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STATISTICAL ANALYSIS PLAN

A PHASE I, RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, SINGLE-CENTRE COMPARATIVE STUDY TO EVALUATE THE PHARMACODYNAMIC PROFILE OF DYSPORT, BOTOX, AND XEOMIN IN THE EXTENSOR DIGITORUM BREVIS MODEL IN HEALTHY ADULT MALE PARTICIPANTS

D-FR-52120-279

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SAP Version	Date
Version 1.0	30 June 2022

APPROVAL PAGE

STUDY NUMBER:	D-FR-52120-279
PROTOCOL TITLE:	A PHASE I, RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, SINGLE-CENTRE COMPARATIVE STUDY TO EVALUATE THE PHARMACODYNAMIC PROFILE OF DYSPORT, BOTOX, AND XEOMIN IN THE EXTENSOR DIGITORUM BREVIS MODEL IN HEALTHY ADULT MALE PARTICIPANTS
SAP VERSION:	Version 1.0
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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

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PPD	BIOTRIAL	Biostatistics Project Leader	eSignature

HISTORY OF CHANGES

Version Number	Date	Description/Rational for change

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	AE of Special Interest
ATC	Anatomic Therapeutic Class
ANCOVA	Analysis of Covariance
C	Concomitant
CI	Confidence Interval
CMAP	Compound muscle action potential
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
D	Day
ECG	Electrocardiogram
EDB	Extensor Digitorum Brevis
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICE	Intercurrent Event
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
P	Prior
PC	Prior and Concomitant
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PDs	Protocol Deviations
PN	Preferred Name
PT	Preferred Term
SAE	Serious AE
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System

ABBREVIATION	Wording Definition
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SMQ	Standardised MedDRA Query
SOC	System Organic Class
TEAE	Treatment-Emergent AE
TFLs	Tables, Figures and Listings
U	Units
W	Week

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol D-FR-52120-279. 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.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP 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

2.1 Study Objectives and Hypotheses

2.1.1 Study Objectives

Table 1: Objectives and Endpoints/Estimands

Objectives	Endpoints and Estimands
Primary	
• To demonstrate longer duration of action of Dysport compared with Botox and Xeomin in Extensor Digitorum Brevis (EDB) Compound Muscle Action Potential (CMAP) when applying a dose ratio based on approved Food and Drug Administration (FDA) total recommended doses	• CMAP total amplitude at Week 28, measured as percentage relative to baseline (%) • Key Intercurrent Event (ICE): o study discontinuation for any reason before timepoint of assessment
Secondary	
• To compare the duration of Pharmacodynamics (PD) action of a single Botulinum toxin type A administration on EBD CMAP	• CMAP total amplitude at Week 40, measured as percentage relative to baseline (%) • Incidence at Week 28 of recovery of CMAP total amplitude, defined as total amplitude return to at least 85% of the Baseline value • Incidence of recovery of CMAP total amplitude at Week 40 The three secondary endpoints listed above, for which the alpha risk will be controlled, will be considered as key secondary endpoints.
• To further characterise the pharmacodynamic profile of a single intramuscular administration of study intervention at reducing the CMAP total amplitude of the stimulated EDB	• Time to onset of action defined as first timepoint where EBD CMAP total amplitude is less or equal to 85% of the baseline value • Duration of response defined as time period between time to onset and time to recovery • Maximal inhibition (maximal effect) reached • Time to maximal effect on the CMAP total amplitude of stimulated EDB

Objectives	Endpoints and Estimands
• To assess safety	• Type, incidence and severity of Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), adverse events (AEs) (or SAEs) leading to withdrawals • Adverse Event of Special Interest (AESIs).
Exploratory	
• To further explore the effect of a single BoNT-A administration on EBD CMAP	• CMAP total amplitude at timepoints, excluding Weeks 28 and 40 • Latency of M-wave at all timepoints

The primary estimand and clinical question of interest related to the primary objective is: "What is the average difference between Dysport 40 U and the active comparators Botox 16 U and Xeomin 16 U in EDB CMAP total amplitude inhibition at Week 28 in healthy adult male participants". An ICE for all estimands is study discontinuation for any reason before timepoint of assessment. Given the expected long-lasting PD effect of the drug and the completion of treatment at the baseline visit, this ICE is not expected to have an impact on the effect of the investigated compounds.

2.1.2 Statistical Hypotheses

The primary endpoint, CMAP total amplitude at Week 28, measured as percentage relative to baseline (%), will be analysed using a Mixed-effects Model for Repeated Measures (MMRM), $\delta_{db} = \mu_{dysport} - \mu_{botox}$ and $\delta_{dx} = \mu_{dysport} - \mu_{xeomin}$ are the contrasts (i.e. mixed model Wald tests) of the Dysport versus Botox versus Xeomin comparisons in the primary endpoint at Week 28 of the study. Two elemental null hypotheses will be investigated,

$H_{0,db,1}$: $\delta_{db} = 0$ and

$H_{0,dx,1}$: $\delta_{dx} = 0$.

