nominal alpha level of 2-sided ~~0.05~~ .	Multiplicity adjustment to control the overall type I error rate at 2-sided 0.10 (or one-sided 0.05) is detailed in Section 9.4.3 for key secondary endpoints. No multiplicity adjustment will be made for other secondary and sensitivity analyses: they will be assessed using a nominal alpha level of 2-sided 0.10 .	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
9.4.2	In addition to the model-based estimate, a sensitivity analysis will be performed in the PPS-Safety analyses: the estimated overall difference and the estimated SD of the paired differences will be calculated using the paired differences of (aboBoNT-A – onaBoNT-A) for each participant within each sequence and the associated ~~95%~~ Wald CI will be derived.	In addition to the model-based estimate, a sensitivity analysis will be performed in the PPS-Safety analyses: the estimated overall difference and the estimated SD of the paired differences will be calculated using the paired differences of (aboBoNT-A – onaBoNT-A) for each participant within each sequence and the associated two-sided 80% (or one-sided 90%) Wald CI will be derived.	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.
9.4.3	In order to preserve an overall type I error rate of 0.05 (one-sided ~~0.025~~) for the primary key and secondary endpoints, a multiplicity adjustment involving Bonferonni adjustment and serial gatekeeping procedure with pre-specified hierarchical order will be performed.	In order to preserve an overall type I error rate of 0.05 (one-sided) for the primary key and secondary endpoints, a multiplicity adjustment involving Bonferonni adjustment and serial gatekeeping procedure with pre-specified hierarchical order will be performed.	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.
9.4.3	The p-value associated with cycle and treatment effects will be provided, and the estimate of the difference between treatment groups and associated ~~95%~~ CI will be provided.	The p-value associated with cycle and treatment effects will be provided, and the estimate of the difference between treatment groups and associated two-sided 80% (or one-sided 90%) CI will be provided.	Corrected to reflect that sample size calculation was performed using a one-sided non-inferiority test.
10.1.4		The sponsor will ensure that appropriate organisational and technical arrangements are implemented to comply with the applicable rules on the protection of personal data. In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data	Added to reflect the Ipsen protocol template update.

Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
		protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: PPD	
10.3.2	An SAE is defined as ~~any serious adverse event~~ that, at any dose:	An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:	Modified to reflect the Ipsen protocol template update.
10.3.3	- Mild: ~~An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.~~ - Moderate: ~~An event that causes sufficient discomfort to interfere with normal everyday activities.~~ - Severe: ~~An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; both AEs and SAEs can be assessed as severe.~~	- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. - Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. - Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care	Modified to reflect the Ipsen protocol template update.

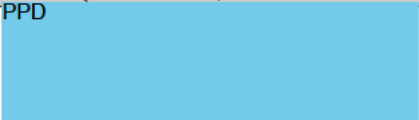
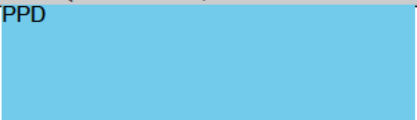
Section	WAS (Version 1.0, 27 APRIL 2021)	IS (Version 2.0, 25 MARCH 2022)	Rationale
		ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

10.10.2 Amendment 2 (02 December 2022)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for the Amendment:

The protocol was amended to extend the recruitment period by 2 months, to update the Inclusion and Exclusion Criteria, to provide some clarification on occupational therapy and/or physiotherapy treatment, to remove the requirement for reporting of suspected or confirmed coronavirus COVID-19 infection as an SAE, to clarify the section on adverse events of special interest, to add an intercurrent event and to remove the reference to the Steering Committee charter. The sponsor signatory's and Medical Monitor's name and contact details were also updated.

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
Sponsor signature page	PPD  Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France	PPD  Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France	Update of the signature page to modify the Sponsor signatory name and contact details
Sponsor signature page	PPD  Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France PPD 	PPD  Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France PPD 	Update of the signature page to modify the Medical Monitor's name and contact details.

