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

Protocol Number: D-FR-52120-279

Compound: IPN52120 (Dysport)

Brief Title: A comparative study to evaluate the pharmacodynamic profile of Dysport, Botox and Xeomin in the extensor digitorum brevis model in healthy adult male participants

Study Phase: I

Acronym: Not Applicable

Sponsor Name: Ipsen Innovation

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I have read and agree to Protocol D-FR-52120-279 entitled "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". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
AE	Adverse event
AESI	Adverse event of special interest
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin type A
CMAP	Compound muscle action potential
COVID-19	Coronavirus disease 2019
CRO	Contract research organisation
ECG	Electrocardiogram
EC	Ethics committee
eCRF	Electronic case report form
EDB	Extensor digitorum brevis
EoS	End of study
EU	European Union
EW	Early withdrawal
FDA	Food and Drug Administration
GCP	Good clinical practice
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
PD	Pharmacodynamics
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS®	Statistical Analysis System®
SoA	Schedule of activities

ABBREVIATION	Wording Definition
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
U	Units
US(A)	United States (of America)
USPI	United States Prescribing Information

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Brief Title:

A comparative study to evaluate the pharmacodynamic profile of Dysport, Botox and Xeomin in the extensor digitorum brevis model in healthy adult male participants

Rationale:

This study is designed to investigate the comparative duration of action on compound muscle action potential (CMAP) of the extensor digitorum brevis (EDB) muscle injected with either Dysport 40 U, Botox 16 U or Xeomin 16 U applying a dose ratio of 2.5:1:1 based on maximum recommended total doses in the United States Prescribing Information (USPI) from the Food and Drug Administration (FDA) for adult upper limb spasticity and glabellar lines indications.

Note: the units of study intervention to be used in this study are specific to each botulinum toxin and are not interchangeable.

Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
• To demonstrate longer duration of action of Dysport compared with Botox and Xeomin in EDB CMAP when applying a dose ratio based on approved FDA total recommended doses	• CMAP total amplitude at Week 28, measured as relative change from Baseline (%) • Key intercurrent event: o Study discontinuation for any reason before timepoint of assessment
Secondary	
• To compare the duration of pharmacodynamic action of a single BoNT-A administration on EBD CMAP	• CMAP total amplitude at Week 40, measured as relative change from 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
• 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 EDB CMAP total amplitude is 85% or lower than 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

• To assess safety	• Type, incidence and severity of TEAEs, SAEs, AEs (or SAEs) leading to withdrawals • AESIs.

AE=adverse event; AESI=adverse event of special interest; BoNT-A=botulinum toxin; CMAP=compound muscle action potential; EDB=extensor digitorum brevis; FDA=United States Food and Drug Administration; SAE=serious adverse event; TEAE=treatment-emergent adverse event

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". A key intercurrent event for all estimands is study discontinuation for any reason before timepoint of assessment.

Overall Design:

This phase I, randomised, active-controlled, double-blind, parallel-group, single-centre comparative study will evaluate the pharmacodynamic profiles of Dysport, Botox and Xeomin in a human EDB model. Healthy male participants will be randomised to receive a single intramuscular injection of either Dysport 40 U, Botox 16 U or Xeomin 16 U in the EDB muscle.

Compound muscle action potential of the EDB will be measured following supramaximal stimulation of the corresponding nerve at Baseline and each study visit. Measurements will be performed using surface electrodes placed over the belly part of the EDB and reference electrodes placed over the tendon of the corresponding muscle.

Condition/Disease: Healthy participants

Study Hypothesis:

The higher quantity of neurotoxin in Dysport than Botox or Xeomin at the approved FDA dose used in therapeutic and aesthetic indications may contribute to the prolonged duration of action exhibited by Dysport compared with other botulinum toxin serotype A (BoNT-A) products [Field 2018]. Using the same dose ratio, this study aims to demonstrate a longer duration of action of Dysport compared to Botox and Xeomin in a well-known and recognised pharmacodynamic model in healthy male participants.

Study Duration: This study will consist of a 14-day screening period, a double-blind period including treatment administration on Day 1 and follow-up period of 40 weeks.

The total study duration will be approximately 10 months.

Treatment Duration: Participants will receive a single study intervention administration on Day 1.

Visit Frequency: Following injection of study intervention on Day 1, all participants will attend follow-up visits on Day 7 and then every 4 weeks (Week 4, 8, 12, 16, 20, 24, 28, 32 and 36) until the end of study (Week 40).

Number of Participants:

Approximately 48 participants will 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%.

Statistical Methods:

Sample Size

Using a 1:1:1 allocation ratio, 45 participants, 15 in each study intervention group provide at least 88% power (2-sided t-test, 5% significance level) to show superiority of Dysport 40 U over Botox 16 U and Dysport 40 U over Xeomin 16 U in each of the direct comparisons, assuming a true treatment difference of 18% relative change from baseline in EDB CMAP total amplitude and common standard deviation in all three treatment arms of 15%.

Primary Analysis

The primary endpoint, CMAP total amplitude at Week 28, measured as relative change from Baseline (%), will be analysed using a mixed-effects model for repeated measures (MMRM). The model will include fixed effects of treatment, time (corresponding to study visit), treatment-by-time interaction and baseline CMAP total amplitude, as well as an unstructured covariance matrix to model the covariance structure of the repeated measures.

Using the mixed-effects model described above, $\delta_{db} = \mu_{dysport} - \mu_{botox}$ 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. 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, 95% confidence interval, and p-value.

The 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 the baseline profiles of the participant and assessments until the timepoint of discontinuation, to depend on whether the participant remains observable in the study or drops out.

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 $\max(p_{db}, p_{dx}) > \alpha$.