These null hypotheses of no difference between the respective treatment arms in the primary endpoint will be tested against the respective two-sided alternative hypotheses

$H_{A,db,1}$: $\delta_{db} \neq 0$ and

$H_{A,dx,1}$: $\delta_{dx} \neq 0$

at a 5% significance level ($\alpha = 0.05$) using a MMRM model and mixed model Wald tests of the respective contrast the Dysport versus Botox versus Xeomin comparisons in the primary endpoint at Week 28 of the study.

To control for the family-wise type I error rate at the two-sided level $\alpha = 0.05$, a Hochberg procedure [Dmitrienko and D'Agostino 2013] will be applied to investigate the two null hypotheses $H_{0,db,1}$ and $H_{0,dx,1}$. The testing procedure uses the following decision rules for the two p-values p_{db} and p_{dx}:

- Both null hypotheses are rejected if $\max(p_{db}, p_{dx}) \leq \alpha$
- Only the null hypothesis corresponding to the smaller p-value $\min(p_{db}, p_{dx})$ is rejected if $\min(p_{db}, p_{dx}) \leq \alpha/2$ and $\max(p_{db}, p_{dx}) > \alpha$.

If both null hypotheses of the primary endpoint are rejected, then the same Hochberg procedure will be applied sequentially to the two respective null hypotheses comparing Dysport with Botox and with Xeomin for secondary endpoints in the following order:

1. CMAP total amplitude at Week 40 post-injection
2. Incidence of recovery of CMAP total amplitude at Week 28 post-injection
3. Incidence of recovery of CMAP total amplitude at Week 40 post-injection

The two null hypotheses of secondary endpoint k, k =2, 3 are tested with a Hochberg procedure, when both null hypotheses of endpoint k-1 are rejected.

2.2 Overall Study Design and Investigational Plan

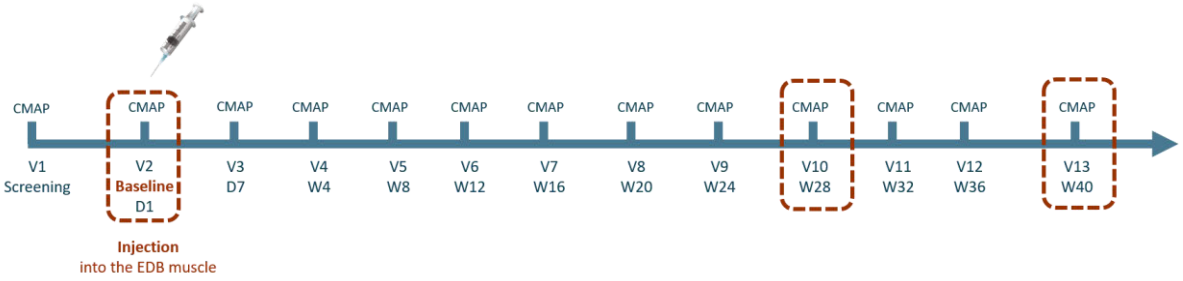
This is a phase I, randomised, double-blind, parallel-group, single-centre comparative study to evaluate the pharmacodynamic profile of Dysport 40 U, Botox 16 U and Xeomin 16 U in the EDB model in healthy adult male participants.

A total of 45 participants will be randomised in a balanced ratio of 1:1:1 to Dysport 40 U, Botox 16 U or Xeomin 16 U to be administered as a single injection on Day 1.

The maximum duration of the study is anticipated to be approximately 10 months from screening to last study visit. The participants will be followed-up for 40 weeks.

The study design is illustrated in Figure 1.

Figure 1 Study Schema



D=day; W=week; V=visit.

2.3 Sample Size Determination and Power

It was anticipated that approximately 48 participants are planned to be screened to achieve 15 participants randomised to Dysport, 15 participants randomised to Botox and 15 participants randomised to Xeomin using a 1:1:1 randomisation ratio and assuming a screening failure rate of 5%.

The sample size calculation is based on the primary efficacy estimand and its endpoint relative change from baseline in EDB CMAP total amplitude at Week 28. Using a 2-sided t-test at the 5% significance level, the chosen sample size provides at least 88% power to detect a treatment difference of 18% relative change from baseline in the Dysport arm than in a comparator arm assuming a common Standard Deviation (SD) in all treatment arms of 15% as observed for Dysport in a legacy study CCI [redacted] – Part B. The treatment difference is based on the observed average EDB CMAP total amplitude at 6 months of Dysport 40 U (CCI [redacted] – Part B) and of Botox and Xeomin 16 U in Wohlfarth [Wohlfarth 2007]. The power analysis was conducted with NQuery version 8.4.1.0. Given the made assumptions and the sample size of 15 participants per arm the probability to show superiority of Dysport to both comparators simultaneously is at least 81%, as shown in a simulation study conducted with software R version 4.0.3.

2.4 Randomisation and Blinding

The sponsor's randomisation manager who is a statistician independent of the study will prepare the list of randomisation numbers for this study. It will be produced in blocks, on a balanced ratio [1 Dysport: 1 Botox: 1 Xeomin].

Recruitment will stop once 45 participants have been randomised.

Randomised participants who discontinue the study early will not be replaced.

CCI [redacted]

During the study, the sponsor, investigator (including study site personnel) and the participant will be blinded to the study intervention. To maintain the blind during the study only a qualified, trained and unblinded person independent of the injector and investigator will prepare (i.e. reconstitute) the study intervention and will have no further involvement in the study.