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
1.1 and 3	Objectives and Endpoints and/or Estimand(s) Primary End Endpoints and/or Estimand(s): <u>Key intercurrent events:</u> • Treatment discontinuation • Prohibited concomitant medication • Visits delayed or not performed, or AEs due to COVID-19	Objectives and Endpoints and/or Estimand(s) Primary End Endpoints and/or Estimand(s): <u>Key intercurrent events:</u> • Treatment discontinuation • Prohibited concomitant medication or prohibited concomitant Physiotherapy Treatment and/or Occupational Therapy (PT/OT) interventions on the study limb • No evidence of safety information • Visits delayed or not performed, or AEs due to COVID-19	Updated to add missing key intercurrent events
1.1	Overall Design This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18-75 years of age inclusive with upper limb spasticity (ULS).	Overall Design This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18-80 years of age inclusive with upper limb spasticity (ULS).	To increase the number of participants who may benefit from the treatment
1.1 and 1.4	Study Duration Recruitment period up to ~~22~~ months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum ~~34~~ months.	Overall Study Duration Recruitment period up to 24 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: 36 months.	To extend the recruitment period and overall study duration by 2 months

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
1.4	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: ~~April~~ 2024, CSR available December 2024.	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: June 2024, CSR available: December 2024.	To reflect the update of the recruitment period duration
2.3.1	Table 2 Potential Risk of Clinical Significance: Other drug therapy in elderly patients Participant selection: The upper age limit for participants is ~~75~~ years of age (Section 5.1).	Table 2 Potential Risk of Clinical Significance: Other drug therapy in elderly patients Participant selection: The upper age limit for participants is 80 years of age (Section 5.1).	To reflect the update of the Inclusion Criteria No.1.
4.1	This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18- ~~75~~ years of age inclusive with ULS.	This is a multicentre, interventional, post-marketing, randomised, double-blind, crossover study to evaluate the clinical safety and efficacy of aboBoNT-A (Dysport®) in comparison with onaBoNT-A (Botox®) when treating male and female adult participants 18- 80 years of age inclusive with ULS.	To reflect the update of the Inclusion Criteria No.1.
5.1	1. Participant must be 18 to ~~75~~ years of age inclusive, at the time of signing the informed consent;	1. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent;	To increase the number of participants who may benefit from the treatment
5.1	5. Participants with MAS score of at least 2 at ~~elbow, wrist and finger flexors~~ ;	Participants with MAS score of at least 2 in two muscle groups (one of these two muscle groups should be the PTMG) and at least 1 in the remaining muscle group ;	To increase the number of participants who may benefit from the treatment

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
5.1	8. Participants who have been stable for at least 3 months prior to study entry in terms of oral antispasticity, anticoagulant and/or anticholinergic medication, if treated and for at least 1 month prior to study entry in terms of occupational therapy and/or physiotherapy treatment, if treated, and are considered by the investigator likely to remain stable for the duration of the study;	8. Participants who have been stable for at least 3 months prior to study entry in terms of oral antispasticity, anticoagulant and/or anticholinergic medication, if treated, and are considered by the investigator likely to remain stable for the duration of the study;	Updated to provide clarification on occupational therapy and/or physiotherapy treatment
5.2	~~16. Participants who received a COVID-19 vaccine injection within 7 days before the first planned study intervention injection, or planned/likely to be vaccinated within 7 days after the first planned study intervention injection~~		No longer applicable as safety profile of COVID-19 vaccines now better understood and should be recorded as per other concomitant medications.
5.2		21. Participants receiving concomitant treatment with the following PT/OT interventions on the study limb: new splinting/orthotics/casting, serial casting, shockwave therapy, dry needling and needle tenotomies. However, PT/OT interventions not intended to reduce study limb spasticity (e.g. functional training exercises) or with a transient (<1 day) reduction of study limb spasticity (e.g. stretching, weight bearing) are allowed.	Added to provide clarification on occupational therapy and/or physiotherapy treatment
5.5	~~COVID-19 vaccine injection cannot be administered within 7 days before and after study intervention injection.~~		No longer applicable as safety profile of COVID-19 vaccines now better understood and should be recorded as per other concomitant medications.