Intervention Groups and Duration:

Intervention Name	Unit Dose Strength	Dose Level	Route of Administration	Dose Frequency
Dysport	300 U/vial	40 U	Intramuscular	Single administration on Day 1
Botox	50 U/vial	16 U	Intramuscular	Single administration on Day 1
Xeomin	50 U/vial	16 U	Intramuscular	Single administration on Day 1

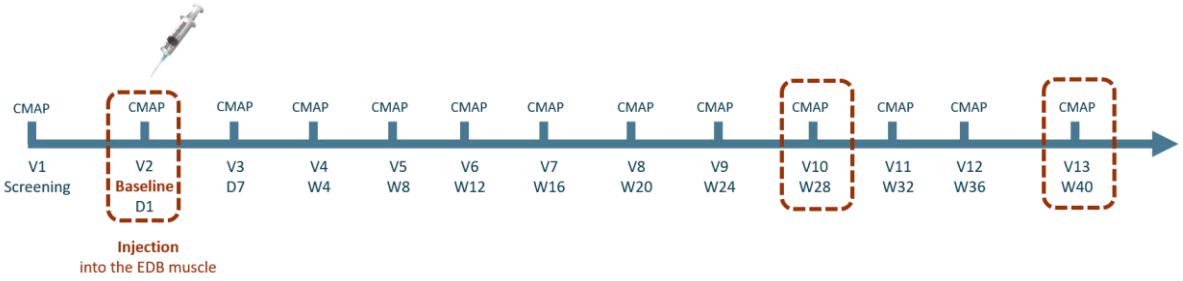
U=units

Data Monitoring/Other Committee: No

1.2 Schema

The scheme for the study is provided in Figure 1.

Figure 1 Study Schema



CMAP=compound muscle action potential; D=day; EBD=extensor digitorum brevis; W=week; V=visit

1.3 Schedule of Activities (SoA)

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

If the coronavirus disease 2019 (COVID-19) pandemic prevents participants from coming to the site, participants can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact (subject to consent) the participant's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol planned assessments will be provided to the investigator in a separate document. Such document will be filed in the trial master file. Independent ethics committees (IECs)/institutional review boards (IRBs) will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 1 Schedule of Activities

Procedure	**SCR**	**BSL**	**Double-blind Period**										**EoS /EW**	**Notes**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	
Scheduled Day/Week	**Day -14 to Day -1**	**Day 1**	**Day 7**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	
Visit window (days)	**-**	**-**	**±1 day**	**± 3 days**		**± 6 days**								
Informed consent	X													
Inclusion and exclusion criteria	X	X												
Demography	X													
Body weight and height	X													
Medical history and surgical history	X													
Alcohol breath test/Drug test	X	X												
Randomisation		X												
Study intervention administration		X												
Physical examination	X	X											X	

Procedure	SCR	BSL	Double-blind Period										EoS /EW	Notes
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	
Scheduled Day/Week	Day -14 to Day -1	Day 1	Day 7	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	
Vital signs	X	X											X	Standing and supine blood pressures and heart rate. Measurements to be taken prior to sampling for laboratory tests where possible.
12-lead ECG	X													
Clinical laboratory tests	X													Haematology, blood chemistry, coagulation and serology
SARS-CoV-2 Test	X	X*												*To be performed predose. PCR test to be performed at screening and rapid antigen test at baseline. Additional testing can be performed if required or in the event of suspected COVID-19 infection during the study. See Section 8.2.5.
EDB CMAP recording	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	

BSL=baseline; CMAP=compound muscle action potential; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; EDB=extensor digitorum brevis; EoS=end of study; EW=early withdrawal; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=screening; W=week

1.4 Brief Summary

This study is designed to investigate the comparative duration of action on CMAP of the EDB muscle injected with either Dysport 40 U, Botox 16 U or Xeomin 16 U applying a dose ratio of 2.5:1:1 based on maximum recommended total doses in the USPI from FDA for adult upper limb spasticity and glabellar lines indications.

Study details include:

Study Duration: Approximately 10 months

Treatment Duration: Single administration on Day 1

Visit Frequency: Following injection of study intervention on Day 1, all participants will attend follow-up visits on Day 7 and then every 4 weeks (Week 4, 8, 12, 16, 20, 24, 28, 32 and 36) until the end of study (Week 40).

2 INTRODUCTION

Use of botulinum toxin type A (BoNT-A) for various therapeutic and aesthetic indications is well established. The most commonly used and commercially available BoNT-A products are Dysport® (manufactured by the sponsor), Botox® and Xeomin®. Each of these products has a unique manufacturing process. Excipients, formulation and non-interchangeable potency units of these BoNT-A products are different (e.g. formulation and purification). However, their mechanisms of action are the same and medicated by the 150 kDa BoNT-A neurotoxin.

BoNT-As are neurotoxin complexes derived from the bacterium Clostridium botulinum. These products prevent acetylcholine release at neuromuscular junctions, blocking neuronal transmission which in turn results in weakness or paresis of the injected muscle. Over a period of months, the nerve function returns, thus treatment may need to be repeated periodically as required.

Botulinum toxins are of significant value in the treatment of a variety of therapeutic indications including blepharospasm, hemifacial spasm, spasticity and cervical dystonia, as well as aesthetic indications (e.g. improvement in the appearance of moderate to severe glabellar or lateral canthal lines).

In a recent study, it has been shown that Dysport may have a longer duration of action compared with other BoNT-A products due to a higher mean 150 kDa BoNT-A content per vial [Field 2018]. Accounting for the differences in potency and total recommended doses according to the United States Food and drug Administration (FDA) for therapeutic and aesthetic indications, study results suggest Dysport contains greater amounts of active neurotoxin when used at total FDA-recommended doses compared with Botox and Xeomin, thus prolonging the block of neurotransmitter release at the neuromuscular junction.

The present study proposes to compare the duration of effect of three commercialized BoNT-A products (Dysport, Botox and Xeomin) administered into the extensor digitorum brevis (EDB) of healthy participants. Together with its nerve supply (peroneal nerve), this muscle is superficial and accessible for electrophysiological, hence commonly used by the scientific community for assessing the onset and quantifying the duration of effects following BoNT administration [Sloop 1996, Eleopra 1997a, 1997b, 2013, Pons 2019], comparing different subtypes of BoNT [Sloop 1997, Eleopra 1998, 2004] or even checking potency of BoNT formulations [Park and Ahn 2013].