Due to slight differences in colour between the study interventions and to maintain the blind during the study, the injector will also be independent from the investigator and be unblinded (note: the injector will be different from the person who will evaluate CMAP). Following injection of the study intervention, the injector will have no further involvement in the study.

For more details to randomisation and blinding, please refer to the section 6.3 of the protocol.

2.5 Schedule of Activities

Schedule of activities is presented in section 1.3 of the protocol.

2.6 Change from Statistical Section of the Protocol

No change from statistical section of the protocol has been done, only clarifications have been made:

- The wording of the primary endpoint has been updated from "CMAP total amplitude relative change from Baseline (%)" to "CMAP percentage relative to baseline (%).

- The following secondary endpoints: CMAP total amplitude at Week 40, incidence at Week 28 of recovery of CMAP total amplitude and incidence of recovery of CMAP total amplitude at Week 40, for which the alpha risk is controlled, are considered as key secondary endpoints.

- The definition of the time to onset of action has been updated from "Time to onset of action is defined as the first timepoint where EDB CMAP total amplitude is 85% or lower than the Baseline value" to "time to onset of action is defined as first timepoint where EBD CMAP total amplitude is less or equal to 85% of the baseline value".

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent Data Monitoring Committee will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed.

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 study treatment. A participant will be considered as randomised if a study intervention group has been randomly assigned. For analyses and displays, participants will be classified according to randomised treatment.

Safety Set

The safety set will contain all participants who receive at least one dose of study medication. For analyses on the safety set, participants will be classified according to treatment received. If

there is any doubt whether a participant was treated or not, he/she will be assumed treated for the purposes of analysis.

Pharmacodynamic Set

The PD analysis set will contain all participants from the randomised set who receive the appropriate dose of study treatment and have CMAP recorded for baseline and at least one post baseline assessment.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 8.

5.1 General Considerations

All statistical analyses will be performed using the Statistical Analysis System® software version using SAS® (Statistical Analysis System) Version 9.4 or higher.

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, demographic and baseline data: by study intervention group and overall,
- For safety data and pharmacodynamic data: by study intervention group.

5.1.1.2 Presentation of Study Intervention Group

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

- Dysport 40 U
- Botox 16 U
- Xeomin 16 U

5.1.1.3 Presentation of Visits / Timepoints

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 2: Analysis visit and short name

Analysis Visit	Short Name
Screening	Scr
Baseline	Bsl
Day 7	D7
Week 4	W4
Week 8	W8
Week 12	W12
Week 16	W16
Week 20	W20
Week 24	W24
Week 28	W28
Week 32	W32
Week 36	W36
Week 40	W40

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 missing category for at least one study intervention group. Except otherwise specified, participants with missing data will be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, arithmetic mean, SD, median, minimum and maximum and 95% CI if needed. Frequency and proportion of missing data will be displayed.

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to Investigational Medicinal Product (IMP) administration (including unscheduled assessments).

For the EDB CMAP, the baseline value used for the analyses will be the average of six measurements, the three measurements at screening and the three measurements at baseline.

5.1.4 Reference Start Date and Study Day

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

The day of the IMP administration will be Day 1. 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 A1.

5.2 Randomisation, Disposition and Analysis Sets

A listing presenting randomisation details will be provided.

The following disposition summaries and listings will be provided:

- Summary table with the number and percentage of participants screened, screen failed, reason for screen failure, randomised, treated, completer, withdrawn and reason for withdrawal by study intervention group and overall on the screened analysis set,
- Summary table with the number and percentage of participants per visit on the randomised set,
- Summary table on duration of participant participation in the study and on the study follow-up duration on the randomised set. The definition of the duration of participant participation is from date of consent to the last study visit. The definition of the study follow-up duration is from date of administration to the last study visit.
- Listing of participant disposition on the randomised set,
- Listing of dates of visit including duration of participant participation and study follow-up duration for the randomised participants,
- Listing of screen failure participants with the criteria not met on the screened analysis set,
- Listing of withdrawal participants with reason for withdrawal on the randomised set.

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

- Listing of participants not meeting at least one inclusion criteria,
- Listing of participants fulfilling at least one exclusion criteria,
- Summary of the number and percentage of participants in each analysis set by study intervention group and overall, based on all randomised participants with reasons for exclusion from each analysis set,
- Listing including flag for exclusion from each analysis set and reason for exclusion from each set.

5.3 Protocol Deviations

An exhaustive list of major Protocol Deviations (PDs) that may occur during the course of the study is defined in the PDs plan. Major PDs will be determined before unblinding of the study, finalised during the blind data review and documented in a PDs list.

Following PDs summary and listing will be provided on the randomised set:

- Number and percentage of participants with major PDs by deviation category
- A listing of major PDs.
- A listing of major PDs potentially having an impact on primary efficacy analysis:
    - Participant received the wrong study intervention (Mis randomisation)
    - CMAP at Week 28 or Week 40 performed out of a specified time window (> +/- 2 weeks)

5.4 Demography and Other baseline characteristics

All demographic and baseline characteristics summaries and listings will be provided on the randomised set. No statistical comparison between study intervention groups will be performed.

