TITLE PAGE

Protocol Number:	SN-SPAS-201
Title:	A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Treatment Efficacy and Safety Study of MYOBLOC® in the Treatment of Adult Upper Limb Spasticity Followed by an Open-Label Extension, Multiple-Treatment Safety Study of MYOBLOC®
Sponsor:	Solstice Neurosciences, LLC, a subsidiary of MDD US Operations, LLC 9715 Key West Avenue Rockville, MD 20850
IND Number:	100,995
EudraCT Number:	2020-005553-24
Investigational Medicinal Product:	MYOBLOC® (rimabotulinumtoxinB)
Indication:	Spasticity
[redacted]	
[redacted]	
[redacted]	
Version Date of Original Protocol (FDA Agreed SPA):	06 October 2016
Phase:	2/3
Amendment/Version No.	4 (Final Protocol)
Version Date	01 September 2021

Confidentiality Statement

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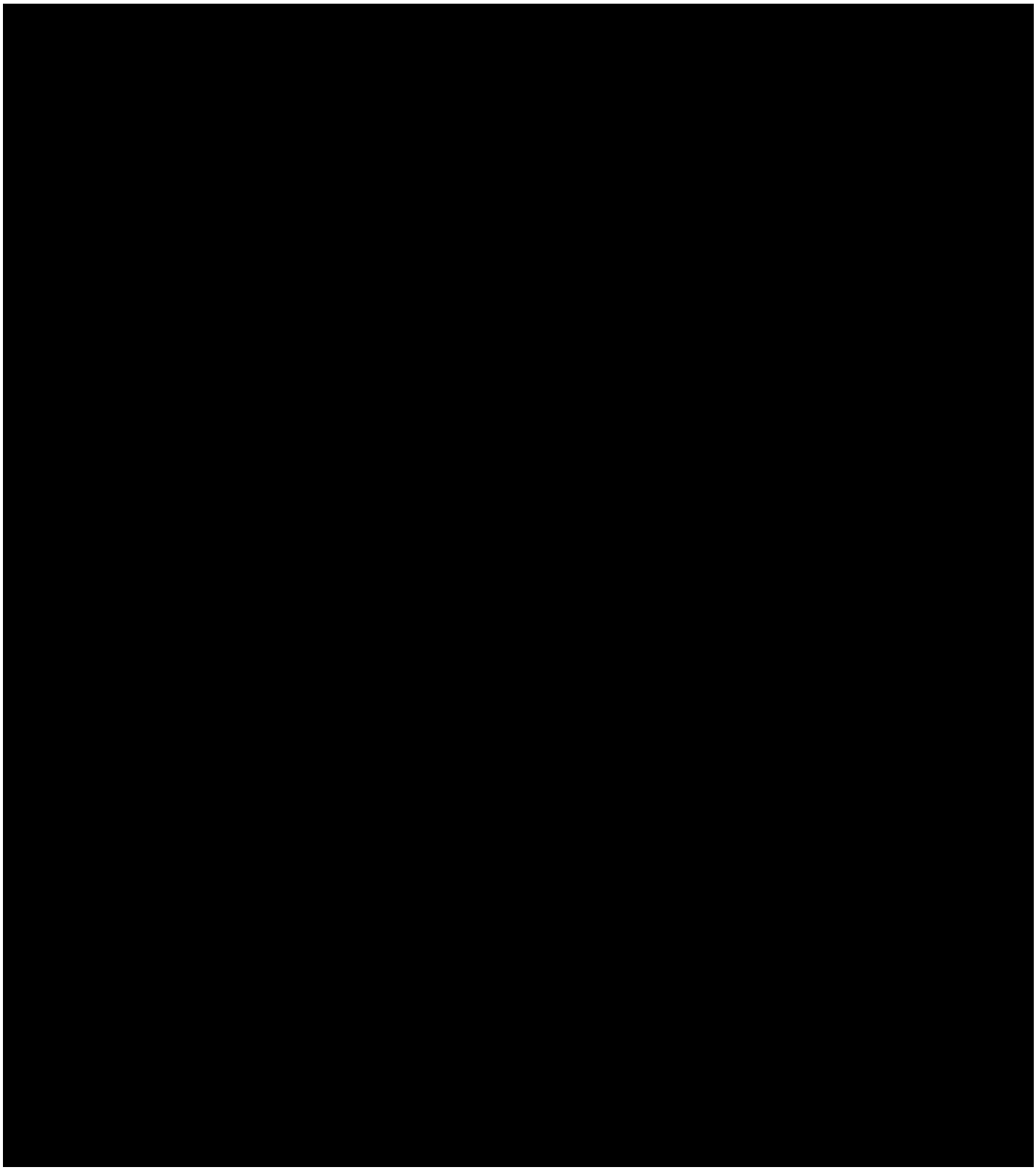
INVESTIGATOR'S SIGNATURE PAGE

I, the undersigned, have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH GCP and all applicable local guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

I have also received and read the Investigator's Brochure for MYOBLOC® (rimabotulinumtoxinB) Injection. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Principal Investigator's Signature	Date
Print Name	
Site Number	

SPONSOR'S PROTOCOL APPROVAL PAGE



STUDY CONTACTS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE(s)	Adverse Event(s)
ALS	Amyotrophic Lateral Sclerosis
BoNT/A	Botulinum toxin type A/onabotulinumtoxinA
BoNT/B	Botulinum toxin type B/rimabotulinumtoxinB
BP	Blood Pressure
CAP	College of American Pathologist
CD	Cervical Dystonia
CGI-C	Clinical Global Impression of Change
[redacted]	
CFR(s)	Code of Federal Regulation(s)
CLIA	Clinical Laboratory Improvement Act of 1988
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Double-Blind Period
DMC	Data Monitoring Committee
DSOT	Distant Spread of Toxin
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EMG	Electromyography
ERV	Expiratory Reserve Volume
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GAC	Global Assessment of Change
GCP	Good Clinical Practice
[redacted]	

Abbreviation or Specialist Term	Explanation
GWMFT	Graded Wolf Motor Function Test
H	High
HIPAA	Health Insurance Portability and Accountability Act
IC	Inspiratory Capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
IRB(s)	Institutional Review Board(s)
IRT	Interactive Response Technology
IRV	Inspiratory Reserve Volume
ITT	Intent-to-Treat
L	Low
LAR	Legally Authorized Representative
LS mean	Least-Squares Mean
MAS	Modified Ashworth Scale
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measure
N	Normal, Number
npTMG	Non-primary Target Muscle Group
OLE	Open-Label Extension
[redacted]	
PFTs	Pulmonary Function Tests
[redacted]	
PIGAC	Principal Investigator Global Assessment of Change
[redacted]	

Abbreviation or Specialist Term	Explanation
PP	Per-Protocol
PROM	Passive Range of Motion
PTMG	Primary Target Muscle Group
QTcF	QT Interval Corrected Using Fridericia's Method
RP3D	Recommended Phase 3 Dose
RR	Respiration Rate
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SVC	Slow Vital Capacity
TBI	Traumatic Brain Injury
TEAE(s)	Treatment-Emergent Adverse Event(s)
TLF	Table/Listing/Figure
ULN	Upper Limit of Normal
US	United States
[redacted]	
VCex	Expiratory Vital Capacity
VCex %pred	Percent Predicted Expiratory Vital Capacity
WBC	White Blood Cell

1. SYNOPSIS

Name of Sponsor/Company:
Solstice Neurosciences, LLC, a subsidiary of MDD US Operations, LLC

Name of Investigational Product: MYOBLOC®

Name of Active Ingredient: RimabotulinumtoxinB

Title of Study:
A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Treatment Efficacy and Safety Study of MYOBLOC® in the Treatment of Adult Upper Limb Spasticity Followed by an Open-Label Extension, Multiple-Treatment Safety Study of MYOBLOC®

Study Center(s): Approximately 30 study sites

[redacted]

Phase of development: 2/3

Objectives:
The primary objective of this trial is to assess the efficacy of MYOBLOC versus placebo in the treatment of adult upper limb spasticity.

The secondary objectives of this trial are:

[redacted]

- To evaluate the long-term safety and tolerability of MYOBLOC after multiple administrations at approximately 13-week intervals over a minimum duration of 1 year.

Methodology:

Double-Blind Period (DBP): A Phase 2/3, randomized, double-blind, placebo-controlled, single-treatment efficacy and safety study.

Phase 2:
Phase 2 will compare the efficacy and safety of 2 doses of MYOBLOC versus volume-matched placebo in the treatment of upper limb spasticity. Ninety subjects will be randomized 1:1:1 to receive a total limb dose of 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo via intramuscular (IM) injection into targeted muscles of the affected upper limb on Day 1. Efficacy and safety will be assessed at Week 2 (±3 days), Week 4 (±3 days), Week 8 (±1 week), and Week 13 (±2 weeks) post-injection and at reevaluation visits when applicable, as described below.