2.1 Study Rationale

The purpose of this study is to investigate the comparative duration of action on compound muscle action potential (CMAP) of the extensor digitorum brevis (EDB) muscle injected with either Dysport 40 U, Botox 16 U or Xeomin 16 U applying a dose ratio of 2.5:1:1 based on maximum recommended total doses in the United States Prescribing Information (USPI) from the Food and Drug Administration (FDA) for adult upper limb spasticity and glabellar lines indications.

Note: the units of study intervention to be used in this study are specific to each botulinum toxin and are not interchangeable.

2.1 Background

In this study, it is planned to explore the pharmacodynamic profile of Dysport 40 U compared with Botox 16 U and Xeomin 16 U on CMAP of the EDB muscle. All three BoNT-A products share the same mechanism of action. However, based on recent study data it is hypothesised that, when given at the total recommended dose, Dysport may have a longer duration of action than other BoNTA products due to higher amounts of neurotoxin per vial [Field 2018]. Thus, a BoNT-A product with longer effect could allow for less frequent need for re-injection.

2.2 Benefit/Risk Assessment

This study will be conducted in healthy male participants. There is no benefit for this study population.

Risks inherent to the administration of BoNT are those related to distant spread from the site of administration. In clinical practice, the risk of occurrence of such undesirable effects may be reduced by using the lowest effective possible dose and by not exceeding the maximum recommended dose per indication as indicated in the respective product labels. Doses that will be investigated in the present study have been shown to safe and well tolerated, also associated with a lack of local diffusion to the adjacent muscles [Pons 2019, Wohlfarth 2007].

There have also been occasional reports of hypersensitivity. This potential risk will be mitigated by appropriate selection of participants.

More detailed information about the known risks and reasonably expected adverse events may be found in the respective product labels for Dysport, Botox and Xeomin.

Safety will be closely monitored during the study. Type, severity, seriousness, duration, reversibility and outcome of treatment-emergent AEs (TEAEs) and adverse events of special interest (AESIs), a well as TEAEs leading to withdrawals will be followed. In addition, all AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs.

2.2.1 Risk Assessment of the Impact of COVID-19 Vaccination on Study Participants

Currently there is no evidence of an increased safety risk in patients treated with BoNT prior to or following vaccination against COVID-19.

The doses of study intervention (BoNT) to be used in the study have been shown to be safe when injected into the EDB muscle. At 40 U, there is no local diffusion of Dysport into adjacent muscles. However, as a precautionary measure and to help minimise confounding factors in the safety assessments, a COVID-19 vaccine should not be administered within 7 days before or after the study intervention injection.

3 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Table 2 Objectives and Endpoints/Estmands

Objectives	Endpoints and Estimands
Primary	
• To demonstrate longer duration of action of Dysport compared with Botox and Xeomin in EDB CMAP when applying a dose ratio based on approved FDA total recommended doses	• CMAP total amplitude at Week 28, measured as relative change from Baseline (%) • Key intercurrent event: o study discontinuation for any reason before timepoint of assessment
Secondary	
• To compare the duration of pharmacodynamic action of a single BoNT-A administration on EBD CMAP	• CMAP total amplitude at Week 40, measured as relative change from 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
• 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 85% or lower than 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
• To assess safety	• Type, incidence and severity of TEAEs, SAEs, AEs (or SAEs) leading to withdrawals • 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

AE=adverse event; AESI=adverse event of special interest; BoNT-A=botulinum toxin; CMAP=compound muscle action potential; EDB=extensor digitorum brevis; FDA=United States Food and Drug Administration; SAE=serious adverse event; TEAE=treatment-emergent adverse event

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 in total amplitude inhibition at Week 28 in healthy adult male participants". A key intercurrent event (ICE) for all estimands is study discontinuation for any reason before timepoint of assessment. Given the 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. More detail on other attributes of the estimand are described in Section 5 (study population of interest), in Section 6 (study intervention), Section 8 (study assessments) and in Section 9 (summary measure on population level, as well as handling of key intercurrent events).

4 STUDY DESIGN

4.1 Overall Design

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 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 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.

4.2 Scientific Rationale for Study Design

The higher quantity of neurotoxin in Dysport than Botox or Xeomin at the approved FDA dose used in therapeutic and aesthetic indications may contribute to the prolonged duration of action exhibited by Dysport compared with other BoNT-A products [Field 2018]. Using the same dose ratio, this study aims to demonstrate a longer duration of action of Dysport compared to Botox and Xeomin in a well-known and recognized pharmacodynamic model in healthy male participants.

This model uses the EDB muscle and records its compound muscle action potential (CMAP) following supramaximal stimulation of the corresponding nerve. The present design will capture the CMAP of injected EDB with either Dysport, Botox or Xeomin. The expected inhibition of the electrophysiological signal following BoNT administration will be followed in parallel study intervention groups and blinded conditions, up to 40 weeks after injection aiming at capturing recovery of the inhibition.

4.2.1 Participant Population to be Studied

This study will enrol healthy male participants between the ages of 18 to 65 years. All participants should be in good health as determined by medical history, physical examination, clinical laboratory testing, electrocardiograms, vital signs and investigator's judgement.

After completion of the study, no additional treatment or medical care is necessary.

4.3 Justification for Dose

Dysport 40 U has already been shown to be well tolerated when injected into the EDB [Pons 2019], as well as demonstrating an absence of local diffusion to the adjacent muscles. This dose level was also associated to a remaining CMAP inhibition 6 months post-injection.

When applying a ratio of 2.5 (Dysport) for 1 (Botox/Xeomin), which is based on the maximum recommended total doses in the USPI from the FDA from adult upper limb spasticity and glabellar lines indications, a dose of 16 U is selected for Botox and Xeomin. Doses of 16 U Botox or Xeomin were also shown to be safe when injected into the EDB [Wohlfarth 2007].