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
6.5	No COVID-19 vaccine injection received within 7 days before the second planned study intervention injection, or planned/likely to be received within 7 days after the second planned study intervention injection.		No longer applicable as safety profile of COVID-19 vaccines now better understood and should be recorded as per other concomitant medications
6.7	Contact the sponsor's medical monitor immediately (email: PPD [REDACTED])	Contact the sponsor's medical monitor immediately (email: PPD [REDACTED])	Updated to reflect the updated contact details of the Medical Monitor
6.8		Physiotherapy Treatment and/or Occupational Therapy (PT/OT) PT/OT interventions not intended to reduce study limb spasticity (e.g. functional training exercises) or with a transient (<1 day) reduction of study limb spasticity (e.g. stretching, weight bearing) are permitted as concomitant therapy as long as the interventions are consistent across both study treatment cycles. Due to potential for durable reduction of spasticity, the following PT/OT interventions on the study limb are prohibited: new splinting/orthotics/casting, serial casting, shockwave therapy, dry needling and needle tenotomies. PT/OT interventions must be standard of care as they will not be compensated for in the study.	Updated to provide clarification on physiotherapy treatment and/or occupational therapy

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
		Any deviations or additional care that the participant receives must be documented.	
8.5.7	Based on the risk assessment summarised in Section 2.3.1, the AESIs for this study are: • Hypersensitivity; • Remote spread of toxin. In rare cases, events such as these can be fatal and therefore participants should be advised to contact the investigator immediately if they develop any of these or any other unusual symptoms. Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties. Full details of these events must be collected in the eCRF. Study intervention must be discontinued immediately in the event of serious hypersensitivity or remote spread of toxin (see Section 7.1). If the AESI meets the seriousness criteria, it should also be reported as an SAE (see Section 10.3, Appendix 3). ~~AESIs should be recorded by function suggestive of possible remote spread of toxin using the form provided in Section 10.9, Appendix 9.~~	Based on the risk assessment summarised in Section 2.3.1, the AESIs for this study are: • Hypersensitivity; • Remote spread of toxin. Events that suggest a possible remote spread of toxin include the events presented by function in Section 10.9 (Appendix 9). These symptoms could be related to toxin spread and in case of occurrence they should be reported and monitored carefully until resolution. AEs suggestive of hypersensitivity reaction are also of special interest and will be analysed using the Medical Dictionary for Regulatory Activities (MedDRA) Hypersensitivity standardised MedDRA queries (SMQ) (narrow). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs. In rare cases, events such as these can be fatal and therefore participants should be advised to contact the investigator immediately if they develop any of these or any other unusual symptoms. Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties. Full details of these events must be collected in the eCRF.	Updated to provide clarification on AESI.

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
		Study intervention must be discontinued immediately in the event of serious hypersensitivity or remote spread of toxin (see Section 7.1). If the AESI meets the seriousness criteria, it should also be reported as an SAE (see Section 10.3, Appendix 3).	
9.4.2	Intercurrent events listed in Section 3 will be handled mainly using a treatment policy strategy. Study discontinuations with associated reasons and timepoints will be investigated and detailed. Participants who do not receive the Cycle 2 injection will not be part of the PPS-Safety; they will be analysed in the Safety Set with Cycle 1 data only as part of robustness analyses. The number of study discontinuations before Week 12 of Cycle 1 or Cycle 2 (i.e. participants who would receive an injection but could not be followed up for the next 12 weeks) is assumed to be negligible, thus no specific strategy is deemed necessary to take into account such cases. The intake of prohibited medications will be ignored: all TEAEs reported in the 12-week period after injection will be considered for the primary endpoint.	Intercurrent events listed in Section 3 will be handled mainly using a treatment policy strategy. Study discontinuations with associated reasons and timepoints will be investigated and detailed. Participants who do not receive the Cycle 2 injection will not be part of the PPS-Safety; they will be analysed in the Safety Set with Cycle 1 data only as part of robustness analyses. The number of study discontinuations before Week 12 of Cycle 1 or Cycle 2 (i.e. participants who would receive an injection but could not be followed up for the next 12 weeks) is assumed to be negligible, thus no specific strategy is deemed necessary to take into account such cases. A listing including all participants who had a cycle where no safety information was recorded, either the subject discontinued before the end of the cycle, or there was no evidence of safety recording (no safety related page filled in: neither physical examination, nor vital signs nor concomitant medications nor AEs) will be provided. The intake of prohibited medications or prohibited concomitant PT/OT interventions on the study limb will be ignored: all TEAEs reported in the 12-week period after injection will be considered for the primary endpoint.	Updated to reflect updated key recurrent events