Following summaries will be provided on:

- Demographic variables (refer to appendix A2 for EudraCT age categories),
- Other baseline characteristics:
    - Height, weight and Body Mass Index,
    - Alcohol breath test, drug of abuse test,
    - 12-lead ElectroCardioGram (ECG),
    - Clinical laboratory test,

Listings will also be provided for all the variables listed above as well as for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) test and serology.

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

Medical and surgical history, prior BoNT therapies, non-drug therapies and surgical procedures will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) in effect within IPSEN at the time of database lock. Medications will be coded using the latest version of World Health Organization-Drug dictionary in effect within IPSEN at the time of database lock.

Medication, non-drug therapies and surgical procedures start and stop dates will be compared to the date of the IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only:

Prior (P)	Start and stop dates prior to the date of study treatment.
Prior and Concomitant (PC)	Start date before the date of study treatment and stop date on or after the date of study treatment.
Concomitant (C)	Start date on or after the date of study treatment.

Summary tables on prior medications/non-drug therapies/surgical procedures will include "P" only, summary tables on concomitant medications/non-drug therapies/surgical procedures will include "C" and "PC".

See detailed rules in appendix A1 for classification of prior and concomitant medication/non-drug therapies, surgical procedures in case of partial/missing date.

The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (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:

- Medical and surgical history by primary System Organic Class (SOC) and preferred term (PT),
- Concomitant medications (PC, C) by ATC class and PN (ATC level 2),
- Concomitant non-drug therapies (PC, C) by primary SOC and PT,
- Concomitant surgical procedures (PC, C) by primary SOC and PT,

Listings will be provided for all the summaries listed above as well as for prior medications, prior BoNT therapies and prior non-drug therapies. These listings should include a flag indicating the category (P, PC, C) as described in the table above.

CCI [redacted]

5.6 Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision at the study site on Day 1. Therefore, participant compliance with study intervention is not expected to be an issue and no listing or summaries will be performed.

5.7 Pharmacodynamic evaluation

5.7.1 General Considerations

The PD set will be used for pharmacodynamic analyses.

A listing of all pharmacodynamic data (raw and derived) should be provided (see listing detail conventions in appendix A3). Descriptive statistics will be provided for all endpoints by study intervention group and timepoint.

For the EDB CMAP, three measurements of CMAP will be taken at each timepoint. For post-baseline measurements, the mean of these three measurements will be used to determine the parameter percentage relative to baseline in CMAP total amplitude, used in all summaries and analyses of the EDB CMAP related endpoints. Baseline value definition is given in section 5.1.2.

5.7.1.1 Significance Testing and Estimations

All statistical tests will be two-sided at the 5% level of significance unless otherwise specified. Confidence Intervals (CI) will be 95%, unless otherwise specified in the description of the analyses.

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 pharmacodynamic endpoints for the statistical analysis.

The Mixed Model for Repeated Measures (MMRM) is implicitly handling missing data as Missing At Random (MAR) without explicit imputation. This missingness assumption appears meaningful given the long term pharmacodynamic effect of the investigated compounds: the effect of the drug will persist after discontinuation and is not expected, given baseline profile of the participant and assessments until the timepoint of discontinuation, to depend on whether the participant remains observable in the study or drops out.

In case of occurrence of a major PDs with the potential to interfere with CMAP total amplitude (see Section 5.3), CMAP data collected after the PDs will be ignored, and will be handled by the model as MAR. This implements a 'per protocol' analysis assessing the treatment difference occurring in case participants adhere to the protocol by using a hypothetical handling strategy for this ICE.

5.7.1.3 Statistical/analytical issues

Adjustments for Covariates

Not applicable.

Interim Analyses and Data Monitoring

Not applicable.

Multicentre Studies

This is a single-centre study.

CCI [redacted]

Multiple Testing

To control for the family-wise type I error rate at the two-sided level $\alpha = 0.05$, a Hochberg -procedure will be applied to investigate the two null hypotheses $H_{0,db} : \delta_{db} = 0$ and $H_{0,dx} : \delta_{dx} = 0$. The testing procedure uses the following decision rules for the two p-values p_{db} and p_{dx} :

- Both null hypotheses are rejected if $\max(p_{db}, p_{dx}) \leq \alpha$
- Only the null hypothesis corresponding to the smaller p-value $\min(p_{db}, p_{dx})$ is rejected if $\min(p_{db}, p_{dx}) \leq \alpha/2$ and $\max(p_{db}, p_{dx}) > \alpha$.

If both null hypotheses of the primary endpoint are rejected, then the same Hochberg procedure will be applied sequentially to the two respective null hypotheses comparing Dysport with Botox and with Xeomin for secondary endpoints in the following order:

4. CMAP total amplitude at Week 40 post-injection
5. Incidence of recovery of CMAP total amplitude at Week 28 post-injection
6. Incidence of recovery of CMAP total amplitude at Week 40 post-injection

The two null hypotheses of secondary endpoint k, k =2, 3 are tested with a Hochberg procedure, when both null hypotheses of endpoint k-1 are rejected.