[redacted]

[redacted]

All [redacted] subjects who complete the 13-week (±2 weeks) treatment session of the DBP will be allowed to participate in the open-label extension (OLE), provided that they meet the retreatment criterion described below no later than 20 weeks post-injection on Day 1. The start of Treatment Session 2 in the OLE will begin the day the subject meets the retreatment criterion and study drug is administered. Thus, if at the Week 13 (±2 weeks) visit of the DBP, or if applicable, at a reevaluation visit, the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the DBP and the Day 1 visit of Treatment Session 2 in the OLE.

Open-Label Extension:

This part of the study will assess the safety and efficacy of MYOBLOC administered via IM injection once every 13 weeks (±2 weeks) over 4 treatment sessions (Treatment Sessions 2, 3, 4, and 5), provided that the retreatment criterion described below and in Section 4.1.4 is met at the end of each session. The start of a new treatment session will begin the day the subject meets the retreatment criterion and study drug is administered. Thus, if at the Week 13 (±2 weeks) visit of a treatment session, or if applicable, at the reevaluation visit, the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the current treatment session and the Day 1 visit of the next treatment session. Safety and efficacy will be assessed at Week 4 (±5 days) and Week 13 (±2 weeks) of each OLE treatment session, and if applicable at reevaluation visits, with a telephone follow-up call made by the Investigator (or designee) at Week 8 (±1 week).

Retreatment Evaluation (applicable to [redacted] subjects in both DBP and OLE) (described further in Section 4.1.4):

At the Week 13 (±2 weeks) visit of any Treatment Session, subjects will be assessed to confirm they meet the retreatment criterion of a Modified Ashworth Scale (MAS) score ≥2 in at least 1 muscle group inclusive of the elbow, wrist, and finger flexors in the affected upper limb that was injected on Day 1 of the DBP before being considered eligible for subsequent treatment sessions. If at a Week 13 (±2 weeks) visit the subject does not meet the retreatment criterion, the subject will return for up to 2 reevaluation visits. The first reevaluation visit must occur no later than 16 weeks post-injection on Day 1 of the current treatment session; and the second reevaluation visit, if needed, must occur no later than 20 weeks post-injection on Day 1 of the current session. The subject should be injected at the first reevaluation visit during which the retreatment criterion is met. The visit at which the retreatment criterion is met, and the study drug is administered will serve as both the end visit of the current treatment session and the Day 1 visit of the subsequent treatment session.

Number of Subjects: [redacted]

Double-Blind Period:

- **Phase 2:** 90 subjects randomized 1:1:1 to 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo. The volume-matched placebo group will consist of 15 subjects assigned to the low-dose group and 15 subjects assigned to the high-dose group, combined to form the final placebo group of 30 total subjects.

[redacted]

Open-Label Extension:

- It is planned that all [redacted] subjects who meet the retreatment criterion no later than 20 weeks post-injection on Day 1 of the DBP will participate in the OLE.

Diagnosis and Main Criteria for Inclusion:

Subject Inclusion Criteria:

1. Able to understand the potential risks and benefits, the study requirements, and provide written informed consent before enrollment into the study; or if unable, the subject's Legally Authorized Representative (LAR) may provide written informed consent.
2. Male or female ≥18 to maximum of 80 years of age, inclusive.
3. Upper limb spasticity due to stroke, traumatic brain injury (TBI), or spinal cord injury that occurred ≥ 6 months prior to randomization. Eligible subjects may have upper limb monoplegia or hemiplegia. Subjects with cerebral palsy are eligible for study enrollment.
4. Modified Ashworth Scale (MAS) scores ≥2 in at least two muscle groups inclusive of the elbow, wrist, and finger flexors at screening and baseline.
5. In the Investigator's opinion, the subject will be available and able to comply with the study requirements for at least 1 year, based on the subject's overall health and disease prognosis.
6. In the Investigator's opinion, the subject will be willing and able to comply with all requirements of the protocol, including completion of study questionnaires. A caregiver may be designated to assist with the physical completion of questionnaires/scales.

Subject Exclusion Criteria:

1. Quadriplegia/tetraplegia, or triplegia with both upper limbs affected.
2. Uncontrolled epilepsy or any type of seizure disorder with a seizure(s) within the previous year.
3. Neuromuscular disorders including, but not limited to, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), multiple sclerosis (MS), myasthenia gravis, or muscular dystrophy.
4. History of major joint contracture(s), in which, based on the Investigator's assessment, the contracture(s) significantly contribute(s) to joint immobility in the affected upper limb.
5. Unresolved fracture(s) in the affected upper limb.
6. Severe atrophy in the affected upper limb.
7. Known hypersensitivity to botulinum toxins type A or B or to any MYOBLOC solution components.
8. Concomitant use or exposure within 5 half-lives of randomization of the following: aminoglycoside antibiotics, curare-like agents, or other agents that may interfere with neuromuscular function.
9. Treatment with a neurolytic agent (e.g., phenol, alcohol blocks) in the affected upper limb within 1 year before randomization.
10. Presence of a spinal stimulator or intrathecal baclofen pump that has not been turned off within 30 days prior to screening.
11. Changes to treatment regimen or any new treatment with oral antispasmodics and/or muscle relaxants within 30 days prior to randomization.
12. Initiation of physical and/or occupational therapy <30 days before randomization. Subjects receiving physical and/or occupational therapy ≥30 days before randomization must be willing to maintain their therapy regimen through Week 4 of the DBP.
13. Prior botulinum toxin type A (BoNT/A) or B (BoNT/B) treatment in the affected upper limb within 24 weeks before screening. Prior BoNT/A or BoNT/B treatment in areas other than the affected upper limb is not exclusionary but must have occurred at least 12 weeks before screening. Prior toxin exposure must have been well tolerated and without any significant long-term side effects in the case of repeated prior exposure.

14. Subjects should not receive nor have any plans to receive any botulinum toxin treatment, other than the study drug (MYOBLOC), from the time that informed consent is obtained until participation in the study is complete.
15. Severe dysphagia (i.e., inability to swallow liquids, solids or both without choking or medical intervention), or dysphagia with a history of aspiration pneumonia, within 6 months before screening.
16. Prior surgery to treat spasticity in the affected upper limb (i.e., tendon lengthening or tendon transfer).
17. Any anticipated or scheduled surgery during the study period, with the exception of dermatological procedures performed under local anesthesia for the purposes of removing precancerous and cancerous lesions.
18. Major surgery within 3 months before screening.
19. Pregnancy or breastfeeding.
20. Females of childbearing potential must agree to practice a medically acceptable method of contraception (e.g., intrauterine device, hormonal contraception started at least one full cycle before study enrollment or barrier method in conjunction with spermicide) for the duration of the study (including 2 months after study completion). For the purposes of this study, all females are considered to be of childbearing potential unless they are confirmed by the Investigator to be post-menopausal (at least 1 year since last menses and laboratory test confirmation), biologically sterile, or surgically sterile (e.g., hysterectomy with bilateral oophorectomy, tubal ligation).
21. History of drug or alcohol abuse within 6 months before screening.
22. Obstructive pulmonary disease with forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <70%.
23. Slow vital capacity (SVC) <60% of predicted.
24. Chronic or current use of inhaled corticosteroids.
25. Ventilator dependence (i.e., 24-hour ventilator dependence when intubated, or due to a failure to wean the subject from the ventilator while hospitalized in the intensive care unit or respiratory care center). Subjects who use oxygen on an as-needed basis or during sleeping hours only via a nasal cannula are eligible for the study.
26. Infection at the planned sites of injection.
27. Treatment with an investigational drug, device, or biological agent within 30 days before screening or while participating in this study.
28. Malignancy diagnosed 3 months before screening.
29. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following :
    - Serum creatinine >1.5 times the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 times ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase >2 times ULN.
30. Has any of the following cardiac findings at screening:
    - Abnormal ECG that is, in the Investigator's opinion/evaluation, clinically significant;
    - PR interval >220 ms;
    - QRS interval >130 ms;
    - QTcF interval >450 ms (for men), or >470 ms (for women) (QT corrected using Fridericia's method);
    - Second-or third-degree atrioventricular block;
    - Any rhythm, other than sinus rhythm, that is interpreted or assessed by the Investigator to be clinically significant.
31. Any other medical illness, condition, or clinical finding that, in the opinion of the Investigator and/or the Sponsor, would put the subject at undue risk.

