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STATISTICAL ANALYSIS PLAN

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

CLIN-52120-452

This statistical analysis plan is based on:
PROTOCOL VERSION AND DATE: 6.0 – 13 JAN 2025

SAP Version	Date
Final Version 1.0	09 February 2024
Final Version 2.0	20 May 2025
Final Version 3.0	23 September 2025

APPROVAL PAGE

STUDY NUMBER:	CLIN-52120-452
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
SAP VERSION:	Final Version 3.0
SAP DATE:	23 September 2025

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date	Signature
PPD	IPSEN	PPD		eSignature
	IPSEN			eSignature
	Parexel			eSignature

HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	9 February 2024	New Document
2.0	28 November 2024	Protocol amendment: Alpha level changed from 0.05 (one sided) to 0.1 (one sided) for primary and secondary efficacy endpoints. Following sample size reassessment, nuisance parameter was updated from 20% to 22% and the number of screened and eligible participants decreased from 650 to 518 and 564 to 450 respectively. 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.
2.0	28 November 2024	Update in the definition of the PPS-Safety.
2.0	28 November 2024	Note added for handling protocol deviations of treatment mis-dispensation after unblinding.
2.0	20 May 2025	Information given that SF-12 score is derived using PRO-CORE software by QualityMetric.
2.0	20 May 2025	Full name given for Appendix A of the FDA draft guidance.
2.0	20 May 2025	Note stating that hypersensitivity reactions and Remote spread Preferred Terms (PTs) are based on the most recent version of MedDRA with removal of table containing all possible PTs.
3.0	20 August 2025	In disposition table, summary of participants completing and not completing each cycle is added.
3.0	20 August 2025	Demographic tables are displayed by sequence on the randomized set, overall on the PPS-Safety set and by treatment on the safety set.
3.0	20 August 2025	Safety analysis sets summary tables are displayed by treatment on the Safety set and efficacy analysis sets summary tables are displayed on the FAS.
3.0	20 August 2025	Sponsor will provide new classification for "OTHER" diagnosis and primary aetiology of spasticity.
3.0	20 August 2025	If any, participants treated with ABO-ABO and ONA-ONA are excluded from the compliance and exposure tables, from all tables and figures for primary and secondary endpoints based on the safety set and from AE summary tables by sequence based on the safety set.

3.0	20 August 2025	Only 2-sided 80% CIs are planned for all primary, secondary and exploratory efficacy endpoints (one-sided 90% CIs are removed).
3.0	20 August 2025	Summary of intercurrent events on PPS-Safety is removed as not applicable on this population.
3.0	20 August 2025	Definition of duration of response amended to use last visit date instead of withdrawal date when participant is lost to follow up.
3.0	20 August 2025	Change from baseline added for MAS scores for finger, wrist and elbow score in addition to Total score.
3.0	20 August 2025	Change from baseline added for DAS scores for all domains in addition to Total score.
3.0	20 August 2025	Change from baseline added for SQOL-6D Total score.
3.0	20 August 2025	Duration of exposure summary displayed by treatment group, overall and by cycle in a same table.
3.0	20 August 2025	Removal of "(In any treatment group)" for table of 5 most common TEAEs.
3.0	20 August 2025	Table and listing related to PCSA are removed as not relevant for this study.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AboBoNT-A	AbobotulinumtoxinA
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomic Therapeutic Class
BoNT-A	Botulinum toxin type A
C	Concomitant
CI	Confidence interval
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
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
GCP	Good clinical practice
HCG	Human chorionic gonadotrophin
HRT	Hormonal replacement therapy
ICE	Intercurrent Event
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
ITT	Intention to treat
IUD	Intrauterine device
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
OnaBoNT-A	OnabotulinumtoxinA
P	Prior
PASS	Power Analysis and Sample Size
PC	Prior and Concomitant
PCS	Physical component summary
PGA	Physician Global Assessment
PN	Preferred name
PPS-Efficacy	Per Protocol Set for Efficacy
PPS-Safety	Per Protocol Set for Safety
PT	Preferred Term
PTMG	Primary target muscle group
PTT	Principal target of treatment
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SDV	Source data verification
SF-12	12-Item Short-form Health Survey
SI	International System of Units
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
TBI	Traumatic brain injury
TEAE	Treatment-emergent adverse event

U	Unit
ULIS	Upper Limb International Spasticity
ULS	Upper limb spasticity
USA	United States of America
WBC	White blood cell(s)
WOCBP	Woman of childbearing potential

1 INTRODUCTION

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol CLIN-52120-452. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Any post-hoc, or unplanned, analyses not identified in this SAP which are performed will be clearly identified in the respective CSR.

The SAP is to be finalised prior to database lock. A separate shell will be provided for tables, figures and listings.

Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Conference on Harmonisation (ICH) E3).

2 PROTOCOL OVERVIEW

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.

2.1 Study Objectives and Hypotheses

Table 1 displays the objectives, corresponding endpoints and key intercurrent events for this study.

Table 1 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	Endpoints: • Rate of TEAEs from injection to 12 weeks[b] Key intercurrent events: • Treatment discontinuation • Prohibited concomitant medication • Visits delayed or not performed, or AEs due to COVID-19
Secondary	
• To evaluate clinical safety • To assess efficacy	Endpoints: • Rate of ADRs, SAEs and AESIs from injection to 12 weeks • Key secondary endpoint: Duration of response based on retreatment criteria • Key secondary endpoint: Muscle tone assessed by the MAS for finger, wrist and elbow flexors at 10 and 12 weeks based on PTMG • Muscle tone assessed by the MAS for finger, wrist and elbow flexors at 1, 4 ± 16, 20, 24 weeks based on PTMG and MAS total score at 1, 4, 10, 12 ± 16, 20, 24 weeks

	• Key secondary endpoint: Perceived function and pain assessed by the DAS at 10 and 12 weeks based on PTT • Perceived function and pain assessed by the DAS at 1, 4 ± 16, 20, 24 weeks based on PTT and DAS total score at 1, 4, 10, 12 ± 16, 20, 24 weeks • Key secondary endpoint: PGA of treatment response at 10 and 12 weeks • PGA of treatment response at 1, 4 ± 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 Sections 5.7.3 and 5.7.4).

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

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 treatment emergent adverse event (TEAE) rate from injection to Week 12.
- 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%.

2.2 Overall Study Design and Investigational Plan

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).

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.

The End of Treatment (EOT) for each participant will be the date of the Cycle 2 injection.

For participants who complete the study, the End of Study (EOS) visit will be the visit at which the retreatment criteria (see Section 6.5.1 of protocol) 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.

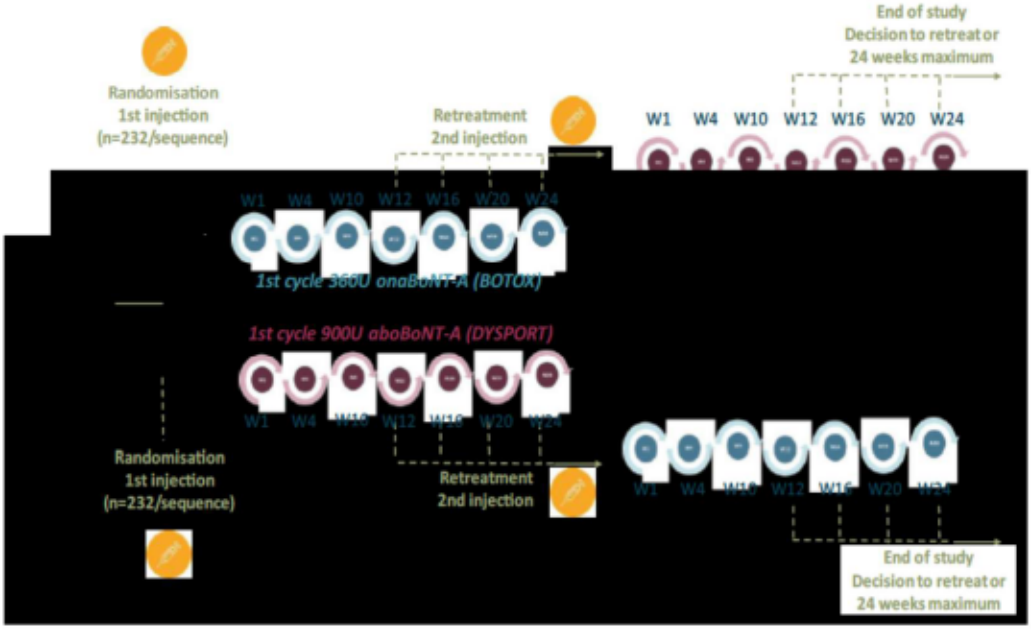
A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Assessment (SoA) (see Section 1.3 of protocol).