Section	WAS (Version 2.0, 25 MARCH 2021)	IS (Version 3.0, 02 DECEMBER 2022)	Rationale
10.1.5	~~A Steering Committee charter will be developed prior to study start to define roles and responsibilities of the Steering Committee members. Meetings will take place as defined in the charter. The Chair of the Steering Committee will be responsible for communicating the committee's recommendations to the study team who will immediately inform the investigators. The Steering Committee charter will be available in the eTMF and will also provide information on any stopping rules.~~		The charter was not developed and should have been removed from the protocol. DIRECTION being a post-marketing study on products with well-known safety profiles, a charter is not required
10.3.2	~~A suspected or confirmed coronavirus COVID-19 infection must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present, e.g. hospitalisation).~~		Suspected or confirmed coronavirus COVID-19 infection is no longer required to be reported as an SAE, unless it meets the seriousness criteria.

Other documents impacted

Informed consent form	Yes	☐	No	☒
Case report form (CRF)	Yes	☒	No	☐
Statistical analysis plan (SAP)	Yes	☒	No	☐

10.10.3 Amendment 3 (12 April 2023)

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment:

The protocol was amended to extend the recruitment period by 12 months. The Medical Monitor's name and contact details were also updated.

Section	Was (Version 3.0, 02 December 2022)	Is (Version 4.0, 12 APRIL 2023)	Rationale
Sponsor signature page	Medical Monitor Name and Contact Information: PPD Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France PPD	Medical Monitor Name and Contact Information: PPD Ipsen Pharma 65, Quai Georges Gorse 92100 Boulogne Billancourt France Email: PPD	To reflect the change of Medical Monitor.
Synopsis & Section 1.4	Overall Study Duration: Recruitment period up to ~~24~~ months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: ~~36~~ months.	Overall Study Duration: Recruitment period up to 36 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: 48 months.	Extension of the recruitment period and overall study duration by 12 months to reach the required number of participants to be randomised (i.e., 564 participants).
Synopsis & 1.4	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: June ~~2024~~ , CSR available: December ~~2024~~ .	Timelines: Expected first participant injected: June 2021, Last Participant's Last Visit: June 2025 , CSR available: December 2025 .	To reflect the update of the recruitment period duration

Section	Was (Version 3.0, 02 December 2022)	Is (Version 4.0, 12 APRIL 2023)	Rationale
Section 6.7	Contact the sponsor's medical monitor immediately (email: PPD [REDACTED])	Contact the sponsor's medical monitor immediately (email: PPD [REDACTED])	To reflect the change of Medical Monitor.

Other documents impacted

Informed consent form Yes ☐ No ☒

Case report form (CRF) Yes ☐ No ☒

Statistical analysis plan (SAP) Yes ☐ No ☒

10.10.4 Amendment 4 (24 May 2024)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikethrough text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 4.0, 12 APRIL 2023)	IS (5.0, 24 MAY 2024)	Rationale
Title page	Regulatory Authority Identifier Number(s): ~~EudraCT number: 2021-000161-32~~	Regulatory Authority Identifier Number(s): EU CT number: 2023-509196-16-00	EU-CT number provided
Synopsis & Section 1.4	Overall Study Duration: Recruitment period up to ~~36~~ months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: ~~48~~ months.	Overall Study Duration: Recruitment period up to approximately 45 months, two treatment cycles, each of 12-24 weeks (no longer than 51 weeks in total), i.e. maximum overall study duration: approximately 57 months.	Extension of the recruitment period and overall study duration by 9 months to reach the required number of participants to be randomized.
Synopsis & Section 1.4	<u>Timelines:</u> Expected first participant injected: June 2021, Last Participant's Last Visit: ~~June 2025~~ , CSR available: ~~December 2025~~ .	<u>Timelines:</u> Expected first participant injected: June 2021, Last Participant's Last Visit: approximately March 2026 CSR available: approximately December 2026 .	To reflect the update of the recruitment period duration
Synopsis & Sections 1.4, 4.1, 6.3.1, 9.2	Number of Participants: ~~650~~ participants will be screened to give ~~564~~ eligible participants	Number of Participants: 518 participants will be screened to give 450 eligible participants	Alpha level changed from 0.05 (one sided) to 0,1 (one sided)