Investigational Product, Dosage and Mode of Administration:

Double-Blind Period [redacted]:

On Day 1 and prior to randomization, the Investigator will select two muscle groups inclusive of the elbow, wrist, and finger flexors to target for treatment. Both selected muscle groups must have a MAS score ≥2 but only one will be designated as the Primary Target Muscle Group (PTMG); the other muscle group will be designated the non-primary Target Muscle Group (npTMG). The designation of the PTMG will be made at the discretion of the Investigator. Randomization will be stratified by the PTMG (elbow, wrist, or finger flexors). Site staff will connect to the Interactive Response Technology (IRT) system to enter the subject's information after confirming eligibility.

On Day 1, a fixed dose will be administered to the PTMG per the dose-per-muscle ranges outlined for each treatment group in Table S-1.

Table S-1. Required PTMG Muscles and Dose-per-Muscle Ranges During the DBP

Primary Target Muscle Group	Upper Limb Muscle	MYOBLOC or Placebo (volume-matched)						Number of Injection Sites
		Low-Dose Group 10,000 Units			High-Dose Group 15,000 Units			
		Minimum (Units)	Maximum (Units)	Total Dose (Units)	Minimum (Units)	Maximum (Units)	Total Dose (Units)	
Elbow flexors*	Biceps brachii	2,500	3,500	5,000	5,000	7,000	10,000	3
	Brachioradialis	1,500	2,500		3,000	5,000		2
Wrist flexors†	Flexor carpi radialis	1,000	1,500	2,500	2,000	3,000	5,000	2
	Flexor carpi ulnaris	1,000	1,500		2,000	3,000		2
Finger flexors ‡	Flexor digitorum profundus	1,000	1,500	2,500	2,000	3,000	5,000	2
	Flexor digitorum superficialis	1,000	1,500		2,000	3,000		2
Required Total Limb Dose[#, ∞]		**10,000 Units**			**15,000 Units**			

DBP = double-blind period; PTMG = primary target muscle group

* If the elbow flexors are selected as the PTMG, both the biceps brachii and brachioradialis muscles are required to be injected within the specified ranges so that the total dose administered to the elbow flexors equals 5,000 Units or 10,000 Units (or volume-matched placebo) if assigned to the low-dose group or the high-dose group, respectively.

† If the wrist flexors are selected as the PTMG, both the flexor carpi radialis and the flexor carpi ulnaris muscles are required to be injected within the specified ranges so that the total dose administered to the wrist flexors equals 2,500 Units or 5,000 Units (or volume-matched placebo) if assigned to the low-dose group or the high-dose group, respectively.

‡ If the finger flexors are selected as the PTMG, both the flexor digitorum profundus and the flexor digitorum superficialis muscles are required to be injected within the specified ranges so that the total dose administered to the finger flexors equals 2,500 Units or 5,000 Units (or volume-matched placebo) if assigned to the low-dose group or the high-dose group, respectively.

[#] Total Limb Dose includes PTMG and npTMG injections.

[∞] The total body maximum dose should not exceed 32,500 Units.

The npTMG selected for treatment will be injected on Day 1 in accordance with the dose-per-muscle ranges listed in Table S-2.

Table S-2. Required npTMG Muscles and Dose-per-Muscle Ranges During the DBP

Non-primary Target Muscle Group	Upper Limb Muscle	MYOBLOC or Placebo (volume-matched)		Number of Injection Sites
		Minimum (Units)	Maximum (Units)	
Elbow flexors*	Biceps brachii	2,500	7,000	3
	Brachioradialis	1,500	5,000	2
Wrist flexors†	Flexor carpi radialis	1,000	3,000	2
	Flexor carpi ulnaris	1,000	3,000	2
Finger flexors‡	Flexor digitorum profundus	1,000	3,000	2
	Flexor digitorum superficialis	1,000	3,000	2
Thumb#	Flexor pollicis longus	1,000	2,500	1-2
	Adductor pollicis	1,000	2,500	1-2
Forearm$	Pronator teres	1,000	3,000	1-2

DBP = double-blind period; npTMG = non-primary target muscle group

* If the elbow flexors are selected as the npTMG, both the biceps brachii and brachioradialis muscles are required to be injected within the specified ranges.

† If the wrist flexors are selected as the npTMG, both the flexor carpi radialis and the flexor carpi ulnaris muscles are required to be injected within the specified ranges.

‡ If the finger flexors are selected as the npTMG, both the flexor digitorum profundus and the flexor digitorum superficialis muscles are required to be injected within the specified ranges.

If the thumb muscles are selected as the npTMG, both the flexor pollicis longus and the adductor pollicis muscles are required to be injected within the specified ranges.

$ If the forearm muscle is selected as the npTMG, the pronator teres muscle is required to be injected within the specified ranges.

If there is study drug remaining after injecting the required muscles of both the PTMG and the npTMG, then additional muscles must be selected for treatment but only those listed in Table S-2 are eligible, and the dose administered must be in accordance with the dose-per-muscle ranges outlined in Table S-2. Under these circumstances, both muscles of a muscle group are **not** required to be injected.

Note that subjects assigned to the low-dose group or to the high-dose group must be administered a total limb dose that equals 10,000 Units or 15,000 Units (or volume-matched placebo), respectively.

[redacted]

[redacted]

All [redacted] subjects who complete Treatment Session 1 of the DBP will be allowed to participate in the OLE provided the retreatment criterion (Section 4.1.4) is met no later than 20 weeks post-injection of Day 1 of the DBP.

Open-Label Extension:

During the OLE, [redacted] subjects will be administered MYOBLOC via IM injection once every 13 weeks (±2 weeks), over 4 treatment sessions (Treatment Sessions 2, 3, 4, and 5) provided the retreatment criterion is met at the end of each session (not to exceed a treatment session interval of 20 weeks). The affected upper limb that was injected on Day 1 of the DBP must be injected at each treatment session throughout the OLE. The selection of muscles to inject in the affected upper limb will be at the discretion of the Investigator; however, only those listed in Table S-3 are eligible for injection, and the dose administered to the selected muscles must be in accordance with the dose-per-muscle ranges listed in Table S-3.

Table S-3. Eligible Upper Limb Muscles and Dose-per-Muscle Ranges During the OLE

Muscle	MYOBLOC Dose (Units)		Number of Injection Sites
	Minimum	Maximum	
Biceps brachii	2,500	7,000	1-3
Brachioradialis	1,500	5,000	1-2
Flexor carpi radialis	1,000	3,000	1-2
Flexor carpi ulnaris	1,000	3,000	1-2
Flexor digitorum superficialis	1,000	3,000	1-2
Flexor digitorum profundus	1,000	3,000	1-2
Flexor pollicis longus	1,000	2,500	1-2
Adductor pollicis	1,000	2,500	1-2
Pronator teres	1,000	3,000	1-2

OLE = open-label extension

Duration of Treatment:

[redacted] **Double-Blind Period**

- 13 weeks (±2 weeks) or until the retreatment criterion is met (maximum 20 weeks post-injection) following a single injection session of multiple upper limb muscles

[redacted]

Open-Label Extension

- 52 weeks: Four 13-week (±2 weeks) treatment sessions, or until the retreatment criterion is met at the end of each session (maximum 20-week treatment session interval)

Total Duration:

- 65 weeks per subject: Five 13-week (±2 weeks) treatment sessions, or until the retreatment criterion is met at the end of each session (maximum 20-week treatment session interval)

Criteria for Evaluation:

Efficacy:

The efficacy assessments listed below will be performed at each clinic visit during [redacted] the DBP and the OLE as outlined in the Schedules of Assessments (Table 9 and Table 10):

- Modified Ashworth Scale (MAS)
- Clinical Global Impression of [redacted] Change (CGI-C)

[redacted]

Safety:

The safety assessments/procedures listed below will be performed during [redacted] the DBP and the OLE as outlined in the Schedules of Assessments (Table 9 and Table 10):

- Occurrence, seriousness, severity, and causality assessment of adverse events (AEs) at each clinic visit/telephone follow-up
- Concomitant medications
- Urinary pregnancy test for females of childbearing potential
- Vital signs (systolic/diastolic blood pressure, pulse, respiration rate, and temperature)
- 12-Lead Electrocardiograms (ECGs)
- Clinical laboratory tests
- Physical examination (complete or brief)
- Neurologic examination
- Pulmonary function tests (PFTs; via spirometry)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

Co-primary Efficacy Endpoints:

Phase 2 [redacted] of the Double-Blind Period

- Change from baseline in tone of the PTMG selected for treatment as measured by the MAS at Week 4 post-injection
- Clinical Global Impression of Change (CGI-C) in functional ability at Week 4 post-injection

[redacted]

[redacted]

Safety Endpoints:

The safety endpoints listed below will be assessed by treatment group throughout [redacted] the DBP and the OLE as outlined in the Schedules of Assessments (Table 9 and Table 10):

- Occurrence, seriousness, severity, and causality assessment of AEs
- Vital signs (systolic/diastolic blood pressure, pulse, respiration rate, and oral temperature)
- 12-Lead Electrocardiograms (ECGs)
- Serum chemistry, hematology, and urinalysis
- Neurologic examination findings
- PFTs (via spirometry)
- C-SSRS

2. INTRODUCTION

2.1. Background and Significance

2.1.1. Spasticity

Spasticity is one of the signs of injury to upper motor neurons caused by damage to the portion of the brain or spinal cord that controls voluntary movement. It is characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) and exaggerated tendon reflexes that inhibit normal neuromuscular function. Spasticity commonly occurs in patients afflicted with a variety of neurologic disorders, including cerebrovascular accident, multiple sclerosis (MS), stroke, traumatic brain injury (TBI), cervical spinal cord injury, and cerebral palsy. Patients are disabled by 3 main features, including paresis, soft tissue contracture, and stretch-sensitive (spastic) muscle overactivity.[1, 2] The disorder can cause significant pain and wide-ranging disabilities, leading to impaired quality of life in many patients to total functional dependence in the most severely afflicted patients.