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 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.

Figure 1 Study Schema



AboBoNT-A = abobotulinumtoxinA; onaBoNT-A = onabotulinumtoxinA; U = units; W = week.

2.3 Sample Size Determination and Power

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.

A blinded sample size reassessment was performed when at least 100 participants had completed the Week 12 visit of Cycle 2 (see Section 3.2) leading to the new figures below.

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%.

Based on statistical hypotheses associated with the primary study objective and the primary safety endpoint (see Section 2.1), 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.

In total, 563 participants were screened to give 464 eligible participants 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) was performed.

2.4 Randomisation and Blinding (if applicable)

The randomisation and the intervention number(s) assignation at dispensation, will be managed by Interactive Web Response System/ Interactive Voice Response System (IWRS/IVRS).

CCI [redacted]

The study interventions aboBoNT-A and onaBoNT-A will be reconstituted and prepared in identical ready-to-administer syringes with identical volumes of diluent, therefore, they 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.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 1.3 from the protocol.

2.6 Change from Statistical Section of the Protocol

There are no changes compared to analyses described in the protocol apart from additions of sensitivity analysis 3 and supplementary analysis 2 and 3.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent DMC will be used in this study.

3.2 Interim Analysis / Primary Analysis

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

The reassessment procedure was performed after at least 100 participants had 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. Subsequently, the nuisance parameter was updated from 20% to 22% in this version of SAP.

The interim analysis was performed on clean data (60% source data verification (SDV)).

Overall summary of TEAE and summary of dropouts were also provided.

3.3 Final Analysis

Planned analyses will be done when all participants complete study and after database lock.

4 ANALYSIS SETS

Screened Set

The screened set will contain all participants who signed an informed consent for this study.

Randomised Set

The randomised set will contain all participants who were randomised to an intervention sequence. 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 treatment.

Full Analysis Set (FAS)

The FAS will contain all participants from the randomised set who received at least one 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.

The ITT principle is preserved, despite the exclusion of participants randomised who did not take any study medication, because the decision of whether or not to begin the treatment could not be influenced by knowledge of the assigned treatment as the study medication is blinded.

For efficacy analyses on the FAS, participants will be classified according to allocated sequence.

Safety Set (SS)

The SS will contain all participants from the randomised set who received at least one 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.

For safety analyses on the SS, participants will be classified according to the treatment or sequence they actually received.

However, for primary and secondary safety endpoints, if participants received the same treatment in both cycles, those participants will be excluded from the analyses on the SS.

Per Protocol Set for Efficacy (PPS-Efficacy)

The PPS-Efficacy will contain all participants from the FAS who completed the 12-week period for both cycles and who did not experience any major protocol deviations that may interfere with efficacy evaluation. Please refer to section 5.3 for details regarding the management of deviations.

Per Protocol Set for Safety (PPS-Safety)

The PPS-Safety will contain all participants from the SS who received 1 dose of aboBoNT-A and 1 dose of onaBoNT-A and who completed at least 11 weeks in the 12-week period for both cycles without any major protocol deviation that may interfere with safety evaluation. Participants who did not complete at least 11 weeks in Cycle 2 but had an adverse event after the second injection and before withdrawal will also be included in the PPS-Safety. Please refer to section 5.3 for details regarding the management of deviations.

Protocol deviations

Protocol deviations will be described and their impact on inclusion in each analysis population will be assessed (see section 5.3). The final list of protocol deviations impacting the safety and efficacy populations will be reviewed prior to database lock. After database lock and unblinding, deviations about treatment mis-dispensation will be re-assessed. If the actual treatment still matches the planned treatment, these deviations will not lead to exclusion of the participant from the PPS-Safety or PPS-Efficacy.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 7.

The service provider Parexel will perform the statistical analysis of the efficacy and safety data.

5.1 General Considerations

All statistical analyses will be performed using the Statistical Analysis System® software version 9.4 or a later version in a secure and validated environment.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

Depending on the type of data, the summary tables will be presented as follows:

- For disposition and baseline data: by sequence and overall.
- For demographic: by sequence and overall, and by treatment and overall.
- For prior medications/non-drug therapies or procedures and for adverse events occurring both prior to treatment and emergent while on treatment: by sequence and overall.
- For concomitant medications/non-drug therapies or procedures: by treatment.
- For extent of exposure, by treatment and cycle.
- For primary safety endpoint: by treatment, and also by cycle (overall and by treatment).
- For efficacy: by treatment.
- For adverse events (prior and emergent): overall presentation by sequence and cycle, AEs by SOC and PT by sequence.
- For treatment emergent adverse events: by treatment.
- For other safety endpoints: by treatment.
- For exploratory endpoints: by sequence and cycle, and by treatment.

5.1.1.2 Presentation of Treatment Group and Treatment Sequence

Tables, Figures and Listings (TFLs) will be displayed using the following treatment group and treatment sequence labels, in the order presented:

Table 2: Treatment group and treatment sequence labels

Treatment Group	**Treatment Group Short Label**
aboBoNT-A (900 Units)	ABO
onaBoNT-A (360 Units)	ONA
Treatment Sequence	**Treatment Sequence Short Label**
aboBoNT-A (900 Units) → onaBoNT-A (360 Units)	ABO - ONA
onaBoNT-A (360 Units) → aboBoNT-A (900 Units)	ONA - ABO

5.1.1.3 Presentation of Cycles and Visits / Timepoints

The study comprises 2 cycles, each cycle can last between 12 weeks and 24 weeks, depending on the time to retreatment.

Cycle 1 covers the period between first injection and second injection or EOS/EW if the participant did not receive the second injection. Cycle 2 covers the period between second injection and EOS/EW.

Summaries by visit will be presented using visit number as collected in the Electronic Case Report Form (eCRF).

Visits in the TFLs will be presented as follows and in the following order:

Table 3: Visits of the study

Long Visit Name	Short Name
Screening (Visit 1) [a]	Scr [a]
Cycle 1- Baseline (Visit 2) [a]	Cycle 1 - Baseline [a]
Cycle 1 - Week 1 (Visit 3)	Cycle 1 - Week 1
Cycle 1 - Week 4 (Visit 4)	Cycle 1 - Week 4
Cycle 1 - Week 10 (Visit 5)	Cycle 1 - Week 10
Cycle 1 - Week 12 (Visit 6) or Cycle 2 – Day 1 (Visit 6) [b]	Cycle 1 - Week 12 or Cycle 2 - D1 [b]
Cycle 1 - Week 16 (Visit 7) or Cycle 2 – Day 1 (Visit 7) [b]	Cycle 1 - Week 16 or Cycle 2 - D1 [b]
Cycle 1 - Week 20 (Visit 8) or Cycle 2 – Day 1 (Visit 8) [b]	Cycle 1 - Week 20 or Cycle 2 - D1 [b]
Cycle 1 - Week 24 (Visit 9) or Cycle 2 – Day 1 (Visit 9) [b]	Cycle 1 -Week 24 or Cycle 2 - D1 [b]
Cycle 2 - Week 1 (Visit 10)	Cycle 2 - Week 1
Cycle 2 - Week 4 (Visit 11)	Cycle 2 - Week 4
Cycle 2 - Week 10 (Visit 12)	Cycle 2 - Week 10
Cycle 2 - Week 12 (Visit 13)	Cycle 2 - Week 12
Cycle 2 - Week 16 (Visit 14)	Cycle 2 - Week 16
Cycle 2 - Week 20 (Visit 15)	Cycle 2 - Week 20
Cycle 2 - Week 24 (Visit 16)	Cycle 2 - Week 24

[a] In exceptional cases, Visit 1 and Visit 2 will be combined on the same day (all screening and baseline assessments being completed before injection), this visit will be indicated as Cycle 1- Day 1.