4.4 End of Study Definition

The end of the study (EoS) is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant.

A participant is considered to have completed the study if he has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

1. Participant must be between18 to 65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, vital signs and cardiac monitoring.

Weight

3. A body mass index (BMI) within the range 18 and 30 kg/m^2 (inclusive).

Sex

4. Participants are male.

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Any medical condition that may put the participant at risk with exposure to BoNT, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function.
2. Complication or history of peripheral neuropathy (e.g. as a result of diabetes mellitus), nerve root impairment or muscle disease.
3. Has or has a history of breathing problems, such as asthma or emphysema.
4. Has or has a history of swallowing problems.
5. Has or has a history of bleeding problems.
6. Has or has a history of blurred or double vision.
7. Has or has a history of dysarthria or dysphonia.

Prior/concomitant Therapy

8. Previous treatment with BoNT (any serotype) during the past 6 months.
9. Has received a COVID-19 vaccine injection within 7 days before the planned study intervention injection or is planning/likely to be vaccinated within 7 days after the planned study intervention injection.
10. Use of agents that could interfere with neuromuscular transmission, including calcium channel blockers, penicillamine, aminoglycosides, lincosamides, polymixins, magnesium sulphate, anticholinesterases, succinylcholine and quinidine.
11. Use of concomitant therapy which, in the investigator’s opinion, would interfere with the evaluation of the safety or efficacy of the study intervention, including medications

affecting bleeding disorders (e.g. antiplatelet agents and/or anticoagulants given for treatment or prevention of cardiovascular/cerebrovascular diseases).

12. Any planned surgery of the foot.

Prior/concurrent Clinical Study Experience

13. Use of any experimental device within 3 months or use of any treatment with an experimental drug within five times the documented terminal half-life of the respective drug or its metabolites or if the half-life is unknown within 3 months prior to the start of the study (prior to Baseline) and during the conduct of the study.
14. Participation in a concurrent study of another investigational drug or device.

Diagnostic Assessments

15. Known positive for hepatitis B antigen, or hepatitis C virus antibody, or for human immunodeficiency virus (HIV) or a diagnosis of acquired immunodeficiency syndrome.
16. Clinically diagnosed significant anxiety disorder, or any other significant psychiatric disorder (e.g. depression) that might interfere with the participant's participation in the study.

Other Exclusions

17. Known hypersensitivity to any of the components of the Dysport/ Botox/ Xeomin formulation (which includes human serum albumin, lactose, sucrose) or allergy to cow's milk protein.
18. Has recent evidence of alcohol abuse, positive drugs of abuse screen, or other relevant neuropsychiatric condition in the opinion of the investigator.
19. Has any mental condition rendering the participant unable to understand the nature, scope and possible consequences of the study.
20. Is likely to be noncompliant or uncooperative during the study, in the judgment of the investigator.
21. Resides in an institution by administrative or court order
22. Is a sponsor employee or clinical research unit personnel directly affiliated with this study or is an immediate family member. Immediate family is defined as a spouse, parent, child or sibling whether biological or legally adopted.
23. Any uncontrolled systemic disease or other significant medical condition which would be harmful for the participant to be entered into the study or continue participation are considered as exclusion criteria.

5.3 Lifestyle Considerations

Besides restrictions already presented in the exclusion criteria (see Section 5.2), participants will be requested to abstain from alcohol for 24 hours prior to admission to the clinical research unit. Excessive alcohol consumption (>14 units per week) should be avoided for the duration of the study. Participants are also requested to abstain from recreational drugs abuse from 48 hours prior to Day -1 and until discharge from the study. Participants will be requested to refrain from smoking while they are in the unit and should also refrain from vigorous physical activity from Screening until the completion of the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure

participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, eligibility criteria and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.

Rescreened participants will have to re-sign an (new) ICF and a new participant number will be allocated. All screening assessments need to be repeated for the rescreened participant.

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

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection at the Baseline visit (Day 1), the study intervention administration may be temporarily postponed depending on the participant's clinical presentation. See Section 7.1.1 for further details.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1 Study Intervention(s) Administered

Table 3 Study Intervention Administered During the Study

Intervention name	Dysport	Botox	Xeomin
Type	Biologic	Biologic	Biologic
Dose formulation	Lyophilised powder	Lyophilised powder	Lyophilised powder
Unit dose strength(s)	300 U/vial	50 U/vial	50 U/vial
Dosage Level(s)	40 U	16 U	16 U
Dose Frequency	Single administration on Day 1	Single administration on Day 1	Single administration on Day 1
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Active-comparator	Active-comparator	Active comparator
IMP and AMP/NIMP	IMP	IMP	IMP
Sourcing	Provided by the sponsor	Provided by the sponsor	Provided by the sponsor
Packaging and labelling	Commercial product will be used. Study intervention will be provided in packs of 1 vial, labelled on primary and secondary packaging for clinical study purpose.	Commercial product will be used. Study intervention will be provided in packs of 1 vial, labelled on primary and secondary packaging for clinical study purpose	Commercial product will be used. Study intervention will be provided in packs of 1 vial, labelled on primary and secondary packaging for clinical study purpose.
Storage requirements	To be stored between 2°C and 8°C	To be stored between 2°C and 8°C	Room temperature (below 25°C)

AMP=auxiliary medicinal product; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; U=units

6.2 Preparation/Handling/Storage/Accountability

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

regulations, institutional policy and any special instructions provided by the sponsor. All destruction must be adequately documented.

6.2.1 Investigational Medicinal Product Preparation

The investigator or an approved representative (e.g. pharmacist) will ensure that all IMPs are reconstituted by an independent reconstitutor (unblinded study staff) and dispensed by qualified staff members. Detailed instructions for storage, reconstitution and preparation before treatment administration will be provided in the "IMP handling manual" or similar documentation.

The vial of Dysport will be reconstituted using sterile 0.9% sodium chloride solution for injection to a concentration of 200 U/mL for administration of a dose of 40 U in 0.2 mL.