Several pharmacologic treatments are currently approved in the United States (US) to treat spasticity, including systemic agents (baclofen, diazepam, dantrolene sodium, and tizanidine) and a botulinum neurotoxin (botulinum toxin type A, onabotulinumtoxinA, BoNT/A, Botox®) by local injection. The sedative effects associated with systemic agents can limit their use, and some patients become tolerant or non-responsive to BoNT/A over time. Botulinum toxin type B (BoNT/B, rimabotulinumtoxinB, MYOBLOC),[3] which has a different mechanism of action than the A serotype (i.e., the serotypes cleave different protein chains),[4, 5, 6] is sometimes used off-label to treat adults and children with spasticity. When used for spasticity, BoNT/B is sometimes used in higher doses than those approved for the treatment of cervical dystonia, even though there is limited established guidance for its safe and effective use. Thus, this study will investigate the safety and efficacy of BoNT/B in adults with upper limb spasticity resulting from an upper motor neuron diagnosis.

2.1.2. MYOBLOC

MYOBLOC® (rimabotulinumtoxinB, BoNT/B) is a sterile liquid formulation of a purified neurotoxin that inhibits the release of acetylcholine at neuromuscular junctions resulting in local muscle weakness (or paralysis) that gradually reverses over time. The neurotoxin is produced by fermentation of the bacterium *Clostridium botulinum* type B (Bean strain). MYOBLOC is provided as a clear and colorless to light-yellow sterile injectable solution in single-use, 3.5-mL glass vials, with each vial of formulated MYOBLOC containing 5,000 Units of botulinum toxin type B per milliliter in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at approximately pH 5.6. One Unit of botulinum toxin corresponds to the calculated median lethal intra-peritoneal dose in mice.

MYOBLOC is currently approved by the Food and Drug Administration (FDA) for use in the US for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia and for the treatment of adults with chronic sialorrhea.

2.1.3. Efficacy of MYOBLOC in Extremity Spasticity

Several studies of MYOBLOC in patients with upper and/or lower limb spasticity have been completed including studies conducted by the Sponsor (Solstice Neurosciences, LLC). In addition, there are reports in the literature of its use in treating spasticity. Variable results have been reported, with some studies or reports showing dramatic improvement and others showing no difference between placebo and active

treatment. The small sample sizes, varying doses, and scales used in these trials have likely contributed to the differences in reported responses.

2.1.3.1. Sponsor's Studies

Study AN072-101SPAS was a multicenter, double-blind, single-treatment, sequential dose-escalation study in 24 subjects with multiple sclerosis (MS) and lower limb adductor spasms.[7, 8] Subjects were randomized to doses of 25,000 Units to 40,000 Units (at 5,000 Unit increments) of MYOBLOC or matched placebo (there was a dose-dependent increase in treatment-related adverse events was observed at 35,000 and 40,000 Units and, therefore, the study did not continue on to the highest planned dose of 45,000 Units). Efficacy measures and scales included the level of muscle tone associated with adductor spasticity of the lower limbs using the Ashworth Scale and Modified Ashworth Scale (MAS) and adductor tone rating scale; range of movement of the lower limbs; frequency of spasms and episodes of clonus; assessment of hygiene; assessment of sexual function; subject pain visual analog scale (VAS); and Investigator, subject, and caregiver global VAS. The study design and small number of subjects per dose of MYOBLOC and placebo limited the efficacy conclusions that could be drawn. In general, there was no apparent benefit of MYOBLOC over placebo, and total body doses up to 30,000 Units were well tolerated.

Study AN072-104SPAS was a Phase 1, randomized, double-blind, placebo-controlled, single-dose study of MYOBLOC versus placebo in MS subjects with adductor spasticity of the lower limbs.[8, 9] A total of 28 subjects were randomized to receive a single dose of either 30,000 Units of MYOBLOC or matched placebo. The dose was split equally between legs and injected into 2 to 4 affected leg muscles per limb. Subjects were followed for 16 weeks after injection, with efficacy measures consisting of muscle tone and range of movement assessments; frequency of spasm and episodes of clonus; hygiene and sexual function assessments; and VAS for pain and overall assessments. Results demonstrated small, but consistent, improvements in the combined and modified combined Ashworth Scale scores and a small benefit in adductor tone from Week 4 onward in subjects treated with MYOBLOC. The treatment difference in change from baseline to Week 4, however, was not statistically significant. No apparent benefit of MYOBLOC over placebo was observed in the other efficacy measures used in this study. The study design and small number of subjects in the MYOBLOC and placebo groups limited the efficacy conclusions that could be drawn.

Study SN-SPAS-602, a retrospective chart review of 101 subjects from multiple clinical sites, was done to estimate the total, per-limb, and per-muscle dosing of MYOBLOC used in the clinical treatment of spasticity in adult subjects.[10] All subjects had a diagnosis of spasticity, with varying etiologies, the two most frequent being spastic hemiparesis/hemiplegia (22.8%) and late-effect cerebrovascular disease (20.8%). The mean total dose of MYOBLOC injected per patient at the first injection session was 12,772 Units, divided among different muscles. Efficacy, as assessed on a 7-point Clinical Global Impression scale ranging from "very much improved" to "very much worse" showed improvement after two injection sessions, with the majority of patients scoring in the "much-improved" or "very-much-improved" categories.

2.1.3.2. Literature Reports

2.1.3.2.1. Double-Blind, Placebo-Controlled Studies

Brashear and colleagues[11] published results from their double-blind, placebo-controlled study in patients with upper limb spasticity who were naïve to botulinum toxin or phenol injections. Nine patients received a total dose of 10,000 Units of MYOBLOC (dose split across 5 upper limb muscles), and 5 patients received matched placebo. Patients were followed for 16 weeks after injection, with efficacy measures consisting of the Ashworth Scale at 4 weeks post-injection (primary); Principal Investigator Global Assessment of Change (PIGAC); patient Global Assessment of Change (patient GAC); and Global Assessment by the occupational therapist (therapist GAC). At the conclusion of 16 weeks, patients were offered enrollment in an open-label phase of the study. Ashworth Scale scores for the wrist flexors decreased significantly in the MYOBLOC group at Week 2 (p=0.003); at Week 4, the greatest improvement observed in patients treated with MYOBLOC was for wrist flexor tone. Patients treated with MYOBLOC also showed improvements in the elbow, finger, and thumb flexors; however, this improvement was not significantly different between treatment groups. This study did not show as robust an effect of a total limb dose of 10,000 Units of MYOBLOC that had been seen in the authors' earlier open-label study, most likely because of (1) the small sample size of the entire study and the low number of placebo patients, and (2) the doses given in these muscles may have been too low to show an effect.

Gracies and colleagues[12] reported results from their double-blind, placebo-controlled, dose-ranging study that evaluated the effects of MYOBLOC in 24 adult hemiparetic patients with disabling over-activity in their elbow flexors. Patients were randomized into 3 treatment groups: placebo, MYOBLOC 2,500 Units into the elbow flexors (10,000 Units total dose), or MYOBLOC 5,000 Units into the elbow flexors (15,000 Units total dose). The noted fixed dose was injected into the elbow flexors, with additional upper limb injections into the shoulder, wrist, or finger muscles allowed as per Investigator discretion up to the fixed total dose for the respective treatment group. Efficacy measures included active range of elbow extension via goniometer; rapid alternating movement frequency in elbow flexion and extension; spasticity grade (Tardieu scale); and elbow flexor tone (Ashworth Scale). Active range of elbow extension improved in both MYOBLOC groups when compared to placebo at 1-month post-injection (p=0.028); the effect wore off 2 months after injection. Improvements in rapid alternating movements over the maximal range of elbow flexion-extension and reduction of elbow flexor tone in the high-dose group were not significant.