[b] If the retreatment criteria (see Section 6.5.1 of protocol) are not met at Week 12, then Week 16, Week 20 and Week 24 visits of each cycle will take place until the retreatment criteria are met. When the retreatment criteria are met and period 2 injection occurred, the visit will be named as Cycle 2 – Day 1 and following visits will belong to Cycle 2.

For tables presented by Treatment, the text "Cycle 1-" or "Cycle 2-" will be omitted, only Week X will be presented.

In QOL tables, Cycle X - End of Cycle will be presented, as QOL is assessed only at the last visit of each cycle.

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is at least one category missing for at least one treatment group. Except otherwise specified, participants with missing data will not be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), first quartile, median, third quartile, minimum and maximum.

Two-sided 95% CI for the mean and for proportions will be reported for demographic and baseline characteristics, exposure, compliance, quality of life and vital signs.

Two-sided 95% CI for the median will be reported for treatment exposure, study duration, time since event leading to spasticity and time since most recent injection for ULS. See section 5.7.1 for general considerations for the primary and secondary efficacy endpoints.

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

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to first Investigational Medicinal Product (IMP) administration. The second baseline measurement corresponding to the end of the first cycle will not be considered in the analysis.

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first IMP administration.

The day of the first IMP administration will be Day 1 (Baseline). Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.

- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the imputations described in appendix A2.

There will be also a reference start date for Cycle 2, which is the date of the injection in Cycle 2. The day will be calculated within each cycle and displayed in the adverse event listings.

5.2 Randomisation, Disposition and Analysis Sets

Mis-Stratification

With stratified randomisation, participants with incorrectly determined strata can lead to a randomisation error, which does not implement the desired balance of strata among treatment sequence. In such a case the analysis should take into account the corrected strata but preserve

the initial/actual randomisation, even if this may lead to a change of the planned size of the strata.

The approach is used for both, efficacy, and safety analyses.

Following disposition summaries and listings will be provided:

- Summary table with the number and percentage of participants screened, screen failed, reason for screen failures, randomised, treated in cycle 1, treated in both cycles-on the screened set,
- Summary table with the number and percentages of randomised participants per country and site on the randomised set,
- Summary table with the number and percentage of participants who completed or did not complete Cycle 1 and Cycle 2 and who discontinued the study with associated reasons, treatments and timepoints on the randomised set,
- Summary table with the number and percentage of participants per cycle and visit on the randomised set,
- Summary table with the number and percentage of participants with at least one visit impacted by the pandemic, overall and for each cycle, the number of visits impacted by the pandemic, overall and for each cycle together with the impacts and the reasons on the randomised set,
- Summary table on duration of participant participation in the study (in weeks),
- Listing of screen failure participants,
- Listing of randomisation details,
- Listing of dates of visit including duration of participant participation for the randomised participants,
- Listing of withdrawn participants on the randomised set.

A participant has completed Cycle 1 if he meets any of these categories:

- Participant is re-injected at Cycle 2
- Participant reached Week 24 assessment and re-treatment criteria was not met
- Participant reached at least Week 12 assessment and re-treatment criteria was met at Week 10, 12, 16, 20 or 24

A participant has completed Cycle 2 if he has completed Cycle 1 and meets any of these categories:

- Participant reached Week 24 assessment and re-treatment criteria was not met
- Participant reached at least Week 12 assessment and re-treatment criteria was met at Week 10, 12, 16, 20 or 24

Duration of participant participation will be derived as follows:

Duration (weeks) = (last study visit - date of informed consent +1) / 7

Following summaries and listings will be provided on the randomised set:

- Listing of participants not meeting at least one inclusion criterion,
- Listing of participants fulfilling at least one exclusion criterion,

- Summary of the number and percentage of participants in each analysis set, by sequence on the randomised set, by treatment on the safety set and by treatment on the FAS with reasons for exclusion from each analysis set,
- Summary of the number and percentage of participants in each analysis set by sequence and by country based on all randomised participants,
- Listing including flag for each analysis set and reason for exclusion from each set.

5.3 Protocol Deviations

An exhaustive list of major protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from the PP-Safety set and the PP-efficacy set is defined in a Protocol Deviation Specification form. Status of protocol deviations (Major, minor) and assignment to analysis sets will be confirmed before unblinding of the study, finalised during the blind data review and documented in a separate document 261930_Protocol_Deviations_2023xxxx_v1.0.xls. After unblinding, any deviation with potential unblinding observed during the study or found after unblinding will be added to the other deviations.

The following protocol deviation summaries and listings will be provided on the randomised set:

Number and percentage of participants with major protocol deviations by deviation category (see DV section of Standard Study Data Tabulation Model (SDTM) user guide).

- A table of number and percentage of participants with major protocol deviations by deviation category by sequence,
- A table of number and percentage of participants with minor protocol deviations by deviation category by sequence,
- A listing of major protocol deviations including exclusion from analysis sets.
- A listing of minor protocol deviations

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries and listings will be provided by sequence for the randomised set, overall for the PPS-Safety and by treatment on the Safety set in case there are more than 10% of difference between the PPS-Safety and the Safety set. No statistical comparison between treatment sequence will be performed and only 95% confidence intervals (CIs) of the within sequence will be reported.

Following summaries will be provided on:

- Demographic variables (Sex, age, race, ethnicity, refer to appendix A5 for EudraCT age categories),
- Disease characteristics (diagnosis, primary aetiology of spasticity, time since event leading to spasticity, pattern of upper limb paresis, affected or not by lower limb spasticity).
- Prior BoNT-A therapy (first administration for ULS, overall number of injection cycles between first ever injection and most recent injection in categories (<5, 5-10, 11-20 or >20 cycles), time since most recent injection for ULS, BoNT-A preparation for ULS injected, total dose for ULS, BoNT-A for other indication(s) than ULS, with type of indication and total dose for other indications classified by brand)

Age will be derived from year of birth using the following formulae:

Age (years) = Year at Screening - Year of Birth

CI of categorical variables will be derived using Wald method.

Diagnosis of neurological condition leading to spasticity and primary aetiology of spasticity will be amended for some eCRF entries 'Other'. Sponsor will provide a file to reclassify the 'Other' terms. In tables, the reclassification, if provided will be used, whereas in listings, both 'Other' and the reclassification will be presented.

Time since event leading to spasticity will be derived using the following formulae:

Time (years) = (Screening date - Onset date of event leading to spasticity) / 365.25

In case of partial date of event, if only day is missing, the first day of the month will be imputed, if day and month are missing, the 1st January will be imputed.

Time since most recent injection for ULS will be derived using the following formulae:

Time (days) = Screening date - date of most recent injection

Listings will also be provided for all the summaries listed above.

5.5 Medical history, non-drug therapies, medications and surgical procedures

All summaries of Significant medical and surgical history (excluding spasticity), non-drug therapies, medications and surgical procedures will be provided on the randomised set.

Medical and surgical history and surgical procedures will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Medications for other indications than spasticity will be coded using the latest version of World Health Organization-Drug dictionary in effect at the time of database lock.

5.5.1 Significant Medical and Surgical History (Excluding Spasticity)

Summary tables on significant medical or surgical history (excluding spasticity) will be summarized by sequence and overall, by system organ class (SOC) and preferred term (PT).

5.5.2 Non-Drug Therapies for Spasticity and Spasticity-Related Pain

Summaries of prior/concomitant non-drug therapies will be presented as entered in eCRF.

- Prior non-drug therapies (at least one therapy, type of therapy, place of therapy, total number of hours per session, total number of sessions per week and total number of weeks) by sequence and overall on the randomised set,
- Concomitant non-drug therapies, by treatment group on the safety set.

Listings will be provided for the summaries listed above. The listing reporting concomitant non-drug therapies should include a flag indicating the study treatment that was concomitant with the therapy (ONA, ABO, or ABO-ONA or ONA-ABO).

5.5.3 Medications for Spasticity and Spasticity-Related Pain

Summaries of prior/concomitant medications for spasticity and spasticity-related pain will be presented as entered in eCRF.