Section	WAS (Version 4.0, 12 APRIL 2023)	IS (5.0, 24 MAY 2024)	Rationale
Synopsis & Section 9.1	Alpha level was set to ~~0.05~~ (one sided), power to 80% and dropout rate to 10%.	Alpha level was set to 0.1 (one sided), power to 80% and dropout rate to 10%.	*Sponsor overestimated how many subjects existed with the specific profile (in terms of location and severity of spasticity) to meet the protocol inclusion criteria. *Sponsor experienced challenges in contracting with sites, in many cases due to changes following COVID, which resulted in delays in recruitment. *Sponsor protocol assumptions underestimated the nuisance parameter, which determines the sample size. Following the estimate of the nuisance parameter based on the first 100 subjects, the blinded Sample Size Reassessment led to an increase of about 10% of the number of randomized subjects.
Section 2.3, Table 2	BoNT-A Adverse Reactions/Clinical Trials/Postmarketing Experience (Section 6 of USPI [...] Other ~~less frequent~~ adverse reactions for aboBoNT-A and onaBoNT-A are detailed in the USPI. The following adverse reactions have been identified during post-approval use: AboBoNT-A: vertigo, photophobia, influenza -like illness, amyotrophy, burning sensation, facial paresis, hypoesthesia, erythema, dry eye and excessive granulation tissue. Hypersensitivity reactions including anaphylaxis have been reported. OnaBoNT-A: abdominal pain, alopecia including madarosis, anorexia, brachial plexopathy,	BoNT-A Adverse Reactions/Clinical Trials/Postmarketing Experience (Section 6 of USPI [...] Other adverse reactions for aboBoNT-A and onaBoNT-A are detailed in the USPI. The following adverse reactions have been identified during post-approval use: AboBoNT-A: vertigo, photophobia, influenza -like illness, amyotrophy, muscle atrophy, burning sensation, facial paresis, hypoesthesia, erythema, dry eye and excessive granulation tissue. Hypersensitivity reactions including anaphylaxis have been reported. OnaBoNT-A: abdominal pain, alopecia including madarosis, anorexia, brachial plexopathy, denervation/muscle atrophy,	Table updated as per current Dysport® USPI and Botox® USPI.

Section	WAS (Version 4.0, 12 APRIL 2023)	IS (5.0, 24 MAY 2024)	Rationale
	denervation/muscle atrophy, diarrhoea; dry eye, eyelid oedema (following periocular injection), hyperhidrosis, hypoacusis, hypoaesthesia, localised muscle twitching, malaise, paresthesia, peripheral neuropathy, radiculopathy, erythema multiforme, dermatitis psoriasiform and psoriasiform eruption, strabismus, tinnitus, and visual disturbances.	diarrhoea; dry eye, eyelid oedema (following periocular injection), hyperhidrosis, hypoacusis, hypoaesthesia, localised muscle twitching, malaise, mephisto sign , paresthesia, peripheral neuropathy, radiculopathy, erythema multiforme, dermatitis psoriasiform and psoriasiform eruption, strabismus, tinnitus, and visual disturbances.	
Section 8.5.4	[...] Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators ~~as necessary~~ .	[...] Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days .	Section updated as per clinical trials coordination group (CTCG) guidance requirement.
Section 10.1.1	This study will be conducted in accordance with the protocol and with the following: - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - Applicable laws and regulations	This study will be conducted in accordance with the protocol and with the following: - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - Applicable laws and regulations such as Regulation EU 536/2014	Section updated as per CTCG guidance requirement.
Section 10.1.6	[...] Protocol and result summary will be made publicly available on the US Clinical Trials Registry (ClinicalTrials.gov). The sponsor also provides clinical trial information to other national clinical trial registries or	[...] Protocol and result summary will be made publicly available on the US Clinical Trials Registry (ClinicalTrials.gov) and if the study is conducted in the EU/EEA on the EU Clinical Trials Portal	Section updated as per CTCG guidance requirement.