2.1.3.2.2. Open-Label Studies

O'Brien and Mancini[13] reported results of an open-label study of MYOBLOC in the treatment of patients with arm or leg spasticity due to cerebrovascular accident, spinal cord injury, or TBI. Nine patients were administered a total dose of 10,000 Units, and 1 patient received a total dose of 5,000 Units into forearm, hand, hamstring, or calf muscles, and patients were followed for 12 weeks post-injection. A reduction of MAS scores, by 1 to 2 points, was most prominent in the wrist and finger flexors at Weeks 4 and 8. Minimal reduction in the Medical Research Council scale and no weakness in non-targeted muscles were observed. Improvements were noted in global assessment scores, goal attainments, and in pain scale scores, primarily in the distal muscles at Weeks 4 and 8.

Brashear and colleagues[14] reported results of their open-label study of MYOBLOC in patients with upper limb spasticity due to stroke or TBI. Ten patients, naïve to botulinum toxin or phenol injections, received a single treatment with MYOBLOC (10,000 Units total dose) and were followed for 12 weeks post-

injection, with efficacy measures consisting of Ashworth Scale at 4 weeks post-injection (primary); PIGAC; patient GAC; and therapist GAC. The change in the Ashworth Scale score was significant at Weeks 4 and 8 for the elbow, at Weeks 4, 8, and 12 for the wrists, and at Week 4 for the fingers. Additionally, a time effect for the Ashworth Scale score was observed at the wrist (p=0.0029) and finger (p=0.0154) but not the elbow (p=0.40). The PIGAC scores were significant at each time point, and the patient and therapist GAC scores were significant at Weeks 4 and 8.

Jayasooriya and colleagues[15] reported the results of their open-label study of MYOBLOC in adults with upper limb spastic hypertonia secondary to cerebrovascular accident (n=8) or trauma (n=3) who had previously been treated with BoNT/A (as Botox®) with doses ranging up to 900 Units, but their responses to therapy had apparently decreased over time, despite increases in BoNT/A dose. Total doses of MYOBLOC administered ranged from 4,250 Units to 17,500 Units (mean=12,325 Units), and patients were followed for 12 weeks post-injection. At Week 6, the mean Ashworth Scale score (primary efficacy variable) improved significantly from baseline (i.e., 2.8 to 1.4, p<0.001), and at Week 12 the mean score was still lower than baseline at 2.2 (p<0.0625).

Hecht and colleagues[16] reported the results of their open-label study of the effects of MYOBLOC on shoulder pain, hypertonia, and function in 14 adults with spastic hemiparesis. Patients received a single treatment with MYOBLOC (10,000 to 12,000 Units total dose) divided over the subscapularis and pectoralis major muscles and were followed for 10 weeks post-injection. Efficacy measures included passive range of motion (PROM), VAS pain, Ashworth Scale, and the Graded Wolf Motor Function Test (GWMFT). PROM for shoulder flexion, abduction, and external rotation improved in 53% of patients over the 10-week follow-up period. Shoulder pain during activity decreased significantly (p=0.002) over the study in 86% of patients. Hypertonia in the pectoralis major was significantly reduced (p=0.013). Spasticity scores for the subscapularis decreased during follow-up, and 86% of patients showed continual improvement in the timed component of the GWMFT at 10 weeks post-injection.

2.1.3.2.3. Case Reports

Case reports describe positive results in patients treated with MYOBLOC, including pain relief in a patient with muscle spasms secondary to scoliosis,[17] increased ambulation and function in a patient with a C4 fracture and incomplete quadriplegia due to a fall,[18] and control of spasms and pain in a patient with complete motor and sensory C6 quadriplegia due to a diving accident.[19] Total doses of MYOBLOC administered in these patients ranged from 10,000 to 20,000 Units.

2.1.4. Safety of MYOBLOC in Extremity Spasticity

2.1.4.1. Sponsor's Studies

Study AN072-101SPAS in 24 subjects with multiple sclerosis and lower limb adductor spasms evaluated the safety and efficacy of MYOBLOC at doses of 25,000 Units to 40,000 Units (at 5,000 Unit increments) versus matched placebo.[7, 8] All of the subjects experienced at least 1 AE, with dry mouth, dysphagia, constipation, and blurred vision being the most frequently reported treatment-related AEs in subjects who received MYOBLOC. Most AEs were mild or moderate in severity. Of AEs reported as severe, only weight loss and dry mouth were considered treatment related. A dose-dependent increase in treatment-related AEs was observed at 35,000 and 40,000 Units and, therefore, the study did not continue on to the highest dose planned (45,000 Units). One death occurred in the study. This was in a subject

with multiple co-morbidities and medications and was considered by the Investigator to be unrelated to MYOBLOC.

Study AN072-104SPAS in 28 subjects with multiple sclerosis and adductor spasticity of the lower limbs evaluated the safety and efficacy of 30,000 Units of MYOBLOC versus matched placebo.[8, 9] Twenty-three subjects (82%) experienced at least 1 AE, with dry mouth, asthenia, dysphagia, and dyspepsia being the most frequently reported treatment-related AEs in subjects who received MYOBLOC. Two MYOBLOC-treated subjects experienced SAEs. One of these subjects had dysphagia, which was considered treatment related by the Investigator. The second subject had an enlarged abdomen, leukorrhea, syncope, and infection; all 4 serious events were considered treatment related by the Investigator. The subject was hospitalized and discontinued from the study due to the enlarged abdomen and leukorrhea. These events resolved, but the subject subsequently died from a chest infection that was considered by the Investigator to be treatment related. This case was highly confounded by the subject's pre-existing co-morbidities, including a pre-treatment history of significant dysphagia, recurrent chest infections, and aspiration pneumonia. Although 30,000 Units of MYOBLOC was reasonably well tolerated in the majority of the subjects in this study, the Investigator considered the infection that led to the death of one subject as potentially related to MYOBLOC.

Study SN-SPAS-602, a retrospective chart review of 101 adult subjects from multiple clinical sites, was done to estimate the total, per-limb, and per-muscle dosing of MYOBLOC used in the clinical treatment of spasticity in adults.[10] The mean total dose of MYOBLOC injected per subject at the first injection session was 12,772 Units (standard deviation [SD] 7,885 Units), divided among different muscles. Treatment with MYOBLOC was well tolerated, with 10% of subjects reporting 12 AEs, including dry mouth, gastroesophageal reflux disease, and hypoesthesia. All AEs were considered temporary and mild to moderate in intensity, and all AEs resolved. No SAEs, no deaths, and no discontinuation of treatment with MYOBLOC due to an AE/SAE were reported.

2.1.4.2. Adverse Event Reports in the Sponsor's Postmarketing Pharmacovigilance Database

As of 31 October 2020, the Sponsor has received a total of 2,717 events reported in approximately 1,108 patients, with the majority of events reported in the adult population, since the initial approval of MYOBLOC, by the FDA in 2000 for CD, and more recently in 2019 for sialorrhea. Age was not always captured in the postmarketing database; however, 64 patients between 1 and 17 years of age reported an adverse event. All other cases are assumed to have occurred in the adult population. Additional details are provided in the MYOBLOC Investigator's Brochure.

The following adverse reactions have been reported during postmarketing safety surveillance for MYOBLOC: angioedema, urticaria, rash, constipation, dry eye, and accommodation disorder. (MYOBLOC Label, 2020). Since these adverse events were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Of the total reported postmarketing AEs, there are 482 SAEs reported by 163 patients. The most common SAEs (N) in decreasing order are dysphagia (35), overdose (14), asthenia (13), dry mouth (12), and dyspnea (12). It should be emphasized that, these most frequently reported SAEs are of low incidence and were not life threatening. Overall, and based on postmarketing experience, MYOBLOC is well tolerated and safe, with a very low frequency of SAEs. A limited number of the reported SAEs were assessed as related to MYOBLOC therapy.

2.1.4.3. Adverse Event Reports in the Literature

Two prospective, controlled studies of MYOBLOC versus placebo in patients with upper limb spasticity have been reported.[11, 12] No adverse effects associated with MYOBLOC (up to 10,000 Units or 15,000 Units) were reported by Gracies and colleagues.[12] In the study by Brashear and colleagues,[11] dry mouth was reported in 8 of 9 MYOBLOC-treated patients versus 1 of 5 placebo-treated patients, and 1 death was reported, but the cause of death (stroke) was determined to be unrelated to MYOBLOC.