- Prior medications (trade name, baclofen administered, indication, duration of treatment) by sequence and overall on the randomised set,
- Concomitant medications (trade name, baclofen administered or not, indication, started or not prior to study entry, continuing or not at end of study) by treatment on the safety set.

Listings will be provided for the summaries listed above. The listing reporting concomitant medications should include a flag indicating the study treatment that was concomitant with the medication (ONA, ABO, or ABO-ONA or ONA-ABO).

5.5.4 Medications for Other Indications

Medication start and stop dates will be compared to the date of the first injection of cycle 1 and second injection in cycle 2 to allow classification as either:

- Prior to Cycle 1
- Concomitant to Cycle 1 only
- Concomitant to Cycle 1 and Cycle 2
- Concomitant to Cycle 2 only

Table 4: Definitions of prior/concomitant

Prior (P)	Start date and stop date are prior to the date of the Cycle 1 injection (or prior to randomisation date if the participant is not treated).
Concomitant (C1)	Stop date after the date of Cycle 1 injection and before the date of the Cycle 2 injection (or after randomisation date if the participant is not treated). Or ongoing if there is no injection 2.
Concomitant (C12)	Start date before the date of the Cycle 1 injection or before the date of Cycle 2 injection and stop date on or after the date of the Cycle 2 injection or ongoing after Cycle 2 injection.
Concomitant (C2)	Start date on or after the date of the Cycle 2 injection.

See detailed rules in appendix A2 for classification of prior and concomitant medication in case of partial/missing date.

Summary tables on prior medications will include "P" only and will be summarized by sequence and overall.

Summary tables on concomitant medications will include "C" combinations (C1, C12 and C2) and will be summarized by treatment.

The therapeutic class will correspond to the second level of ATC code, that is, corresponding to the first 3 figures.

Following summaries, presenting count and percentages of participants will be provided on the randomised set:

- Prior medications (P) by ATC class and PN (ATC level 2), by sequence and overall,
- Concomitant medications (C1, C12, C2) by ATC class and PN (ATC level 2), by treatment,

Listings will be provided for all the summaries listed above. The listings reporting concomitant medications should include a flag indicating the study treatment that was concomitant with the medication (ONA, ABO, or ABO-ONA or ONA-ABO).

5.5.5 Concomitant Surgical Procedures

Summaries of concomitant surgical procedures will be presented

- by SOC and PT, by treatment

A listing will be provided. The listing should include a flag indicating the study treatment that was concomitant with the surgery (ONA or ABO).

5.6 Compliance

Compliance will be provided on the safety set and PPS-Safety.

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 muscles for injection 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 injection volume for each muscle and the number of injection sites are shown in table 5 below. 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

CCI

Syringe Label	Muscle Injected	Volume/ Muscle (mL)	Injection Sites	AboBoNT-A Dose (U) Total 900 U	OnaBoNT-A Dose (U) Total 360 U
	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 compliance will be derived for each treatment (or for each cycle), by muscle and overall, as follows:

Compliance for each of the Flexor muscles (%) = Volume administered in mL/ 0.5 × 100

Compliance for Biceps (%) = Volume administered in mL/ 1.6 × 100

Overall compliance (%) = Total volume administered in mL / 3.6 × 100

Following summary and listing will be provided on the safety set and PPS-Safety:

- Descriptive statistics of compliance at each injection visit by treatment including volume and dose (derived from volume) administered by muscle and overall and for the overall compliance the number and percentage of participants by class of compliance (<80, [80, 120], >120).
- A listing of treatment compliance.

Participants treated with the same treatment in each cycle (sequence ABO–ABO or ONA–ONA) will be excluded from PPS-Safety by definition. However, for summaries on the safety set, these participants will also be excluded. They will be included in listings.

The dose will be derived as follows and presented in the listings:

ABO dose (U)= Volume administered in mL * 250

ONA dose (U)= Volume administered in mL * 100

5.7 Safety primary endpoint analysis and efficacy secondary endpoints analysis

5.7.1 General Considerations

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 will be confirmed in the Safety Set for a robust interpretation. In these summaries on the safety set, participants treated with the same treatment in each cycle ABO-ABO or ONA-ONA will be excluded. They will be included in listings.

A listing of all TEAEs will be provided (see listing detail conventions in Appendix A4).

The FAS set will be used for efficacy analyses unless explicitly stated differently. Analyses in the PPS-Efficacy will be performed additionally for key secondary endpoints.

A listing of all efficacy data (raw and derived) will be provided (see listing detail conventions in Appendix A4). Descriptive statistics will be provided for all endpoints.

5.7.1.1 Significance Testing and Estimations

For primary safety endpoint, all statistical tests will be one-sided at the 10% level of significance. For key secondary efficacy endpoints, multiplicity adjustment to control the overall type I error rate at one-sided 0.1 is done with Bonferroni method (see Section 5.7.1.3).

Two-sided 80% CI (the upper limit corresponds to the one-sided 90% CI) will be reported for the primary endpoint of estimated difference in TEAE rate and for the mean and median for secondary efficacy endpoints duration of response, MAS, DAS and PGA.

For other exploratory endpoints, all statistical tests will also be one-sided at the 10% level of significance using two-sided 80% CI.

5.7.1.2 Handling of Dropouts and missing data

Diligent attempts will be made to limit the amount of missing data and to follow-up all randomised participants to collect the primary and secondary efficacy endpoints for the statistical analysis.

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

5.7.1.3 Statistical/analytical issues

Adjustments for Covariates

The randomisation is stratified by BoNT-A status (BoNT-A previously treated for ULS or naïve). But the stratification factor and other factors such as age, gender or country are assumed not to have an impact or contribute to the sequence effect and therefore will not be accounted for in this crossover analysis for the analysis of the non-inferiority of aboBoNT-A versus onaBoNT-A.

Interim Analyses and Data Monitoring

Please refer to section 3.

Multicentre Studies

This is a multicentre study conducted in 3 countries: France, Canada and US and 90 centres.

Multiple Comparisons/Multiplicity

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 α/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 α/3 level), then at Week 10 only if the test at Week 12 is significant (same alpha levels as for tests at Week 12).

5.7.2 Analysis of Primary Safety Endpoint

5.7.2.1 Endpoint, Treatment Effect and Estimand Definition

Definition of TEAE:

All adverse events (AEs) recorded in the eCRF will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of the database lock. They will be classified by SOC and PT.

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/EW if the participant did not receive the second injection. Cycle 2 covers the period between second injection and EOS/EW.

Complete AE start date	
YYYY-MM-DD < YYYY-MM-DD of [First IMP admin.]	Not TEAE
YYYY-MM-DD >= YYYY-MM-DD of [First IMP admin.] and < YYYY-MM-DD of [Second IMP admin.]	TEAE cycle 1
YYYY-MM-DD >= YYYY-MM-DD of [First IMP admin.] and <= EOS/EW date if no Second IMP admin.	TEAE cycle 1
YYYY-MM-DD >= YYYY-MM-DD of [Second IMP admin.] and <= EOS/EW date.	TEAE cycle 2

The rules in case of partial/missing start dates can be found in appendix A3. In the case where it is not possible to define an AE as treatment emergent or not in any cycle, the AE will be classified as treatment emergent in cycle 1.

Definition of primary endpoint:

The primary safety endpoint is based on the TEAE incidence rate from injection to Week 12, i.e. number of participants with TEAEs that occurred during each cycle from injection to 12 weeks after injection (until 84 days after injection or until the day prior to next injection day or until EOS/EW day whichever occurs first).

Estimands:

Estimand framework is addressed in this study only for the analysis of the primary endpoint.