Convergence of the MMRM Model

If the default Newton-Raphson algorithm used by statistical analysis software PROC MIXED fails to converge, the Fisher scoring algorithm up to iteration 2 will be used (via the SCORING=2 option of the PROC MIXED statement) to obtain the initial values of covariance parameters [Mallinckrodt 2008]. If this alternative also fails to converge, then in addition the no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T is the number of post baseline measurement timepoints incorporated in the MMRM analysis) will be used, which effectively performs the Cholesky decomposition of the covariance matrix and is numerically more stable.

When the above strategies fail, then, in addition to the changes described above, a model with the less complex heterogeneous Toeplitz covariance structure (TOEPH) will be fitted. When the above strategies fail, then, in addition to the changes described above, a model with the less complex compound symmetry covariance structure (CS) will be fitted. When all above measures fail, then the primary endpoint, CMAP total amplitude at Week 28, measured as percentage relative to baseline (%), will be analysed using an Analysis of Covariance (ANCOVA) model with covariates treatment and baseline CMAP amplitude.

The first algorithm that leads to convergence in this sequence of fallback measures will be the algorithm used for the primary analysis of the study.

5.7.2 Analysis of Primary Pharmacodynamic Endpoint

5.7.2.1 Endpoint, Treatment Effect and Estimand Definition

To assess the primary objective, the primary estimand has the following key attributes:

- Population of interest: healthy adult male participants as defined by the listed inclusion/exclusion criteria in Section 5.1 and 5.2 of the protocol.
- Variable/endpoint of interest: CMAP total amplitude at Week 28, measured as percentage relative to baseline (%), calculated as [value at Week 28 (mean of the three measurements/baseline value (means of the six measurements)]*100.

- ICEs are the following:
  a) Study discontinuation
  b1) PDs with potential impact on relevant CMAP total amplitude assessments (i.e. participant received the wrong study intervention and CMAP at Week 28 performed out of a specified time window (> +/- 2 weeks)
  b2) PDs with no expected impact on relevant CMAP assessments (e.g. other time window violations, PDs related to covid-19)
- Treatment regimen: Dysport, Botox or Xeomin will be administered as described in Section 6 of the protocol and potential intake of permitted concomitant medications (for a list see Section 6.8 of the protocol).
- Population-level summary of the treatment effect of interest: the difference in average percentage relative to baseline in each study intervention group in CMAP total amplitude at the respective timepoint.

For ICEs (a) and (b1) a hypothetical strategy will be used, the treatment difference which would have been measured if the ICE would not have happened is of interest and will be assessed taking into account the long term pharmacodynamic effect of the investigated compounds. This implies that assessments after the occurrence of a major protocol deviation interfering with CMAP total amplitude will be ignored for the primary analysis. No imputation of missing CMAP will be done (MMRM analysis, please refer to section 5.7.1.2). For ICEs (b2), a treatment policy will be used.

5.7.2.2 Primary Analysis

The primary endpoint, CMAP total amplitude at Week 28, measured as percentage relative to baseline (%), will be analysed using a mixed-effects model for MMRM. The model will include fixed effects of treatment, time (corresponding to study visits when CMAP is measured, i.e. Day 7, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40), treatment-by-time interaction and baseline CMAP amplitude, as well as an unstructured covariance matrix to model the covariance structure of the repeated measures.

Using the mixed-effects model described above, the Dysport versus Botox and Dysport versus Xeomin comparisons in the primary endpoint at Week 28 of the study will be investigated using the according partial tests (i.e. mixed model Wald tests). Results of the primary analysis will contain an estimate of the treatment difference between Dysport and comparators Botox and Xeomin in CMAP total amplitude at Week 28, as well as Standard Error (SE), 95% CI, and p-value.

The SAS code to be used is presented in appendix A4.

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

5.7.2.3 Sensitivity Analysis

No sensitivity analyses will be performed.

5.7.2.4 Supplementary Analysis

In case of occurrence of major PDs with the potential to interfere with CMAP total amplitude (see section 5.3), a supplementary analysis using the same MMRM model used for the primary analysis will be conducted using a treatment policy strategy to handle this ICE. All collected CMAP data will be taken into account in this supplementary analysis, even when occurring after PDs.

5.7.2.5 Subgroup Analysis

No subgroup analyses will be performed.

5.7.3 Analysis of Key Secondary Pharmacodynamic Endpoints

5.7.3.1 Endpoint, Treatment Effect and Estimand Definition

To assess the secondary objectives, the key secondary endpoints and estimands have the following key attributes:

- Population of interest: healthy adult male participants as defined by the listed inclusion/exclusion criteria in Section 5.1 and 5.2 of the protocol.
- Secondary endpoint of interest:
  - CMAP total amplitude at Week 40, measured as percentage relative to baseline (%), calculated as [value at Week 40 (mean of the three measurements)/baseline value (means of the six measurements)]*100
  - Incidence at Week 28 of recovery of CMAP total amplitude
  - Incidence of recovery of CMAP total amplitude at Week 40

The recovery is considered to be reached for all the visits occurring after the time to recovery, i.e. the first visit for which CMAP total amplitude return to at least 85% of the baseline value.