The vials of Botox and Xeomin will be reconstituted using sterile 0.9% sodium chloride solution for injection to a concentration of 80 U/mL for administration of a dose of 16 U in 0.2 mL.

A ready to administer syringe containing the study intervention will be provided to the injection responsible delegated person in order to maintain the blinding.

6.2.2 Investigational Medicinal Product Storage and Security

The investigator or an approved representative (e.g. pharmacist) will ensure that all IMPs and any other study related material are stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

All study interventions must be stored as indicated in Table 3. Sterile 0.9% sodium chloride solution for reconstitution can be stored at room temperature.

6.2.3 Investigational Medicinal Product Accountability

All IMPs and any other study related material are to be accounted for on the IMP accountability log provided by the sponsor. Used vials, empty or not, must be retained at site in accordance with local regulations. It is essential that unused supplies, as well as used supplies or empty boxes of used supplies, are retained for verification (by sponsor's unblinded representative). Unused supplies, as well as used supplies or empty boxes of used supplies, will be either destroyed at the site or in the local depot. Drug accountability records will be maintained by the independent reconstitutor (unblinded study staff) documenting the subject allocated treatment number and the number of vials used and not used.

6.3 Measures to Minimize Bias: Randomisation and Blinding

6.3.1 Randomisation

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].

After eligibility is confirmed at Day 1, participants will be assigned a randomisation number and to the associated study intervention group, in sequential order within the centre. Each participant will be treated with the intervention allocated to this randomisation number. This will be done by an unblinded pharmacist (independent reconstitutor) in charge of the study intervention preparation, by considering the first unused treatment allocation envelope among the set of envelopes provided to the centre. The assigned randomisation number will have to be specified on the treatment kit, vial and syringe used for the study intervention reconstitution.

The investigator, the unblinded pharmacist, and investigator staff will under no circumstances change the randomisation number or the study intervention group allocated to the participant.

Recruitment will stop once 45 participants have been randomised. Randomised participants who terminate their study participation for any reason before starting intervention will retain

their randomisation number (the randomisation number will not be reused). The next participant will be assigned the next randomisation number.

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

The sponsor's randomisation manager will keep the master list of randomisation numbers. Access to this list must be restricted until authorisation is given to release it for final analysis.

6.3.2 Maintenance of Blinding

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. This person will be fully trained in the method of preparing the study intervention and the importance of their role in maintaining the blind for the participant, the investigator and the rest of the team.

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

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.

Two sets of individual code break envelopes (an envelope per randomisation number) will be prepared by the sponsor's randomisation manager to enable emergency code break procedures for individual participants without compromising the blind of the study. One set will be provided to the investigational site and one set will be provided to the central department of pharmacovigilance at the sponsor.

The code break material will be retained by the investigator (or representative) in a secured area.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

The investigator must reseal the envelope. The investigator will sign, date and provide reason for the code break on the emergency code break form and on the sealed envelope. The date and reason for identifying the intervention will be recorded in the eCRF.

Once the study is complete, all code break material (sealed and opened) must be inventoried and returned to the sponsor.

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

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision at the study site on Day 1. Therefore, participant compliance with study intervention is not expected to be an issue. The date, time and volume of administration will be recorded in the source documents and in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Dose Modification

No dose modification will be required in this study.

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

The participants will not receive any additional study intervention following the end of the study.

6.7 Treatment of Overdose

For this study, any dose of Dysport, Botox or Xeomin greater than that defined in Section 6.1 will be considered an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant signs and/or symptoms of excessive muscle weakness or muscle paralysis. Note: symptoms of overdose may not present immediately following injection. Should accidental injection or ingestion occur the participant should be medically supervised for several weeks.
- Document the quantity of the excess dose, as well as the duration of the overdose. See Section 10.3.1 for reporting requirements concerning overdose.

6.8 Concomitant Therapy

Any prior medications/nondrug therapies used by the participant within 30 days prior to the Screening visit (and not continued during the study) or concomitant medications/nondrug therapies given during the study will be indicated on the eCRF. Dose and generic name or trade name will be indicated.

The investigator will be advised not to use any dermal topics (including anaesthetic topics) on the participant prior to the injection of study intervention on Day 1. In addition, the following concomitant medications are not permitted during this study:

- Any form of BoNT (other than the specific study intervention) for administration into any site of the body.
- Any experimental new drug or device.
- Medications that affect neuromuscular transmission, such as curare-like non-depolarising agents, lincosamides, polymyxins, anticholinesterases and aminoglycoside antibiotics, within the past 30 days of Baseline and during the study.
- Medications that affect bleeding disorders (antiplatelet agents and/or anticoagulants given for treatment or prevention of cardiovascular /cerebrovascular diseases).
- Concomitant medications for other purposes are allowed at the investigator's discretion. It is recommended that the dosage for these medications is kept constant throughout the study. Where medically appropriate, all concomitant medications being taken by a participant at entry into the study should continue at the same dose.

Concomitant use of anticholinergic drugs (which may potentiate systemic anticholinergic effects) is permitted if the dosage has been stable for the 6 weeks prior to study intervention and is expected to remain at this stable dose throughout the study.

Concomitant use of any vaccine against COVID-19 is permitted from 7 days after injection of study intervention. COVID-19 vaccination dates should not be delayed to enable study participation. Participants who are unable to adhere to the COVID-19 vaccination guidance outlined in this protocol should not be included in the study (also see Section 5.2).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In this study, there will be only one treatment cycle administered on Day 1 of the study, thus discontinuation of the study intervention is not applicable. In the event, a participant is randomised, but does not receive study intervention, the participant will not remain in the study and the EoS/EW assessments will not be performed

7.1.1 Temporary Discontinuation

In case of suspected or confirmed COVID-19 (SARS-CoV-2) infection at the Baseline visit (Day 1), the study intervention administration may be temporarily postponed depending on the participant's clinical presentation. In some cases, the investigator may request a participant be retested before the intervention administration is administered.