CCI [redacted]

To assess the primary objective on the PPS-Safety, the following primary estimand will be defined by the following key attributes:

- Population of interest: participants with upper limb spasticity of any aetiology (US/France) or post-stroke ULS (Canada) as defined by the listed Inclusion/Exclusion criteria in Section 5.1 and 5.2 of the protocol
- Variable/Endpoint of interest: TEAE incidence rate from injection to Week 12 in each cycle
- Key Intercurrent event (ICE) / Intercurrent Event Strategy (ICES):
  - Prohibited concomitant medication **Treatment Policy Strategy**: all TEAEs meeting above start date conditions will be included in the analysis
  - Visits delayed or not performed, or AEs due to COVID-19: **Treatment Policy Strategy**: all TEAEs meeting above start date conditions will be included in the analysis
  - No evidence of safety information and participant attended at least Week 12 of cycle 2 after injection visit: **Treatment Policy Strategy:** participant will be assumed to have not experienced any TEAE.
  - No evidence of safety information and participant attended at least Week 12 of any cycle after injection visit **Treatment Policy Strategy:** participant will be assumed to have not experienced any TEAE for the concerned cycle.
  - No evidence of safety information and participant did not attend any visit of the cycle after first injection visit **Treatment Policy Strategy:** participant will be excluded from the analysis.
  - No evidence of safety information and participant did not attend any visit of the cycle after second injection visit **Treatment Policy Strategy:** the second cycle of the considered participant will be excluded from the analysis. In any case, the participant will be excluded from the PPS-Safety.

Of note: assessment of retreatment criteria completed is evidence of safety information.

- Treatment regimen:

  Sequence 1: aboBoNT-A (900 Units) → onaBoNT-A (360 Units)

  Sequence 2: onaBoNT-A (360 Units) → aboBoNT-A (900 Units)

  and potential intake of permitted concomitant medications (see list in protocol section 6.3)
- Population-level summary of the treatment effect of interest: the difference in TEAE rate of participants, between aboBoNT-A (900 Units) group and the onaBoNT-A (360 Units) group.

5.7.2.2 Primary Analysis

Analysis will be based on the primary estimand described in Section 5.7.2.1.

A generalised linear mixed model approach based on binomial distribution with identity link 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 of the interaction in the full model 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, if the associated p-value of the interaction in the full model is less or equal to 0.10, the results will also be presented by cycle.

The SAS code can be found in section 8, appendix A1.

Testing non-inferiority of aboBoNT-A over onaBoNT-A in treatment of upper limb spasticity by rejecting the null hypothesis described below at one-sided significance level α=0.1:

H0: The difference between aboBoNT-A and onaBoNT-A is more than 5%. aboBoNT-A has more than 5% TEAEs as compared to onaBoNT-A.

The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 80% CI (showing the upper limit which corresponds to the one-sided 90% CI) will be provided.

If the upper bound of this CI is lower than 5% in the PPS-Safety analyses, the non-inferiority of aboBoNT-A versus onaBoNT-A will be demonstrated.

A listing will be provided including all participants who had a cycle where no safety information was recorded, either the participant 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). For these participants, the listing will provide the reason and timing for study discontinuation for discontinued participants and any AE that may have occurred before the cycle.

Following summaries will be provided on the PPS-safety and listings on the safety set:

- Overall summary of treatment-emergent adverse events from injection to Week 12 by treatment (PPS-safety)
- Overall summary of treatment-emergent adverse events from injection to Week 12 by cycle (PPS-safety)
- Analysis of rate of TEAEs from injection to Week 12 (PPS-safety)
- A summary of intercurrent events from injection to Week 12 (Safety Set excluding ABO-ABO and ONA-ONA participants)
- A forest plot of difference of rates of TEAEs (PPS-safety)
- A plot with the 10 most frequent TEAEs (Preferred Term) from injection to Week 12 (PPS-safety)
- A listing of treatment emergent adverse events from injection to Week 12 (Safety Set)
- A listing of participants with no safety information recorded during a cycle (Safety Set)
- A listing of intercurrent events (Safety Set)

5.7.2.3 Sensitivity Analyses

Sensitivity analysis 1

A sensitivity analysis will be performed using the Safety set (excluding ABO-ABO and ONA-ONA participants) as part of robustness analyses.

To assess the primary objective on the Safety set, the following primary estimand will be defined by the following key attributes:

CCI [redacted]

- Population of interest: participants with upper limb spasticity of any aetiology (US/France) or post-stroke ULS (Canada) as defined by the listed Inclusion/Exclusion criteria in Section 5.1 and 5.2 of the protocol
- Variable/Endpoint of interest: TEAE incidence rate from injection to Week 12 in each cycle
- Key Intercurrent event (ICE) / Intercurrent Event Strategy (ICES):
  - Treatment discontinuation due to AE non-related: **Treatment Policy Strategy**: all TEAEs from Cycle 1 meeting above start date conditions will be included in the analysis
  - Treatment discontinuation due to AE related: **Treatment Policy Strategy**: all TEAEs from Cycle 1 meeting above start date conditions will be included in the analysis
  - Treatment discontinuation for other reason than AE: **Treatment Policy Strategy**: all TEAEs from Cycle 1 meeting above start date conditions will be included in the analysis
  - Prohibited concomitant medication **Treatment Policy Strategy**: all TEAEs meeting above start date conditions will be included in the analysis
  - Visits delayed or not performed, or AEs due to COVID-19: **Treatment Policy Strategy**: all TEAEs meeting above start date conditions will be included in the analysis
  - No evidence of safety information and participant attended at least Week 12 of cycle 2 after injection visit: **Treatment Policy Strategy:** participant will be assumed to have not experienced any TEAE.
  - No evidence of safety information and participant attended at least Week 12 of any cycle after injection visit **Treatment Policy Strategy:** participant will be assumed to have not experienced any TEAE for the concerned cycle.
  - No evidence of safety information and participant did not attend any visit of the cycle after first injection visit **Treatment Policy Strategy:** participant will be excluded from the analysis.
  - No evidence of safety information and participant did not attend any visit of the cycle after second injection visit **Treatment Policy Strategy:** the second cycle of the considered participant will be excluded from the analysis.

Of note: assessment of retreatment criteria completed is evidence of safety information.

- Treatment regimen:

  Sequence 1: aboBoNT-A (900 Units) → onaBoNT-A (360 Units)

  Sequence 2: onaBoNT-A (360 Units) → aboBoNT-A (900 Units)

  and potential intake of permitted concomitant medications (see list in protocol section 6.3)
- Population-level summary of the treatment effect of interest: the difference in TEAE rate of participants, between aboBoNT-A (900 Units) group and the onaBoNT-A (360 Units) group.

The analysis will be done as in the main analysis with a generalised linear mixed model.

The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 80% CI (showing the upper limit which corresponds to the one-sided 90% CI) will be provided.

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 intercurrent event is defined for these participants and no specific strategy is planned to take into account such cases.

Following summaries will be provided on the safety set (excluding ABO-ABO and ONA-ONA participants):

- Overall summary of treatment-emergent adverse events from injection to Week 12 by treatment (Safety Set)
- Overall summary of treatment-emergent adverse events from injection to Week 12 by cycle (Safety Set)
- Analysis of rate of TEAEs from injection to Week 12 (Safety Set)
- A forest plot of difference of rates of TEAEs (Safety Set)

Sensitivity analysis 2

On the PPS-Safety, the estimated overall difference and the estimated SD of the paired differences of TEAE rate (aboBoNTA – onaBoNT-A) for each participant within each sequence will be calculated using Wald test.

The associated two-sided 80% CI (showing the upper limit which corresponds to the one-sided 90% CI) will be derived.

A forest plot of paired difference of rates of TEAEs will also be provided.

5.7.2.4 Supplementary Analyses

Supplementary analysis 1

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.

This analysis will be performed on the PPS-Safety with the same estimands as in the primary analysis.

The estimated difference in TEAE rate (aboBoNT-A – onaBoNT-A) and associated two-sided 80% CI (showing the upper limit which corresponds to the one-sided 90% CI) will be provided.

Supplementary analysis 2

On the PPS-Safety, the number of TEAEs will be compared using a generalized linear model with Poisson distribution and identity link, treatment and cycle as fixed effects, treatment by cycle interaction and participant as repeated factor. The treatment by cycle interaction (carryover effect) will be tested: if the associated p-value of the interaction in the full model 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, if the associated p-value of the interaction in the full model

is less or equal to 0.10, the interaction will be kept in the final model and the results will also be presented by cycle.

This will be superiority testing and the associated two-sided 80% CI will also be derived.

If the upper bound of this CI is lower than 0, the superiority of aboBoNT-A versus onaBoNT-A will be demonstrated.