Adverse events reported in open-label studies of MYOBLOC in patients with spasticity were mainly dry mouth, including 16 of 24 patients who received up to 17,500 Units of MYOBLOC.[14, 15] Some temporary and self-limited AEs (i.e., focal weakness, fatigue, dry mouth, flu-like symptoms) were reported by O'Brien and Mancini[13] in their 12-week open-label study of MYOBLOC (10,000 Units, n=9; 5,000 Units, n=1). No AEs were reported by Hecht and colleagues[16] in their open-label study of MYOBLOC (10,000 to 12,000 Units, n=14). In case reports in the literature, temporary local discomfort at the MYOBLOC injection site was reported in a patient with lower limb spasticity[17]; no AEs were reported in 4 other patients with lower limb spasticity[20] or 2 patients with quadriplegia.[18, 19]

2.2. Study Rationale

[redacted] The placebo-controlled, double-blind period (DBP) of the study is designed [redacted] to evaluate the efficacy of multiple doses of MYOBLOC in the treatment of adult upper limb spasticity. [redacted] The open-label extension (OLE) period of the study is designed [redacted] to collect long-term safety data assessing potential distant toxin spread after multiple administrations of MYOBLOC over a minimum duration of 1 year.

2.2.1. Dose Selection and Dosage Regimen

Initial dosing in this study will be 10,000 Units and 15,000 Units with a dosing interval of approximately 13 weeks (±2 weeks). The maximum upper limb dose will not exceed 20,000 Units, the maximum lower limb dose (if selected for treatment in the OLE) will not exceed 17,500 Units, and the maximum total body dose will not exceed 32,500 Units.

The totality of the available data[10, 11, 12, 13, 14, 15] suggest that doses of 10,000 Units and 15,000 Units of rimabotulinumtoxinB may be effective for the treatment of upper limb spasticity. In contrast, data support that single upper limb starting doses above 15,000 Units of MYOBLOC may present safety concerns. Inconsistency of the reported results at doses of 10,000 Units and 15,000 Units indicate further evaluation is warranted and necessary in order to establish clinically relevant and effective doses.

Studies on the use of MYOBLOC in the treatment of cervical dystonia show that increased doses may be necessary over time and that gradual increases are generally well tolerated with total doses of ≥25,000 Units used in the long-term treatment of cervical dystonia[3] (with dosing in much greater proximity to high-risk muscles involved with swallowing and pulmonary function). Accordingly, a maximum upper limb dose of 20,000 Units will be permitted provided a 15,000 Unit dose administered at a previous session is well tolerated. In studies investigating MYOBLOC in the treatment of cervical dystonia, the duration of effect has been observed to be between 12 and 16 weeks.[3] Although the duration of effect of

MYOBLOC in the treatment of upper limb spasticity has yet to be established, the duration of effect of botulinum toxin type A when used to treat upper limb spasticity has been reported to be between 12 and 20 weeks post-injection[24]; therefore, a minimum treatment session interval of 13 weeks (±2 weeks) post-injection and a maximum treatment session interval of 20 weeks post-injection was selected for this study.

A considerable body of data from the published literature, previously conducted prospective clinical trials, and patient experience from a retrospective review of charts of patients treated with MYOBLOC for spasticity support its safety at a total body dose of up to 32,500 Units at a single administration with an increased frequency of AEs being observed at total body doses exceeding 35,000 Units.[7, 8, 9, 10, 11, 12, 13, 14, 15] Based on these data, the maximum upper limb dose will not exceed 20,000 Units, the maximum lower limb dose (if selected for treatment in the OLE) will not exceed 17,500 Units, and the maximum total body dose will not exceed 32,500 Units in this study.

3. TRIAL OBJECTIVES AND PURPOSE

The overall purpose of this trial is [redacted] evaluating the efficacy and safety of MYOBLOC [redacted] n the treatment of adult upper limb spasticity.

3.1. Primary Objective

The primary objective of this trial is to assess the efficacy of MYOBLOC versus placebo in the treatment of adult upper limb spasticity.

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is designed as a 2-part study consisting of a DBP followed by an OLE period. [redacted] This study is planned to be conducted at approximately 30 study sites and will include [redacted] 90 subjects in Phase 2 [redacted], both male and female. All [redacted] subjects who meet the retreatment criterion (Section 4.1.4) no later than 20 weeks post-injection on Day 1 of the DBP will be eligible to participate in the OLE.

Excluding the 21-day screening period, the planned duration of participation for each subject in [redacted] the DBP is 13 weeks (±2 weeks) (Treatment Session 1; Figure 1). The planned duration of participation for each subject in the OLE is 52 weeks, or four 13-week (±2 weeks) treatment sessions: Treatment Sessions 2, 3, 4, and 5 (Figure 2). Each treatment session will be a minimum of 13 weeks (±2 weeks) and a maximum of 20 weeks. The start of a new treatment session will begin once the retreatment criterion is met and study drug is administered. The database will be locked and treatment assignments will be unblinded after the last Phase 3 subject completes the last visit of the DBP, including any reevaluation visits if applicable (see Section 6.1.2 and Section 11.7.5 for details).

All subjects will be screened for eligibility to participate in the study, including: review of inclusion and exclusion criteria; medical, surgical, and medication history; complete physical examination (including vital signs, height, and weight); 12-lead electrocardiogram (ECG); pulmonary function tests (PFTs) via spirometry; neurologic examination; clinical laboratory testing; and urine pregnancy testing (females of childbearing potential only). Eligible subjects will have the following procedures/assessments conducted on Day 1 before randomization and subsequent injection of study drug or volume-matched placebo: brief physical examination (including vital signs); ECG; a urine pregnancy test (a negative result must be confirmed prior to injection), neurologic examination; Columbia Suicide Severity Rating Scale (C-SSRS[25]); PFTs via spirometry; efficacy assessments (administered by a qualified assessor) including the MAS and Clinical Global Impression [redacted]

On Day 1 and prior to randomization, the Investigator will select two muscle groups inclusive of the elbow, wrist, and finger flexors to target for treatment. Both selected muscle groups must have a MAS score ≥2 but only one will be designated as the Primary Target Muscle Group (PTMG); the other muscle group will be designated the non-primary Target Muscle Group (npTMG). The designation of the PTMG will be made at the discretion of the Investigator. Randomization will be stratified by the PTMG (elbow, wrist, or finger flexors). Site staff will connect to the IRT system to enter the subject's information after confirming eligibility.

Subsequent study visits will occur at 2 weeks (±3 days), 4 weeks (±3 days), 8 weeks (±1 week), and 13 weeks (±2 weeks) post-injection during the DBP, and at 4 weeks (±5 days), and 13 weeks (±2 weeks) post-injection with a telephone follow-up made by the Investigator (or designee) 8 weeks (±1 week) post-injection during the OLE. It is anticipated that most subjects will meet the retreatment criterion at the Week 13 (±2 weeks) visit of each treatment session. If a subject does not meet the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session, then the study drug will not be administered, and the subject will return to the clinic for a maximum of two reevaluation visits until the retreatment criterion is

met. The first reevaluation visit must occur no later than 16 weeks post-injection of Day 1 of the current session; and the second must occur no later than 20 weeks post-injection of Day 1 of the current session. The subject should be injected at the first reevaluation visit during which the retreatment criterion is met. The visit at which the retreatment criterion is met, and study drug is administered will serve as both the end visit of the current treatment session and the Day 1 visit of the subsequent treatment session. Subjects will not be considered non-compliant if visit windows extend as a result of extraordinary events (e.g., personal emergencies, holidays, vacations, any other issues with study visit scheduling) that would make it impossible for subjects to complete a visit within the defined visit windows. Such occurrences should be clearly and carefully documented in the subject's source document and the comment section on the electronic case report form (eCRF) for that visit, with approval granted in advance by the Medical Monitor as feasible. The determination of the maximum visit window deviation will be per Medical Monitor discretion.

Efficacy and safety assessments will be performed throughout the study as detailed in the Schedules of Assessments in Table 9 (DBP) and Table 10 (OLE).

4.1.1. Double-Blind Period: Treatment Session 1

The DBP is designed as a [redacted] randomized, double-blind, placebo-controlled, single-treatment study (Figure 1).

Phase 2 will compare the efficacy and safety of 2 doses of MYOBLOC versus volume-matched placebo in the treatment of upper limb spasticity. Ninety subjects will be randomized 1:1:1 to receive a total limb dose of 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo via intramuscular (IM) injection into targeted muscles of the affected upper limb on Day 1 (Section 6.2.2.1) (Figure 1). Efficacy and safety will be assessed at Weeks 2 (±3 days), 4 (±3 days), 8 (±1 week), and 13 (±2 weeks) post-injection and at reevaluation visits when applicable.