In the event of suspected or confirmed COVID-19 infection after study intervention administration on Day 1, the participant will be required to isolate for at least 14 days and have a negative SARS-CoV-2 test before returning to the study site for the next follow-up visit. A participant may be permanently discontinued at the discretion of the investigator if further study participation is deemed to be harmful for the participant, or other participants in the study and/or study site personnel.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or compliance reasons.
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The reason for discontinuation will be recorded in the eCRF.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.
- If the participant withdraws consent, it should be explained in detail in the medical records by the investigator as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up. This information must be entered in the eCRF.
- If a participant withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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

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

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

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and cannot be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The site should counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, two certified letters to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not receive study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers and exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study participation.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or to record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 12 mL.
- Repeat or unscheduled samples may be taken for safety reasons or in case of technical issues with the samples.

8.1 Efficacy/Pharmacodynamic Assessments

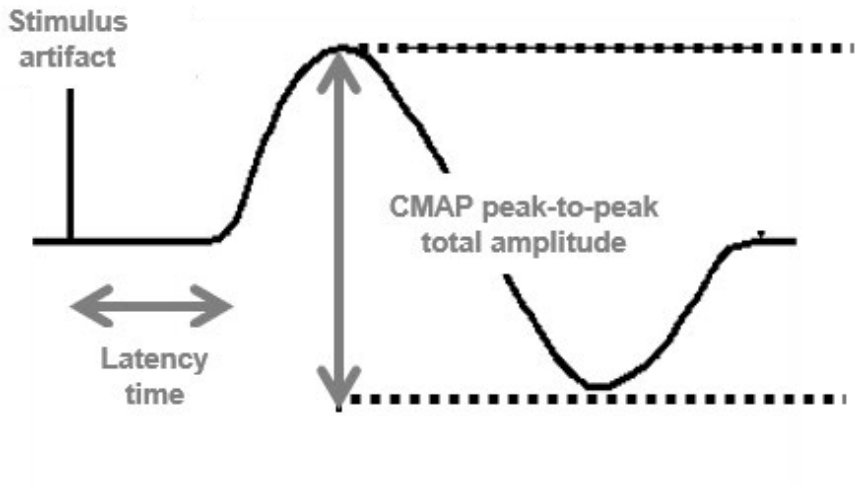
Planned timepoints for all pharmacodynamic assessments are provided in the SoA (see Section 1.3).

8.1.1 Compound Muscle Action Potential

The CMAP procedure will be performed on the injected foot by a neurophysiologist (different from the study intervention injector) at the study centre.

The effect in the EDB injected muscles will be quantified by the electrophysiologic evaluation of the CMAP peak-to-peak total amplitude (mV), elicited by supramaximal electrical stimulation of the peroneal nerve at the ankle. Latency for the M wave will also be collected (Figure 2).

Figure 2 Compound Muscle Action Potential



Surface electrodes will be used as recording electrodes (placed over the muscle belly) and reference electrodes (placed over the tendon of the corresponding muscle). The point of maximum response of both EDB, as assessed during the screening period will be marked with indelible ink to allow recording from the same site on subsequent occasions.

At each visit (including the screening visit), three measurements of CMAP will be carried out at approximately 2-minute intervals. The three values of CMAP recorded will be averaged to calculate the corresponding visit value.

The intensity in mA required to cause supramaximal stimulation should be recorded for each CMAP assessments throughout the study.

Surface skin temperature of the injected foot will be recorded and ascertained to be above 32°C prior to each CMAP test.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded at Visit 1 only. The investigator should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs (systolic and diastolic blood pressures and heart rate) will be recorded during the study. Vital signs will be measured with the participant standing and in a supine position after resting for 3 minutes. At Baseline (Day 1), vital signs will be recorded before treatment.

8.2.3 Electrocardiograms

A 12-lead ECG will be recorded at a paper speed of 25 mm/sec at Visit 1 with the participant in a supine position after 5 minutes of rest.

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
- If clinically significant/any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 10.2, must be conducted in accordance with the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 SARS-CoV-2 Testing

SARS-CoV-2 testing will be performed as outlined in the SoA (Section 1.3). Prior to the Screening visit, potential participants will be contacted by telephone and instructed not to visit the study site for at least 14 days if they have COVID-19 symptoms, have been in close contact with a positive individual, or have tested positive with COVID-19 following a SARS-CoV-2 test in the last 2 weeks. At the Screening visit, participants will be scheduled at least 5 minutes apart from one another to lessen the likelihood of infection spread. Participants will have a swab of the nose or back of the throat tested for COVID-19 infection using reverse transcription polymerase chain reaction (PCR).

Only participants who have a negative COVID-19 test at Screening will be allowed to attend the study site on Day 1 for study intervention administration. At the Baseline visit on Day 1, participants will be re-tested using a rapid SARS-CoV-2 antigen test (approximately 15 minutes) and confirmed negative prior to injection of the study intervention.

The investigator may request a participant be re-tested at any time during the study if required or in the event of suspected COVID-19 infection using PCR.

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

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 10.3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

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

8.3.2 Method of Detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilisation, the event is otherwise explained or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

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

8.3.5 Pregnancy

- Details of all pregnancies in female partners of male participants will be collected from the signing of the ICF and until completion of the study and within 90 days after the participants last dose of study intervention or completion of the study (whichever is greater).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate forms (SAE form in the eCRF and Drug Exposure Form – paper form) and submit it to the sponsor within 24 hours of learning of the female partner of male participant pregnancy (after obtaining the necessary signed informed consent from the female partner).
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

8.3.6 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for this study include:

- AEs of possible remote spread effect of toxin
- AEs suggestive of hypersensitivity reaction.

These events must be collected in the eCRF.

If they meet the seriousness criteria, they should also be reported as SAEs (refer to Appendix 10.3).

Adverse events of special interest are AEs that may not be serious but are of special importance to a particular drug or class of drugs. Such events might be precursors to more serious medical conditions, for example, muscle pain and elevated creatine phosphokinase may be indicative of potential rhabdomyolysis.