The SAS code can be found in sectionA1, appendix A1.

Supplementary analysis 3

A supplementary analysis will be performed on the Safety set (excluding ABO-ABO and ONA-ONA participants) to analyse the incidence rate of related TEAEs.

This will be superiority testing. The same analysis as the sensitivity 1 of the primary endpoint will be performed.

If the upper bound of this CI is lower than 0%, the superiority of aboBoNT-A versus onaBoNT-A will be demonstrated.

A related TEAE 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 related in case of missing causality assessment.

Supplementary analysis 4

A supplementary analysis will be performed on the Safety set (excluding ABO-ABO and ONA-ONA participants) to analyse the AESI incidence rate.

This will be superiority testing. The same analysis as the sensitivity 1 of the primary endpoint will be performed.

If the upper bound of this CI is lower than 0, the superiority of aboBoNT-A versus onaBoNT-A will be demonstrated.

5.7.2.5 Subgroup Analysis

Descriptive statistics will be provided for the primary endpoint within each category of the following variables if sample size allows (at least 30 participants in each category):

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

5.7.3 Analysis of Key Secondary Efficacy Endpoint: Duration of response

5.7.3.1 Endpoint and Treatment Effect

Estimand framework is not addressed in this study for secondary endpoints.

The duration of response (DOR) is 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. If the reason of withdrawal is lost to follow up, the last visit date will be used instead of the date of withdrawal.

- 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/EW if the participant completes the study or discontinues from the study after Cycle 2 injection without meeting retreatment criteria. If the reason of withdrawal is lost to follow up, the last visit date will be used instead of the date of withdrawal.

Retreatment criteria will be captured both in the eCRF at each visit (from Week 10 visit) and in logs in IWRS.

In case of inconsistencies between eCRF and IWRS, the status in eCRF will be considered.

DOR will be calculated for each cycle as:

DOR (days) = date of retreatment criteria met or withdrawal date or completion date – date of injection+1

DOR will be presented by treatment in summary tables.

5.7.3.2 Main Secondary Analysis

On the FAS, the duration of response will be described and compared between treatment groups using a mixed effects model with treatment, cycle and treatment by cycle interaction as fixed effects and participant as random effect. The treatment by cycle interaction (carryover effect) will be tested: if the associated p-value of the interaction in the full model 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, if the associated p-value of the interaction in the full model is less or equal to 0.10, the interaction will be kept in the final model and the results will also be presented by cycle.

The within-participant variance covariance matrix will be assumed to be unstructured.

The SAS code can be found in section 8, appendix A1.

The p-value associated with cycle and treatment effects will be provided, and the estimate of the difference between treatment groups and two-sided 80% CI will be provided.

This will be superiority testing. If the lower bound of this CI is greater than 0, the superiority of aboBoNT-A versus onaBoNT-A will be demonstrated.

In addition, a summary table presenting count and percentages of participants meeting retreatment criteria, participants retreated from 12 weeks (Week 12, Week 16, Week 20, Week 24) and participants not meeting retreatment criteria in each cycle will be provided on the FAS.

A bar chart of duration of response with mean and CI will also be presented by treatment and cycle and by treatment overall.

5.7.3.3 Sensitivity Analysis 1

The same analysis as the main secondary analysis will be performed using the PPS-Efficacy as part of robustness analyses.

5.7.3.4 Sensitivity Analysis 2

Sensitivity analyses will be performed in participants having available values for both treatments, i.e. participants having an injection in cycle 1 and an injection in cycle 2.

A Wilcoxon signed-rank test will be performed to test the difference in DOR between treatment groups at one-sided 10% significant level.

The median difference and associated two-sided 80% CI will be provided in a summary table.

5.7.3.5 Subgroup Analysis

Descriptive statistics will be provided for key secondary endpoint "Duration of response" within each category of the following variables if sample size allows (at least 30 participants in each category):

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

5.7.4 Analysis of Other Key Secondary Efficacy Endpoints

Estimand framework is not addressed in this study for secondary endpoints.

Modified Asworth Scale (MAS)

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.

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.

The main assessment of MAS will be based on the primary target muscle group (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.

MAS score for the PTMG and MAS score of all joints 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.

MAS total score will be described quantitatively at each timepoint (baseline, Week 1, 4, 10, 12 ± 16, 20, 24) and at the end of the cycle.

Change from baseline of MAS score for the PTMG, MAS score of all joints and MAS total score will be described quantitatively.

MAS (PTMG) numerical scores at Week 12 will be compared between treatment groups in the same way as the DOR using a mixed effects model but at the α/3 (0.1/3) level (one-sided) (see Multiple Comparisons/Multiplicity in section 5.7.1.3).

Uncorrected p-values and Bonferroni adjusted p-values will be presented.

If significant at Week 12, the comparison will be repeated at Week 10 with the same alpha level. If not significant at Week 12, Week 10 data will be presented but will not be considered as confirmatory.

Non-parametric sensitivity analysis will also be performed using a Wilcoxon Signed-Rank test to test the difference between treatment groups at same alpha level. Estimates from Hodges Lehmann and CI from Tukey will be provided (Hollander&Wolfe, 1999).

Disability Assessment Scale (DAS)

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

The DAS total score is calculated as the sum of the scores for all four domains analysed (hygiene, dressing, limb position and pain), ranging between 0 and 12 (each domain ranging from 0=No disability to 3=Severe disability).

DAS score for the PTT and DAS score of all domains 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.

DAS total score will be described quantitatively at each timepoint (baseline, Week 1, 4, 10, 12 ± 16, 20, 24) and the end of the cycle.

Change from baseline of DAS score for the PTT, DAS score of all domains and DAS total score will be described quantitatively.

DAS (PTT) scores at Week 12 will be compared between treatment groups in the same way as the DOR using a mixed effects model but at the α/3 (0.1/3) level (one-sided) (see Multiple Comparisons/Multiplicity in section 5.7.1.3).

Uncorrected p-values and Bonferroni adjusted p-values will be presented.

If significant at Week 12, the comparison will be repeated at Week 10 with the same alpha level. If not significant at Week 12, Week 10 data will be presented but will not be considered as confirmatory.

Non-parametric sensitivity analysis will also be performed using a Wilcoxon Signed-Rank test to test the difference between treatment groups at same alpha level.

Physician's global assessment (PGA)

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).

PGA score will also be categorized in 2 different ways as follows:

-Any improvement (+1: slightly improved, +2: improved, +3: much improved and +4: markedly improved)

-No change or worsening (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change).

and:

-Strong improvement (+3: much improved and +4: markedly improved)

-No strong improvement (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved)

PGA of treatment response and binary categories of PGA will be described qualitatively and quantitatively at each timepoint (Week 1, 4, 10, 12 ± 16, 20, 24) and at the end of the cycle.

PGA scores at Week 12 will be compared between treatment groups in the same way as the DOR using a mixed effects model but at the $\alpha/3$ (0.1/3) level (one-sided) (see Multiple Comparisons/Multiplicity in section 5.7.1.3).

Uncorrected p-values and Bonferroni adjusted p-values will be presented.

If significant at Week 12, the comparison will be repeated at Week 10 with the same alpha level. If not significant at Week 12, Week 10 data will be presented but will not be considered as confirmatory.

Non-parametric sensitivity analysis will also be performed using a Wilcoxon Signed-Rank test to test the difference between treatment groups at same alpha level.

5.7.5 Analysis of Exploratory Endpoints

5.7.5.1 SF-12

Participants will be asked to complete the SF-12 health survey at baseline, Week 4, Week 12 and at end of each cycle. 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.

PRO CoRE, a QualityMetric Scoring Software will be used to derive the SF-12 summary score.

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

Individual domains, PCS-12 score, and MCS-12 score will be descriptively summarized on the FAS by sequence and by treatment together with change from baseline.

Listing of the SF-12 V2 domains and components scores will be provided by sequence and cycle.

5.7.5.1 SQoL-6D

Participants will be asked to complete the SQoL-6D questionnaire at baseline, Week 4, Week 12 and at end of each cycle. 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.