- ICEs are the following:
  - b) Study discontinuation
  - b1) PDs with potential impact on relevant CMAP total amplitude assessments (i.e. participant received the wrong study intervention and time window violation at the corresponding time point (> +/- 2 weeks)),
  - b2) PDs with no expected impact on relevant CMAP assessments (e.g. other time window violations, PDs related to covid-19)
- Treatment regimen: Dysport, Botox or Xeomin will be administered as described in Section 6 of the protocol and potential intake of permitted concomitant medications (for a list see Section 6.8 of the protocol).
- For ICEs (a) and (b1) a hypothetical strategy will be used, the treatment difference which would have been measured if the ICE would not have happened is of interest and will be assessed taking into account the long term pharmacodynamic effect of the investigated compounds. This implies that assessments after the occurrence of a major protocol deviation interfering with CMAP total amplitude will be ignored for the analysis. For CMAP total amplitude at Week 40, no imputation will be done (MMRM analysis). For the incidence of recovery, it will be considered as "No recovery" if the next available percentage CMAP relative to baseline (%) is inferior to 85% and will be imputed to the worst scenario "Recovery" if not or in case of no available CMAP after this ICE.

5.7.3.2 Main Secondary Analyses

5.7.3.2.1 CMAP Total Amplitude at Week 40

CMAP total amplitude at Week 40 will be analysed using the same MMRM model used for the primary analysis.

5.7.3.2.2 Incidence of Recovery of CMAP Total Amplitude at Week 28 and Week 40

Incidence of recovery of CMAP total amplitude at Weeks 28 and 40 will be analysed for each of the two timepoints by estimating proportion of participants with recovery in each of the treatment arms, p_D in the Dysport arm, p_B in the Botox arm, p_X in the Xeomin arm, as well as the risk differences $p_D - p_B$ and $p_D - p_X$ with point estimates as well as according exact

(Clopper-Pearson) 95% CI for p_D , p_B and p_X and exact unconditional 95% CI for the risk differences.

A Fisher's Exact Test (one-sided, significance level 2.5%) will be used for testing each of the comparisons of Dysport to Botox or Xeomin respectively in the framework of the multiple testing procedure described in Section 5.7.1.3.

5.7.3.3 Subgroup Analysis

No subgroup analyses will be performed.

5.7.3.4 Supplementary Analysis

In case of occurrence of major PDs with the potential to interfere with CMAP total amplitude (see section 5.3), a supplementary analysis using the same models used for the main secondary analyses will be conducted using a treatment policy strategy to handle this ICE. All collected data will be taken into account in this supplementary analysis, even when occurring after PDs.

5.7.4 Analysis of Other Secondary Pharmacodynamic Endpoints

To further characterise the pharmacodynamic profile of a single intramuscular administration of study intervention at reducing the CMAP total amplitude of the stimulated EDB, the following secondary pharmacodynamic endpoints will be evaluated:

- Time to onset of action defined as first timepoint where EBD CMAP total amplitude is less or equal to 85% of the baseline value
- Time to recovery is defined as the first timepoint when total amplitude returns to at least 85% of the baseline value (the recovery is considered to be reached for all the visits occurring after the time to recovery).
- Duration of response defined as time between time to onset and time to recovery of CMAP total amplitude
- Maximal inhibition (maximal effect) reached defined as the maximal measured inhibition of CMAP amplitude of stimulated EDB
- Time to maximal effect on the CMAP total amplitude of stimulated EDB defined on an individual basis as the time between baseline and the timepoint of maximal inhibition of CMAP amplitude of stimulated EDB.

All the endpoints defined above will be analysed descriptively only and listed.

Skin temperature and stimulation intensity will be also collected for quality control, described and listed.

5.7.5 Analysis of Exploratory Endpoints

The following exploratory endpoint will be analysed using the same MMRM model used for the primary analysis:

- CMAP total amplitude at all timepoints, measured as percentage relative to baseline (%), calculated as [value at the timepoint (mean of the three measurements)/ baseline value (means of the six measurements)]*100.

Graphical representation of adjusted means (SE) coming from the MMRM model will be performed over time by study intervention group.

Latency of M-wave at all timepoints will be analysed descriptively only and listed.

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 A3). There will be no statistical comparison between the study intervention groups for safety data.

Baseline value definition is given in section 5.1.2. Rules to handle multiple observations of the same parameter that occurred for the same visit/timepoint are explained in section 6.2.

5.8.2 Extent of exposure

Participants will receive a single study intervention administration on Day 1, so no derivation of duration of exposure will be done.

A listing will be presented for drug administrations.

5.8.3 Adverse Event

All Adverse Events (AEs) recorded in the eCRF will be coded using the latest version of MedDRA dictionary effective within IPSEN at the time of the database lock. AEs will be classified as Treatment-Emergent AEs (TEAEs) according to the rules below:

- Events with start date and time on or after the date and time of IMP administration,
- Events whose intensity increased on or after the date and time of IMP administration,

Refer to Appendix A1 for handling of partial date. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the most conservative case, i.e. treatment-emergent.