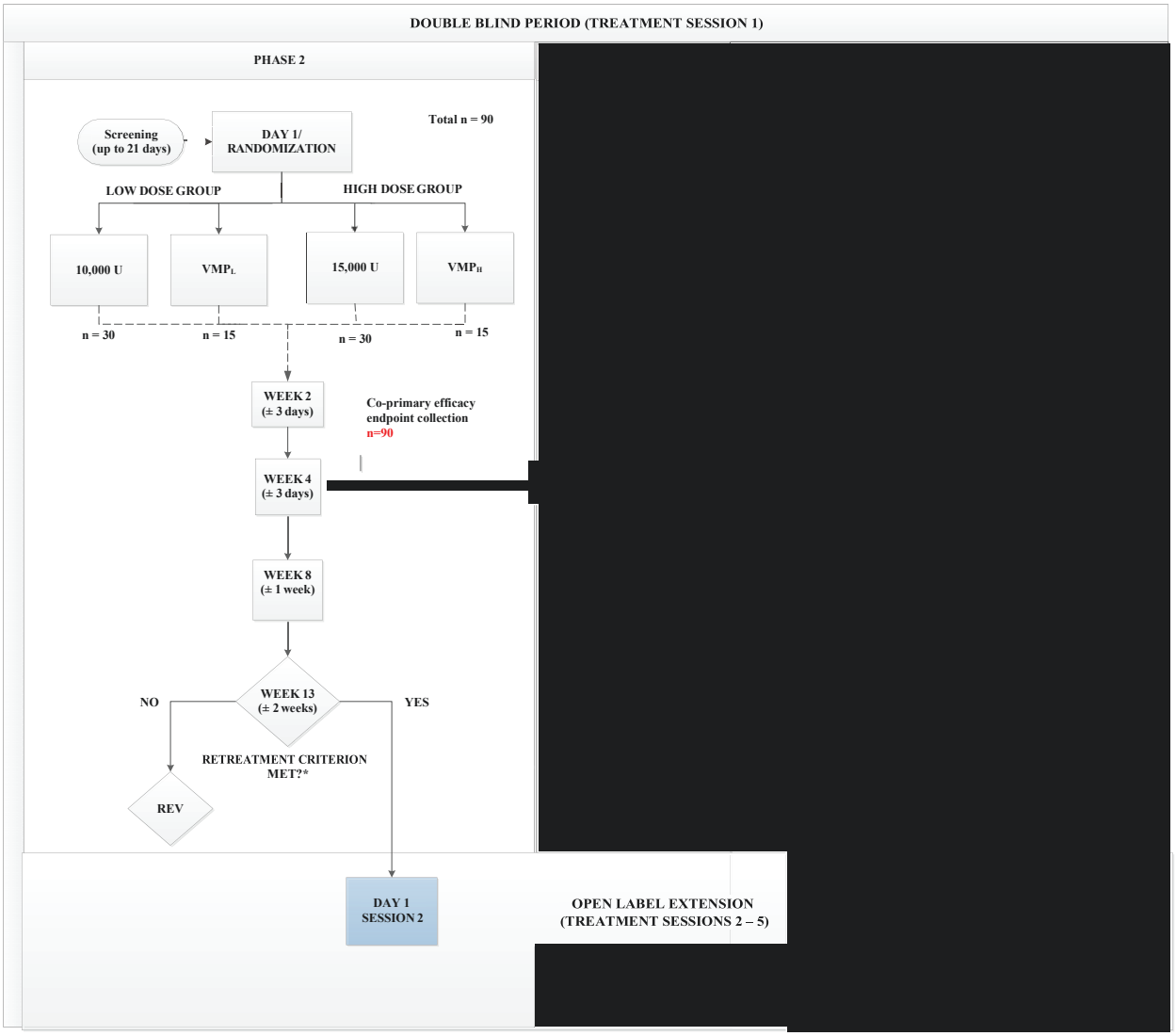
[redacted]

4.1.2. Transition from the Double-Blind Period to Open-Label Extension

All [redacted] subjects who complete the 13-week (±2 weeks) treatment session of the DBP will be allowed to participate in the OLE, provided the retreatment criterion is met (Section 4.1.4) no later than 20 weeks post-injection of Day 1. The start of Treatment Session 2 in the OLE will begin the day

the subject meets the retreatment criterion and study drug is administered. Thus, if at the Week 13 (±2 weeks) visit of the DBP, or if applicable, at a reevaluation visit, the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the DBP and the Day 1 visit of Treatment Session 2 in the OLE. Section 4.1.4 outlines the procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit.

Figure 1: Study Design: [redacted] Double-Blind Period



REV = reevaluation visit; [redacted] U= Units of MYOBLOC (supplied in vials containing 5,000 Units of MYOBLOC/1 mL), VMP_L = Low volume-matched placebo (2.0 mL); VMP_H = High volume-matched placebo (3.0 mL); n = Number of subjects

*See Section 4.1.4 for the retreatment criterion and reevaluation procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit.

4.1.3. Open-Label Extension: Treatment Sessions 2, 3, 4, and 5

This part of the study will assess the safety and efficacy of MYOBLOC administered via IM injection once every 13 weeks (±2 weeks) over 4 treatment sessions (Treatment Sessions 2, 3, 4, and 5) provided that the retreatment criterion (Section 4.1.4) is met at the end of each session (Figure 2). The start of a new treatment session will begin the day the subject meets the retreatment criterion and study drug is administered. Thus, if at the Week 13 (±2 weeks) visit of a treatment session, or if applicable, at the reevaluation visit of a treatment session, the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the current treatment session and the Day 1 visit of the next treatment session. Safety and efficacy will be assessed at Weeks 4 (±5 days) and 13 (±2 weeks) of each OLE treatment session, and if applicable at reevaluation visits, with a telephone follow-up call made by the Investigator (or designee) at Week 8 (±1 week). Section 4.1.4 outlines the retreatment criterion and procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session.

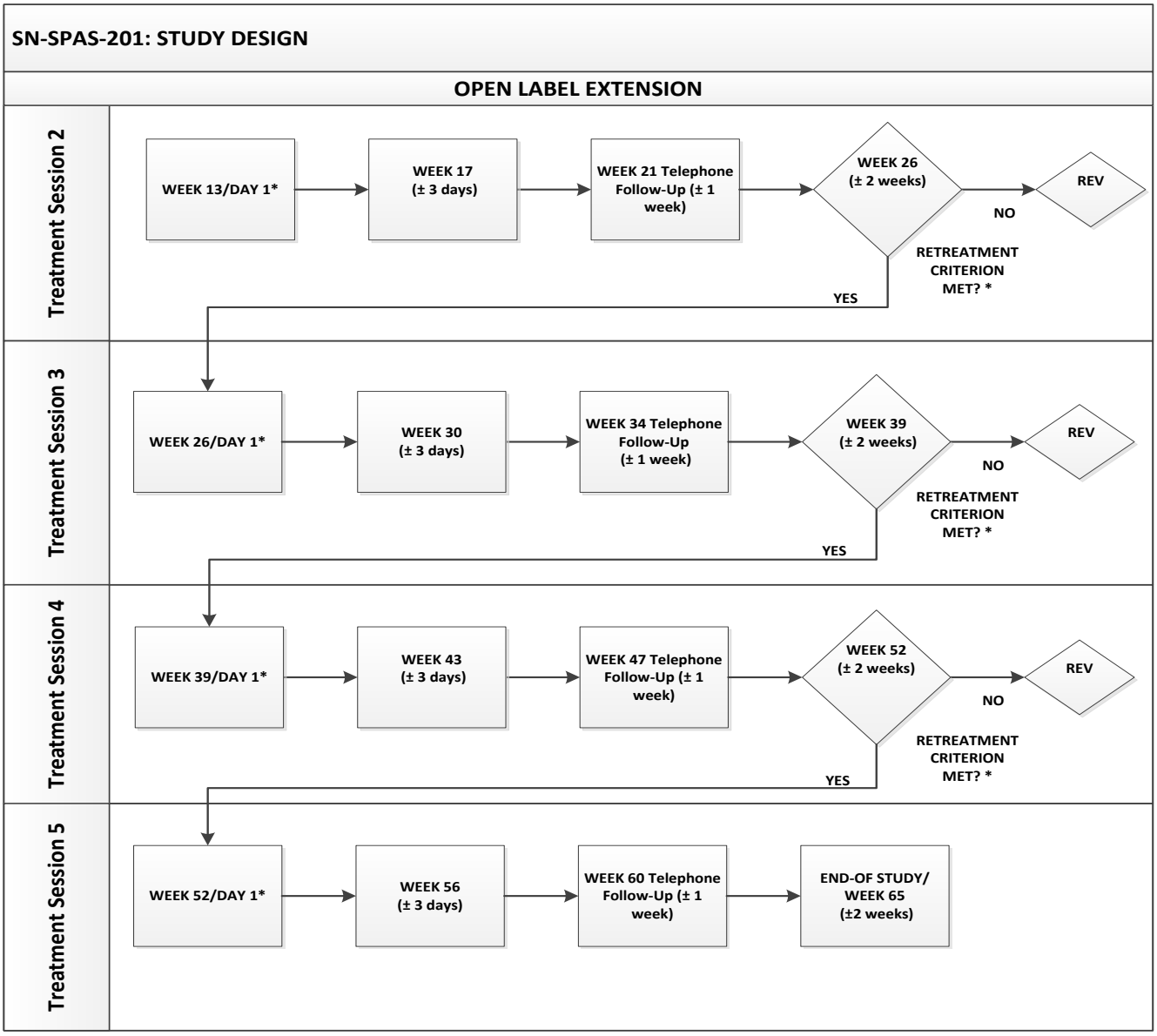
All [redacted] subjects will receive a single limb dose of 15,000 Units administered to the same upper limb injected on Day 1 of the DBP at each treatment session throughout the OLE as outlined in Section 6.2.2.2.