The total score will be calculated if at least 50% of the items have been completed. The mean of the 6-dimension scores will be calculated and the total score ranging from 0 to 100 will be derived as follows, with a higher score indicating better QoL:

Total score = [(4-Mean)/4]*100

A frequency table will be produced on the FAS to summarize answers provided to each of the 6 dimensions of the SQoL-6D system at each scheduled visit by sequence and also by treatment. The total SQoL-6D score and change from baseline will also be summarized at each scheduled visit by sequence and also by treatment.

A by-participant listing of SQoL-6D will be provided.

5.8 Safety

5.8.1 General Consideration

All safety summaries and analyses will be based upon the Safety Set. All safety data will be included in participant data listings (see listing detail conventions in Appendix A4). There will be no statistical comparison between the treatment groups for safety data (other than safety data related to the primary endpoint).

5.8.2 Extent of exposure

The duration of exposure will be calculated as follows:

Duration of treatment cycle (in weeks)	○ For participants who are retreated at the end of the cycle: (date of retreatment) – (treatment injection date)/7. ○ For participants who are not retreated at the end of the cycle: ((last attended visit date of the treatment cycle) – (treatment injection date) + 1)/7.

The following extent of exposure summaries will be presented:

- Summary of the duration of exposure to treatment, by treatment group and cycle.
- Listing of exposure data.

In summary of extent of exposure, participants who received the same treatment in each cycle ABO-ABO or ONA-ONA will be excluded. They will be included in listings.

5.8.3 Adverse Events

All AEs recorded in the eCRF will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of the database lock and will be classified by SOC and PT.

AEs will be classified as Treatment-Emergent AEs (TEAEs) according to the rules described in section 5.7.2. The rules in case of partial/missing start dates can be found in appendix A2. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent in cycle 1.

A related TEAE 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 related in case of missing causality assessment.

The following summaries will be provided by sequence:

- An overview table summarizing the number and percentage of participants with at least one of the following AEs together with the corresponding number of events for each of these AE categories listed below:
  - any AE (overall and in each cycle),
  - any Serious Adverse Event (SAE) (overall and in each cycle),
- summary of the number and percentage of participants reporting an AE by sequence, SOC and PT

AE summaries will be ordered by decreasing frequency for SOC and PT within SOC in the sequence aboBoNT-A- onaBoNT and then similarly by decreasing frequency in the sequence onaBoNT-A- aboBoNT-A, and then alphabetically for SOC and PT within SOC.

In the summary of AEs by sequence, participants who received the same treatment in each cycle, ABO-ABO or ONA-ONA, will be excluded. They will be included in listings.

The following summaries will be provided by treatment. The tables will be duplicated: one table for the whole cycle duration and one table from injection to Week 12:

- An overview table summarizing the number and percentage of participants with at least one of the following AEs together with the corresponding number of events for each of these AE categories listed below:
  - any TEAE,
  - any mild, any moderate and any severe TEAE,
  - any non-treatment related TEAE, any treatment related TEAE,
  - TEAE leading to discontinuation from the study,
  - any treatment emergent SAE,
  - any treatment emergent adverse event of special interest (AESI)
  - any non-serious TEAE
- A summary of the number and percentage of participants reporting a TEAE by treatment group, SOC and PT,

- A summary of the 5 most common TEAEs by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a related TEAE by treatment group, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, intensity, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, causality, SOC and PT,
- A summary of the number and percentage of participants reporting a TEAE by treatment group, time to onset (<=28 days and >28 days), SOC and PT,
- A summary of the outcome of TEAEs,
- A summary of the action taken for TEAEs,
- A summary of non-serious TEAE by treatment group, SOC and PT.

AE summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in the aboBoNT-A group and then similarly by decreasing frequency in the onaBoNT-A group, and then alphabetically for SOC and PT within SOC.

AEs will be counted as follows:

- Participants with more than one AE within a cycle and within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a cycle and within a particular PT are counted only once for that PT;
- Participants reporting a TEAE more than once within a cycle and within that SOC/ PT but with different levels of seriousness, all the reported seriousness will be used in the corresponding seriousness summaries;
- Participants reporting a TEAE more than once within a cycle and within that SOC/ PT but with different intensities, all the reported intensities will be used in the corresponding intensity summaries;
- Participants reporting a TEAE more than once within a cycle and within that SOC/ PT but with different relationships, all the reported relationships will be used in the corresponding relationship summaries;
- If the intensity is missing for a TEAE, it will be considered as missing in the summary tables;
- If the causality is missing for a TEAE, it will be considered related in the summary tables;
- The non-serious TEAEs table should include a specific row “any non-serious TEAE above 5%;
- A TEAE is counted only in the cycle where it started (if there is a change in the seriousness or in the intensity after a BoNT-A injection, an additional AE should have been collected in the eCRF).

In addition, a listing with all AE data will be provided by sequence and treatment including non-TEAEs. Treatment-emergence status will be flagged in the listing.

Deaths, SAEs, and Other Significant AEs

Adverse events of special interest (AESIs) for abobotulinumtoxin A are Treatment Emergent Adverse Events (TEAEs) that suggest a possible remote spread of effect of the toxin or events suggestive of hypersensitivity like reactions.

- TEAEs due to possible remote spread of the effects of AbobotulinumtoxinA (Dysport®) will be identified using the list of MedDRA preferred terms (PTs) compatible with the mechanism of action of botulinum toxin A and based on Appendix-A of the 'FDA Draft Guidance for the Industry involved in developing botulin toxin drug product for Upper Facial Lines'.
- TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions. A list of MedDRA preferred terms, used to identify any potential AESI, is provided in Appendix A6.

All potential remote spread of toxin AESIs identified using the search strategy described above will be medically evaluated during the study, before the database lock and unblinding, by the sponsor to identify events which could possibly represent 'remote spread of effect of toxin' due to study treatment administration. Potential remote spread of toxin AESIs will be excluded if they are confounded by presence of alternative clinical aetiologies (medical history, concomitant medication or diagnosis which could account for the symptoms); if they are considered to be local effects instead of remote spread of toxin as judged by the site of injection; the time period between the last study treatment administration and event onset is not in accordance with the expected mechanism of action; or due to insufficient information/evidence to make an assessment.

In the TFLs, in addition to the table presenting AESIs of hypersensitivity, a table of pre-adjudicated potential remote spread of toxin events and a table of adjudicated potential remote spread of toxin events will be produced for transparency and traceability, but for all AE summary tables only the final adjudicated list of remote spread of toxin AESIs confirmed by the sponsor as "a possible remote spread event" will be included.

The following summaries will be provided by sequence:

- A summary of the number and percentage of participants reporting a SAE by SOC and PT

The following summaries will be provided by treatment. The tables will be duplicated: one table for the whole cycle duration and one table from injection to Week 12:

- A summary of the number and percentage of deaths (including SAEs with fatal outcome and deaths as PT), by treatment group (if numbers allow),
- A summary of the number and percentage of participants reporting a serious TEAE, by treatment group, SOC and PT,
- A summary of the number and percentage of participants with TEAEs leading to discontinuation of study treatment, by treatment group, SOC and PT (if numbers allow).

- A summary of AESIs of hypersensitivity with the number and percentage of participants and the number of occurrences presented by treatment group, primary SOC and PT.
- A summary of pre-adjudicated AESIs of potential remote spread of toxin events with the number and percentage of participants and the number of occurrences presented by treatment group, primary SOC and PT.
- A summary of adjudicated AESIs of potential remote spread of toxin events with the number and percentage of participants and the number of occurrences presented by treatment group, primary SOC and PT.

The following listings will be provided:

- A listing of all deaths that occurred during the study,
- A listing of all SAEs (including non treatment-emergent SAEs),
- A listing of all TEAEs leading to discontinuation of study treatment,
- A listing of participants having AESIs of hypersensitivity,
- A listing of participants having pre-adjudicated AESIs of potential remote spread of toxin events,
- A listing of participants having adjudicated AESIs of potential remote spread of toxin events.

5.8.4 Laboratory Data

Not applicable. Laboratory tests are performed but laboratory data will not be recorded in database nor analysed.