The following summaries will be provided:

- An overview table summarizing the
  - number and percentage of participants with at least one of the following AEs: any AE; any TEAE; TEAEs by intensity; TEAE by causality; AESIs by type of AESI (hypersensitivity and Remote Spread of Toxin AESIs), related and not related Serious Adverse Event (SAE), treatment-emergent SAE, TEAE leading to discontinuation from the study,
  - corresponding number of events for each of the AE categories listed above,
- A summary of the number and percentage of participants reporting at least one TEAE and the number of events, by study intervention group, SOC and PT,
- A summary of the number and percentage of participants reporting at least one treatment related AE and the number of events, by study intervention group, SOC and PT,
- A summary of the number and percentage of participants reporting at least one TEAE and the number of events, by study intervention group, by decreasing overall frequency of PT.

AEs summaries will be ordered in term of decreasing frequency for SOC and PT within SOC in overall participants and then alphabetically for SOC and PT within SOC.

In the overall summary, only the final adjudicated list of Remote Spread of Toxin AESIs confirmed by the sponsor as "a possible remote spread event" will be included.

In summary presentations, AEs will be counted as follows:

- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT;
- Participants reporting a TEAE more than once within that SOC/ PT, the TEAE with the worst-case relationship to study medication (order: related > not related > missing) will be used in the corresponding relationship summaries;
- If the causality is missing for a TEAE, it will be considered related in the summary tables.

In addition, a listing with all AEs data will be listed by study intervention group including non-TEAEs, Treatment-emergence status will be flagged in the listing.

A specific listing will be performed for treatment-related AEs.

Deaths, SAEs, and Other Significant Adverse Events (AE)

AESIs for Dysport are 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 Dysport will be identified using the list of MedDRA PTs compatible with the mechanism of action of Dysport and based on the FDA.
- TEAEs potentially representing hypersensitivity reactions will be identified using the Standardised MedDRA Query (SMQ) (narrow search query) for hypersensitivity reactions.

The list of MedDRA preferred terms, used to identify any potential AESI, is provided in the data review plan.

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.

The following summary tables on AESIs will be performed:

- AESIs with the number and percentage of participants and the number of events presented by study intervention group, by primary SOC and PT, presented by type of AESI (hypersensitivity and Remote Spread of Toxin AESIs).
- In addition, a table of pre-adjudicated potential Remote Spread of Toxin events will be produced for transparency and traceability by study intervention group and by 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,
- A listing of all AEs leading to discontinuation of study,
- A listing of participants having AESIs.

5.8.4 Vital Signs

A summary of the actual and change from baseline in each vital signs parameter by study intervention group and timepoint will be performed as well as a listing of vital sign data by study intervention group, with abnormal value highlighted. A listing of participants with Potentially Clinically Significant Abnormalities (PCSA)values as defined in Appendix A5 will also be prepared. All data for a vital signs parameter will be displayed for a participant having at least one post-baseline PSCA value.

5.8.5 Physical Examination

The following summary and listings will be provided:

- A shift from baseline (normal vs abnormal) to end of study visit by study intervention 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

Time window (+/- 2 weeks) is used to calculate the protocol deviations defined as ICE for the analysis.

No other time windows are needed for analyses.

6.2 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and 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.

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.

Participants who have withdrawn early from the study have their last assessment entered as visit 90 in the eCRF. By convention, for these participants, the visit number will be reassigned to the next empty visit number (i.e. if a participant has Visit 1, 2, 3 and 90 entered in the database, the visit number 90 will be reassigned to visit number 4) for summary tables.

6.3 Handling of COVID-19 Pandemic

Specific outputs will be provided as described in Ipsen's biostatistics recommendations for the "Management of COVID-19 pandemic related issues" to assess the impact of the COVID-pandemic as follows:

- Summary table with the number and percentage of participants exposed as well as impacted or infected and with the number of participants withdrawn due to COVID-19 with their reasons of withdrawal.
- Exposed participant is a participant ongoing at start of pandemic (January 03, 2020) or included during the pandemic phase (end of the pandemic not reached).
  Impacted participant is a participant who has been infected by SARS-CoV-2 or for whom the conduct of the study has been impacted (visit impacted; withdrawal related to COVID-19 pandemic). Participant infected are reported in SAEs.
- Summary table by visit with the number and percentage of participants having a visits impacted by COVID-19 with the type of impact and the reason(s) why COVID-19 pandemic impacted the visit.
- Summary table with the number and percentage of participants having a PDs due to COVID-19 Status by deviation category and listing of deviation due to COVID-19.
- Addition of "any Confirmed COVID-19 cases" in the overall summary table of AEs and listing of TEAEs including in the SMQ dedicated to COVID-19.
- Listing of COVID-19 tests.

7 DERIVED DATA (IF APPLICABLE)

Not applicable

8 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 European Medicines Agency (EMA) or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Clinical trials in small populations
- Missing data in confirmatory clinical trials
- Multiplicity issues in clinical trials
- Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, Committee for Human Medicinal Products (CHMP). EMA/158330/2020, https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en.pdf

Reference to FDA guidelines:

- Multiple Endpoints in Clinical Trials

Other references:

- Standard Ipsen Study Data Tabulation Model (SDTM) user guide
- Standard Analysis Dataset Model (ADaMs) user guide
- Ipsen Global Style guide
- Dmitrienko A and D'Agostino, R. Traditional multiplicity adjustment methods in clinical trials. Stat Med. 2013:23:(19):5172-5218
- Wohlfarth K, Muller C, Sassin I et al. Neurophysiological double-blind trial of botulinum neurotoxin type A free of complexing proteins. Clin Neuropharm. 2007;30:86-94
- Mallinckrodt CH, Lane PW, Schnell D et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Inform J. 2008;42:303-19

9 APPENDICES

A1. Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded.