Other types of nonserious events may be important in and of themselves, such as those that could affect quality of life in a meaningful way (e.g. impotence, hair loss).

Adverse events of special interests with BoNT are events that suggest a possible remote spread effect of the toxin and are presented by function in Section 10.4 (Appendix 4). These symptoms could be related to toxin spread and in case of occurrence they should be reported and monitored carefully until resolution. AEs suggestive of hypersensitivity reaction are also of special interest and will be analysed using the Medical Dictionary for Regulatory Activities (MedDRA) Hypersensitivity standardised MedDRA queries (SMQ) (narrow). All AEs will be monitored by the sponsor to determine if they meet the criteria of AESIs.

8.3.7 Reporting of Study Intervention Errors Including Misuse/Abuse

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

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

Biomarkers are not evaluated in this study.

8.7 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics or Medical resource utilization and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary endpoint, CMAP total amplitude at Week 28, measured as relative change from 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,

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

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

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

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

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

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.

9.2 Sample Size Determination

Approximately 48 participants will 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 in all treatment arms of 15% as observed for Dysport in a historical study [redacted] – Part B. The treatment difference is based on the observed average EDB CMAP total amplitude at 6 months of Dysport 40 U ([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.

9.3 Analysis Sets

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

Participant Analysis Set	Description
Screened	All participants who signed an informed consent form
Randomised	The randomised set will contain all participants who are 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	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 will be assumed treated for the purposes of analysis.
Pharmacodynamic (PD)	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.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The COVID-19 pandemic may have an impact on this study. Participants substantially affected directly or indirectly by COVID-19 will be flagged with a protocol deviation. If the protocol deviation is major and is suspected to interfere with CMAP total amplitude, it will be handled as intercurrent event as described in Section 9.4.2.1. Further details will be provided in the SAP.

Statistical analyses will be performed by an external CRO, managed by the sponsor's biometry department. Statistical evaluation will be performed using Statistical Analysis System (SAS)® version 9.4 or higher.

9.4.1 General Considerations

Subject disposition will be summarized descriptively for all screened subjects. Discontinuations will be summarized descriptively for all randomized subjects. Demographics and other baseline characteristics will be summarized descriptively in the randomized set by study intervention group and overall.

Data collected in this trial will be summarized according to their nature as follows:

- Continuous variables: arithmetic mean, standard deviation, minimum and maximum values, median and quartiles depending on the number of observations.
- Categorical variables: absolute and relative frequencies.

A summary table of protocol deviations and the corresponding listing will be prepared.

9.4.1.1 Pharmacodynamic Evaluation

Individual pharmacodynamic endpoints will be tabulated by treatment and timepoint. For the EDB CMAP, three measurements of CMAP will be taken at each timepoint including baseline. The mean of these three measurements will be used to determine the parameter relative change from baseline in CMAP total amplitude, used in primary and secondary analyses of the EDB CMAP related endpoints. 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.

At each visit time to latency will be evaluated. Skin temperature and stimulation intensity will be also collected for quality control and descriptive statistics.

Individual pharmacodynamic endpoints will be tabulated by treatment allocation and timepoint.

Further details on general statistical considerations will be specified in the statistical analysis plan (SAP).

9.4.2 Analysis of Primary Endpoint(s)

9.4.2.1 Primary Estimand

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.
- Variable/endpoint of interest: CMAP total amplitude at Week 28, measured as relative change from Baseline (%).
    a) Key Intercurrent event (ICE): study discontinuation
    b) Major protocol deviation interfering with CMAP total amplitude.
- Treatment regimen: Dysport, Botox or Xeomin will be administered as described in Section 6 and potential intake of permitted concomitant medications (for a list see Section 6.8).
- Population-level summary of the treatment effect of interest: the difference in average relative change from baseline in each study intervention group in CMAP total amplitude at the respective timepoint.

For ICEs (a) and (b) a hypothetical strategy will be used, the treatment difference which would have been measured if the intercurrent event 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.

9.4.2.2 Primary Analysis

The primary endpoint, CMAP total amplitude at Week 28, measured as relative change from Baseline (%), will be analysed using a mixed-effects model for MMRM. The model will include fixed effects of treatment, time (corresponding to study visit), 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, 95% confidence interval, and p-value.

9.4.2.3 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 relative change from 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.

9.4.2.4 Missing Data Handling

The 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 protocol deviation interfering with CMAP total amplitude, CMAP data collected after the protocol deviation 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 intercurrent event.

9.4.2.5 Sensitivity and Supplementary Analyses

In case of occurrence of a major protocol deviation interfering with CMAP total amplitude, a supplementary analysis will be conducted using a treatment policy strategy to handle this intercurrent event. All collected CMAP data will be taken into account in this supplementary analysis, even when occurring after the protocol deviation.

9.4.3 Analysis of Secondary Endpoints

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

Recovery of CMAP total amplitude is defined as a return of total amplitude to at least 85% of the Baseline value. 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% confidence intervals for p_D , p_B and p_X and exact unconditional 95% confidence interval 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 9.1.

9.4.3.2 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.

9.4.3.3 Time to Onset of Action

Time to onset of action will be analysed descriptively. Onset of action is defined as the first timepoint where EDB CMAP total amplitude is 85% or lower than the Baseline value.

9.4.3.4 Duration of Response

Duration of response will be analysed descriptively. Duration of response is defined as the time between onset of action and recovery of CMAP total amplitude (where recovery is defined as return to at least 85% of the Baseline value).

9.4.3.5 Maximal Effect

Maximal Effect for each participant is defined as the maximal measured inhibition of CMAP amplitude of stimulated EDB. Maximal Effect will be analysed descriptively.

9.4.3.6 Time to Maximal Effect

Time to maximal effect will be analysed descriptively. Time to maximal effect is defined on an individual basis as the time between Baseline and the timepoint of maximal inhibition of CMAP amplitude of stimulated EDB.

9.4.4 Safety Analyses

All safety analyses will be made on the Safety Population.