5.8.5 Vital Signs

Vital signs are collected on the day of first injection (Baseline) and at Week 12 (and Week 16, Week 20, Week 24 until the retreatment criteria are met) of each cycle and at EOS or early withdrawal visit.

The following summaries and listings will be provided:

- A summary of the actual and change from baseline in each vital sign parameter by treatment group and timepoint,
- A listing of vital sign data by sequence.

5.8.6 Physical Examination

Physical examination is performed on the day of first injection (Baseline) and at Week 12 (and Week 16, Week 20, Week 24 until the retreatment criteria are met) of each cycle and at EOS or early withdrawal visit.

The following summary and listings will be provided:

- A summary table of physical examination data by treatment group
- A listing of physical examination data,
- A listing with any participants with at least one physical examination abnormality.

6 DATA HANDLING

6.1 Visit window

No visit windows are needed for the analyses. There is a cut off of 84 days for the primary endpoint based on the TEAE incidence rate from injection to Week 12 (see section 5.7.2).

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

There will be no unscheduled visits. All listings will include retests if any.

Retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine vital signs values.

If a value requires a retest (for vital signs) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of likely values.

7 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6 (R2): Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to EMA or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Choice of a non-inferiority margin
- Clinical trials in small populations
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Multiplicity issues in clinical trials

Reference to FDA guidelines:

- Multiple Endpoints in Clinical Trials

Reference to SDTM User guide:

- SDTM Implementation Guide 3.2

Ipsen Global Style guide

- Liu JP, Hsueh HM, Hsieh E, Chen JJ. Tests for equivalence or non-inferiority for paired binary data. Stat Med. 2002 Jan 30;21(2):231-45. doi: 10.1002/sim.1012. PMID: 11782062.
- Jun-mo Nam (1987) Establishing Equivalence of Two Treatments and Sample Size Requirements in Matched-Pairs Design, Biometrics Vol. 53, No. 4 (Dec., 1997), pp. 1422-1430 (9 pages)

- Dongsun Cao (2011) Statistical Analysis of Adverse Events in Randomised Clinical Trials using SAS
- Hollander M., Wolfe DA (1999), Nonparametric statistical Methods, 2nd edition, Wiley

8 APPENDICES

A1. SAS code

Following code could be used but might be adapted.

Primary safety endpoint: Main analysis of TEAE Incidence rate

```
proc GLIMMIX data=response;
 class SEQ (ref='SEQ1') TREAT (ref='ONA') CYCLE (ref='Cycle1') SUBJID;
 model RESP = TREAT CYCLE TREAT*CYCLE / dist=bin link=identity solution;
 random SEQ(SUBJID);
 lsmeans TREAT / cl alpha=0.2;
 estimate "TRT" TREAT 1 -1 / cl exp alpha=0.2;
run;
```

Primary safety endpoint : Supplementary analysis 2 of number of TEAEs per participant

```
proc GENMOD data = teae;
 class SEQ (ref='SEQ1') TREAT (ref='ONA') CYCLE (ref='Cycle1') SUBJID;
 model TEAE = TREAT CYCLE TREAT * CYCLE / dist = Poisson;
 repeated subject= SUBJID/ type=un corrw covb;
 lsmeans TREAT / PDIFF CL E alpha=0.2;
 estimate "TRT" TREAT 1 -1 / exp alpha=0.2;
run;
```

Secondary efficacy endpoint: Main analysis of Duration of response

```
proc MIXED data=DOR;
 class SEQ (ref='SEQ1') TREAT (ref='ONA') CYCLE (ref='Cycle1') SUBJID;
 model DOR= TREAT CYCLE TREAT*CYCLE;
 random SEQ(SUBJID) / type=un;
 lsmeans TREAT / PDIFF CL E alpha=0.2;
 estimate "TRT" TREAT 1 -1 alpha=0.2;
run;
```

A2.Partial/Missing Date Convention

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

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / partial, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or the stop date indicates differently.
- Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e.: for an AE started in FEB2004 after the first IMP administration performed on 31JAN2004, the days since last dose will be "≥2", similarly the duration of ongoing AEs or medication will be "≥xx" according to the start and last visit dates).

Algorithm for Prior/ Concomitant

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration (ABO or ONA) and to the date of the second IMP administration (ONA or ABO respectively) to allow classification as either Prior or Concomitant only for each of the treatments, or Concomitant to both treatments In case a participant is randomised but not treated, the start and stop dates will be compared to the randomisation date.

If the start date of a medication is partial or missing, the medication will be assigned to the most recent treatment received on or before the medication start date (taking into account date stopped).

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete AE start dates is described in Table 1. Classification of AE according to its treatment-emergent status is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose First IMP administration = 2002-08-10, Second IMP administration = 2002-11-02 and several AEs have incomplete start dates.

Table 4: Data imputation algorithm for AE start date

Description of incomplete date	Imputed numeric date	Example		
		Character date	Imputed date	
Day is missing				
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01	Not TEAE
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-10, AE end date)	Not TEAE if AE end date< First IMP admin,

CCI [redacted]

				TEAE cycle 1 if AE end date >=First IMP admin.
YYYY-MM > YYYY-MM of [First IMP admin.] and < YYYY-MM of [Second IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01	TEAE cycle 1
YYYY-MM > YYYY-MM of [First IMP admin.] and <= YYYY-MM of EOS/EW date if no Second IMP admin.	YYYY-MM-01	2002-09-XX	2002-09-01	TEAE cycle 1
YYYY-MM = YYYY-MM of [Second IMP admin.]	Min ([Second IMP admin.], AE end date)	2002-09-XX	Min (2002-11-02, AE end date)	TEAE cycle 1
YYYY-MM > YYYY-MM of [Second IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01	TEAE cycle 2
Day and month are missing				
YYYY < YYYY of [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01	Not TEAE
YYYY = YYYY of [First IMP admin.] and YYYY < YYYY of [Second IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-10, AE end date)	Not TEAE if AE end date< First IMP admin, TEAE cycle 1 if AE end date >=First IMP admin.
YYYY = YYYY of [First IMP admin.] and YYYY = YYYY of [Second IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-10, AE end date)	Not TEAE if AE end date< First IMP admin, TEAE cycle 1 otherwise.
YYYY > YYYY OF [First IMP admin.] and YYYY = YYYY of [Second IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-10, AE end date)	TEAE cycle 1
YYYY > YYYY OF [Second IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01	TEAE cycle 2
YYYY = YYYY OF [First IMP admin.] and <= YYYY of EOS/EW date if no	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-10, AE end date)	Not TEAE if AE end date< First IMP admin,

Second IMP admin.				TEAE cycle 1 if AE end date >=First IMP admin.
YYYY > YYYY OF [First IMP admin.] and <= YYYY of EOS/EW date if no Second IMP admin.	YYYY-01-01	2003-XX-XX	2003-01-01	TEAE cycle 1
Day, month, and year are missing				
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-10, AE end date)	Not TEAE if AE end date< First IMP admin, TEAE cycle 1otherwise.

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

If AE end date is partial, imputation could be done assuming the latest possible date (i.e. last day of month if day unknown, or 31st of December if day and month are unknown).

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be considered as emergent and will be allocated to the first IMP administration where onset could have occurred (taking into account date and time stopped).

A3. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, lower quartile, upper quartile, SD and standard errors (SE) of the mean, and 95%, 90% or 80% CI values will be reported to one decimal place greater than the raw data recorded in the database. If a parameter is expected to be positive and the lower bound of the 95%, 90% or 80% CI is negative, it will be set to 0. The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database. In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small, the data displays will show the percentages, but in the CSR only frequency counts should be described.

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

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. However, in the analyses, the limit of detection will be used (e.g. 0.1 or 100).

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A4. Listings conventions

Any listings will contain at least the following data: participant identifier, age, gender and site. When dates are presented, the associated study days should be included. They should be sorted by participant identifier, sequence and visit.

A5.EudraCT categories for age

For EudraCT results summaries, in addition to quantitative descriptive statistics of age, demographic tables should include presentation of age using the following EudraCT categories:

Adults (18-64 years)
From 65 to 84 years

A6.AESI: Hypersensitivity reactions and Remote spread

Hypersensitivity reactions and Remote spread PTs are based on the most recent version of MedDRA.