Algorithm for Prior/Concomitant

Medications, non-drug therapies, BoNT therapies and surgical procedures start and stop dates will be compared to the date of the first IMP administration to allow classification as either Prior only, Prior and Concomitant, or Concomitant only.

In case of partial start and/or stop dates, temporary date imputations will be done to determine the classification and derive the duration of occurrence:

- If a partial start date is reported, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date is reported, the last day of the month will be imputed for missing days and December will be imputed for missing month.

In case incomplete start or stop date does not allow the classification, the occurrence will be classified as concomitant.

The duration of the occurrence will be calculated using the start and end date of the occurrence as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing occurrence (e.g. at the end of the study or at the time of interim analysis if any):

- If the start date is complete, the duration will be reported as "≥ xx" and the date of end of study date or last attended visit will be considered as end date,
- If the start date is incomplete, the duration is not calculated.

Algorithm for Medical Histories

In case of partial start and/or stop dates, temporary date imputations will be done to determine the duration of occurrence:

- If a partial start date is reported, the first day of the month will be imputed for missing day and January for missing month,
- If a partial stop date is reported, the last day of the month will be imputed for missing days and December will be imputed for missing month.

The duration of the occurrence will be calculated using the start and end date of the occurrence as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing medical history:

- If start date is complete, the duration will be "≥ xx" using the screening visit date and the start date of the medical history.
- If start date is incomplete, the duration is not calculated.

Algorithm for Adverse Events

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 adverse event start dates is described in Table 3. Classification of adverse event 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 = 2002-08-11 and several AEs have incomplete start dates.

Table 3: Data Imputation Algorithm for AE Start Date (ASTDT)

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
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

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).

AEs duration will be calculated using the start and end date of the AE as end date – start date + 1. In case of partial start/end date the temporary imputed date will be used.

The duration of the AE will be calculated using the start and end date of the AE as end date – start date + 1. In case of partial start or end dates, the duration will be reported as "≤ xx" since at least one date is imputed and maximised.

In case of ongoing AE (e.g. at the end of the study or at the time of interim analysis):

- If start date is complete, the duration will be reported as "≥ xx" and the date of end of study date or last attended visit will be considered as end date.
- If start date is incomplete, the duration is not calculated.

A2. 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 (as applicable):

In utero
Preterm newborn - gestational age < 37 weeks
Newborns (0-27 days)
Infants and toddlers (28 days-23 months)
Children (2-11 years)
Adolescents (12-17 years)
Adults (18-64 years)
From 65 to 84 years
85 years and over

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, SE of the mean will be reported to one decimal place greater than the raw data recorded in the database.

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 statistics.

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 could 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'.

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

A4. SAS code

a. MMRM analysis

The SAS code for the MMRM is the following:

CCI [redacted]

Where AVISITN includes all post-baselines visits when CMAP is measured, CMAPBL is the baseline of CMAP total amplitude and AVAL is the percentage relative to baseline of CMAP total amplitude (%).

If the PROC MIXED fails to converge, the first algorithm that leads to convergence in the following sequence of fallback measures will be the algorithm used for the primary analysis of the study:

1) Addition of scoring option

CCI [redacted]

2) Addition of the no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement

CCI [redacted]

3) Use of Toeplitz covariance structure

CCI [redacted]

4) Use of compound symmetry covariance structure

CCI [redacted]

CCI [redacted]

CCI

5) ANCOVA model with covariates treatment and baseline CMAP amplitude

CCI

[redacted]

b. Exact (Clopper-Pearson) 95% confidence intervals for proportion

To obtain the exact (Clopper-Pearson) 95% CI for proportion of participants with recovery in each of the treatment arms, the following SAS code will be used:

CCI

[redacted]

c. Exact unconditional 95% confidence interval for the risk differences and Fisher's Exact Test

To optain the exact unconditional 95% CI for the risk differences as well as the Fisher's Exact Test (right-sided, significance level 2.5%), the following SAS code will be used:

CCI

[redacted]

Where AVAL is recovery of CMAP amplitude, AVISIT is Week 28 or Week 40. Same model will be performed with TRTP in ("Dysport" "Xeomin").

A5. PCSA criteria for vital signs parameters

PSCA criteria for vital signs parameters are defined as follow:

Parameter	PCSA criteria
Systolic Blood Pressure	≤ 90 mmHg and change from baseline ≤ -20 mmHg ≥ 180 mmHg and change from baseline ≥ 20 mmHg
Diastolic Blood Pressure	≤ 50 mmHg and change from baseline ≤ -15 mmHg ≥ 105 mmHg and change from baseline ≥ 15 mmHg
Heart Rate	≤ 50 bpm and change from baseline ≤ -15 bpm ≥ 120 bpm and change from baseline ≥ 15 bpm
Weight	≤ -5% change from baseline ≥ 5 % change from baseline

A6. Listings conventions

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