Summary statistics will be presented by study intervention group and overall for vital signs, physical examination, at each assessment.

Adverse Events

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

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

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

All AEs, TEAEs, treatment-related AEs and study procedure-related AEs will be summarised by system organ class and preferred term in tables with the number of subjects with at least one AE and total number of AEs, the number of subjects with at least one treatment-related AE and the number of treatment-related AEs, and the number of subjects with at least one study procedure-related AE and number of study procedure-related AEs.

All AEs, treatment-related AEs, study procedure-related AEs and concomitant medications will be listed.

9.4.5 Subgroups Analyse(s)

No subgroup analyses will be performed

9.4.6 Exploratory Analyse(s)

Exploratory analyses including analysis of CMAP endpoints at timepoints different from Weeks 28 and 40 and latency of M-wave at all timepoints will be specified in the SAP.

9.5 Interim Analyses

No interim analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

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

10.1.2 Financial Disclosure

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

10.1.3 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included participant, based on the calculated costs of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

10.1.4 Insurance, Indemnity and Compensation

The sponsor will provide product liability insurance for all participants included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

10.1.5 Informed Consent Process

- The ICF and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.
- The ICF used during the informed consent process and any participant recruitment materials must be approved by the IRB/EC before use, and available for audit and inspection.
- The investigator or his/her authorised representative will explain to the participant the nature and objectives of the study and possible risks associated with the participation. They will answer all questions raised by the participant regarding the study and allow sufficient time for discussion.
- Participants must be informed that their participation is voluntary.
- The investigator or his/her authorised representative will obtain written informed consent from each participant before any study-specific procedure is performed. The investigator will retain the original of each participant's signed ICF.
- A copy of the signed ICF(s) must be provided to the participant.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- The ICF will contain a separate section that addresses the use of all data for optional future research. These data may only be used for scientific health-related research to find new ways to detect, treat, prevent or cure health problems. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. A specific consent will be required to document a participant's agreement to allow any data to be used for future research.

A participant who is rescreened will be required to sign another ICF.

If a pregnancy is reported for a female partner of a male participant during the study, the female partner will be asked to sign appropriate consent for the sponsor to follow the outcome of the pregnancy

10.1.6 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his medical records may be examined by the sponsor's auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Dissemination of Clinical Study Data

The sponsor seeks to publish the results of its clinical trials in biomedical journals, whatever the outcome. Clinical trial results may also be presented at international congresses as posters or oral presentations.

Protocol and result summary will be made publicly available on the US Clinical Trials Registry (ClinicalTrials.gov) and for studies run in the European Union (EU)/European Economic Area on the EU Clinical Trials Register (www.clinicaltrialsregister.eu). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation.

A clinical study report will be prepared if at least one participant has signed informed consent and received intervention, regardless of whether the study is completed or prematurely terminated. The clinical study report may be disclosed according to regulatory requirements.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on electronic eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study should be retained by the investigator according to the ICH-GCP guidelines, to local regulations, or as specified in the study agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

10.1.8.1 Study Monitoring

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

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

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all participants) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF and will assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator. The investigator or an approved representative (e.g. pharmacist) will ensure that all IMP is reconstituted and dispensed by unblinded qualified staff member who will document the participant allocated treatment number. Participants and investigators will remain blinded to treatment assignment during the study.

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

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

10.1.8.2 Information to Study Personnel

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

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

10.1.8.3 Investigator's Regulatory Obligations

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation that supports the information entered in the eCRF. Source data must be attributable, legible, contemporaneous, original, accurate and complete.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9.1 Recording of Study Data

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

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

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

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

10.1.9.2 Data Management

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

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigator site, (for further details see Section 10.1.8.1). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an

exact copy of the eCRF and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted CRO.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

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

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

For screen failure participants, at least the Unique Participant Identifier, the date of informed consent signature, the reason why the participant failed screening and the potential AEs which occurred during the screening phase will be reported in the eCRFs and collected in the sponsor's database. Rescreened participants will sign a new ICF and a new participant identification number will be allocated.

10.1.9.3 Record Archiving and Retention

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

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

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

10.1.10 Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Tests

Parameters	Screening	Intervention Period	EoS
Haematology			
Platelet count	X		
Red blood cell count	X		
Haemoglobin	X		
Haematocrit	X		
Red blood cell indices: MCV MCH %Reticulocytes	X		
White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	X		
Coagulation			
International normalised ratio	X		
Clinical Chemistry			
Urea	X		
Creatinine	X		
Glucose (non-fasted)	X		
Potassium	X		
Sodium	X		
Calcium	X		
Aspartate aminotransferase / Serum glutamic-oxaloacetic transaminase	X		
Alanine aminotransferase / Serum glutamic-pyruvic transaminase	X		
Alkaline phosphatase	X		
Total and direct bilirubin	X		
Total protein	X		
Other Screening Tests			
Urine drug screen	X		
SARS-CoV-2	X	X [a]	
Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody)	X		

COVID-19=coronavirus disease 2019; EoS=end of study; HIV=human immunodeficiency virus; MCH=mean corpuscular haemoglobin; MCV=mean corpuscular volume

a To be performed predose on Day 1 and at any other timepoint during the intervention period as required or in the event of suspected COVID-19 infection during the study.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

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

10.3.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

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

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

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

A suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection must be reported as serious (seriousness criteria should be "other medically significant" if no other seriousness criteria are present (e.g. hospitalisation).

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

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

AE and SAE Recording

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours of awareness of the event.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found on the SAE form and the cover sheet.

SAE Reporting to sponsor via paper

- The site will email the SAE form or fax the cover sheet and SAE form to the sponsor if the electronic data collection tool is unavailable. It must be retrospectively recorded as soon as the electronic data collection tool becomes available.
- Contacts for SAE reporting can be found on the SAE form and the cover sheet.

10.4 Appendix 4: Adverse Events of Special Interest by Function Suggestive of Possible Remote Spread of Effect of Toxin

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

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