Section	WAS (Version 4.0, 12 APRIL 2023)	IS (5.0, 24 MAY 2024)	Rationale
	databases according to local requirements/legislation.	(https://euclinicaltrials.eu/home). Where applicable, the sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation. A lay protocol synopsis and a summary of the study results will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and Sponsor website.	
Section 10.1.8.3	[...] Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least ~~15~~ years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product.	[...] Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 25 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product.	Section updated as per CTCG guidance requirement.

Other documents impacted

Informed consent form	Yes ☒	No ☐
Case report form (CRF)	Yes ☐	No ☒
Statistical analysis plan (SAP)	Yes ☒	No ☐

11 REFERENCES

Bakheit AMO. Botulinum toxin treatment of muscle spasticity. Milton Keynes, UK: AuthorHouse™ UK Ltd.; 2007.

Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987;67:206-7.

Botox® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use. United States Prescribing Information, revised 11/2023. Allergan Pharmaceuticals Ireland/Allergan USA, Inc.

Danchenko N, Lundkvist J, Lysandropoulos A et al. Economic evaluation of abobotulinumtoxinA vs onabotulinumtoxinA in real-life clinical management of post-stroke upper limb spasticity. *Neurology* 2019;92(15 suppl):P5.6-020.

Dashtipour K, Chen JJ, Walker HW, Lee MY. Systematic literature review of abobotulinumtoxinA in clinical trials for adult upper limb spasticity. *Am J Phys Med Rehabil* 2015;94(3):229-38.

De Sainte-Marie D, Lysandropoulos A. Botulinum neurotoxins are used at low doses in the treatment of spasticity in clinical practice: results from a market research analysis. *Toxins* 2019;156 suppl 1:S22.

Dysport® (abobotulinumtoxinA) for injection, for intramuscular use. United States Prescribing Information, revised 09/2023. Ipsen Biopharm Ltd/Ipsen Biopharmaceuticals, Inc.

Gracies JM. Pathophysiology of spastic paresis. II. Emergence of muscle overactivity. *Muscle Nerve* 2005;31(5):552-71.

Gracies JM, Brashear A, Jech R et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. *Lancet Neurol* 2015;14(10):992-1001.

Gracies JM, Esquenazi A, Brashear A et al; International AbobotulinumtoxinA Adult Lower Limb Spasticity Study Group. Efficacy and safety of abobotulinumtoxinA in spastic lower limb: Randomized trial and extension. *Neurology* 2017;89(22):2245-53.

Gracies JM, O'Dell M, Vecchio M et al; International AbobotulinumtoxinA Adult Upper Limb Spasticity Study Group. Effects of repeated abobotulinumtoxinA injections in upper limb spasticity. *Muscle Nerve* 2018;57(2):245-54.

Graham HK, Aoki KR, Autti-Rämö I et al. Recommendations for the use of botulinum toxin type A in the management of cerebral palsy. *Gait Posture* 2000;11(1):67-79.

Jacinto J, Varriale P, Pain E et al. Patient perspectives on the therapeutic profile of botulinum neurotoxin type A in spasticity. *Front Neurol* 2020;11:388.

Macfarlane A, Turner-Stokes L, De Souza L. The associated reaction rating scale: a clinical tool to measure associated reactions in the hemiplegic upper limb. *Clin Rehabil* 2002;16:726-35.

Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines. London: RCP 2018.

Sanger TD, Delgado MR, Gaebler-Spira D et al. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics* 2003;111(1):e89-97. doi: 10.1542/peds.111.1.e89.
Simpson DM. Treatment of spasticity with botulinum toxin. *Muscle Nerve* 2000;23:447-9.

Turner-Stokes L, Fheodoroff K, Jacinto J et al. ULIS (Upper Limb International Spasticity), a 10-year Odyssey: An international, multicentric, longitudinal cohort of person-centered spasticity management in real-life practice. *J Int Soc Phys Rehabil Med* 2019;2:138-50.

Ward AB. A summary of spasticity management-a treatment algorithm. *Eur J Neurol* 2002;9 (Suppl 1):48-52.

Ware JE Jr, Kosinski M, Keller SD. How to Score the SF-12 Physical and Mental Health Summary Scales. 3d. Boston: The Health Institute, New England Medical Center; 1998.