[redacted]

Beginning at Treatment Session 3, if a subject also has spasticity in a lower limb that warrants treatment, then the muscles in the lower limb may also receive study drug injections provided that a 10,000 Unit single upper limb dose administered at a previous treatment session was well tolerated at the discretion of the Investigator in consultation with the study's Medical Monitor/Sponsor. Also beginning at Treatment Session 3, incremental single limb and total body dose increases will be permitted, provided that the doses administered at the previous session(s) were well tolerated. Section 6.2.2.2 outlines the minimum and maximum single limb and total body doses permitted to be administered during the OLE.

If the lower limb is injected, the MAS, CGI-C, [redacted] must also be completed.

Figure 2: Study Design: Open-Label Extension



REV = Reevaluation visit

*See Section 4.1.4 for the retreatment criterion and procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit of an OLE treatment session (i.e., Week 26 of Treatment Session 2; Week 39 of Treatment Session 3, and Week 52 of Treatment Session 4).

4.1.4. Retreatment Criteria

It is expected that most subjects will qualify for retreatment at the end of every 13-week (±2 weeks) treatment session. Retreatment eligibility will be based on the following criterion:

- MAS scores ≥2 in at least 1 muscle group inclusive of the elbow, wrist, and finger flexors in the affected upper limb that was injected on Day 1 of the DBP.

Retreatment eligibility will be assessed at the Week 13 (±2 weeks) visit of all treatment sessions (both DBP and OLE sessions) and at reevaluation visits when applicable (see below).

4.1.4.1. Retreatment Evaluation Procedures

If at the Week 13 (±2 weeks) visit of a treatment session the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the current treatment session and the Day 1 visit of the next treatment session. The study physician should not refer to any previously recorded efficacy assessments (CGI-C) when making current assessments. The CGI assessments will be recorded in the site's source documents and the results will be transferred to the eCRF.

Study procedures to be conducted during the reevaluation visit include:

- CGI-C
- MAS
- Vital signs (systolic/diastolic blood pressure, pulse, respiration rate, and temperature)

Review of AE/SAEs and Concomitant Medications

If at the Week 13 (±2 weeks) visit of a treatment session the subject does not meet the retreatment criterion, then study drug will not be administered and the subject will return for a maximum of two reevaluation visits until the retreatment criterion is met: the first of which must occur no later than 16 weeks post-injection of Day 1; and the second of which must occur no later than 20 weeks post-injection of Day 1 of the current treatment session (see below).

First reevaluation visit (maximum 16 weeks post-injection of Day 1 of the current treatment session):

- If at the first reevaluation visit the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the current treatment session and the Day 1 visit of the next treatment session.
- If at the first reevaluation visit the subject still does not meet the retreatment criterion, then study drug will not be administered, and the subject will return for a second reevaluation visit (see below).

Second reevaluation visit (maximum 20 weeks post-injection of Day 1 of the current treatment session):

- If at the second reevaluation visit the subject meets the retreatment criterion and study drug is administered, then that visit will serve as both the end visit of the current treatment session and the Day 1 visit of the next treatment session.
- If at the second reevaluation visit the subject still does not meet the retreatment criterion, then study drug will not be administered, and the subject will be discontinued.

4.2. Study Endpoints

4.2.1. Co-Primary Efficacy Endpoints

Phase 2 and Phase 3 of the Double-Blind Period

- Change from baseline in tone of the PTMG selected for treatment as measured by the MAS at Week 4 post-injection.
- Clinical Global Impression of Change (CGI-C) in functional ability at Week 4 post-injection.

[redacted]

[redacted]

4.2.4. Safety Endpoints

The endpoints listed below will be assessed by treatment group throughout Phase 2 and Phase 3 of the DBP and the OLE as outlined in the Schedules of Assessments (Table 9 and Table 10):

- Occurrence, seriousness, severity, and causality assessment of AEs
- Vital signs (systolic/diastolic blood pressure, pulse, respiration rate, and temperature)
- 12-Lead Electrocardiograms (ECGs)
- Serum chemistry, hematology, and urinalysis
- Neurologic examination findings
- PFTs (via spirometry)
- C-SSRS

4.3. Number of Subjects

[redacted]

Double-Blind Period

- **Phase 2:** 90 subjects randomized 1:1:1 to 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo.

[redacted]

Open-Label Extension

- All [redacted] subjects who complete the DBP will be allowed to participate in the OLE provided the retreatment criterion is met no later than 20 weeks post-injection of Day 1 of the DBP.

4.4. Duration of Treatment and Subject Participation

[redacted] **Double-Blind Period**

- 13 weeks (±2 weeks) or until the re-treatment criterion is met (maximum 20 weeks post-injection) following a single injection session of multiple upper limb muscles

[redacted]

Open-Label Extension

- 52 weeks: Four 13-week (±2 weeks) treatment sessions, or until the re-treatment criterion is met at the end of each session (maximum 20-week treatment session interval)

Total Duration:

- 65 weeks per subject: Five 13-week (±2 weeks) treatment sessions, or until the retreatment criterion is met at the end of each session (maximum 20-week treatment session interval)

For the purposes of this study, 6 months and 1 year of exposure are defined as follows:

- 6 months of exposure: any subject receiving at least 2 injections of MYOBLOC, separated by intervals no greater than 20 weeks, and completing the 13-week post-injection follow-up visit after the second dose
- 1 year of exposure: any subject receiving at least 4 injections of MYOBLOC, separated by intervals no greater than 20 weeks, and completing the 13-week post-injection follow-up visit after the fourth dose

4.5. Treatment Assignment

Double-Blind Period

- **Phase 2:** 90 subjects will be randomized 1:1:1 to 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo. The volume-matched placebo group will consist of 15 subjects assigned to the low-dose group and 15 subjects assigned to the high-dose group, combined to form the final placebo group of 30 total subjects.

[redacted]

Open-Label Extension

- All subjects will receive MYOBLOC during the OLE portion of the study.

4.6. Sponsor Criteria for Study Termination

The Sponsor has the right to terminate this study at any time. Investigators and study sites will be notified by telephone and in writing if the Sponsor decides to suspend or discontinue the study conduct for any reason. The written notice will provide the reason that the study was suspended or discontinued along with instructions on how to proceed.

Reasons for terminating the study may include, but are not limited to, the following:

- Discovery (from this or other studies) of an unexpected, serious, or unacceptable health hazard to subjects
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Subject enrollment is unsatisfactory
- Insufficient adherence to protocol requirements and/or an unacceptably high rate of missing, erroneous, or improperly collected data that threaten the scientific integrity of the study

Reasons for suspending enrollment at a site may include, but are not limited to, the following:

- Failure of the Investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the research facility to the Sponsor
- Subject enrollment is unsatisfactory
- Insufficient adherence to protocol requirements and/or an unacceptably high rate of missing, erroneous, or improperly collected data that threaten the scientific integrity of the study

5. SELECTION AND WITHDRAWAL OF SUBJECTS

Adult subjects ages 18 to 80 years, inclusive, with upper limb spasticity will be eligible for the study. Potential subjects may be accepted for screening after the nature and purpose of the investigation have been explained and after they and/or their caregiver have voluntarily given written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization to use their personal health information (Section 12.2).

5.1. Subject Inclusion Criteria

To be eligible for participation, subjects with limb spasticity must meet all of the following criteria:

1. Able to understand the potential risks and benefits, the study requirements, and provide written informed consent before enrollment into the study; or if unable, the subject's Legally Authorized Representative (LAR) may provide written informed consent.
2. Male or female ≥18 to maximum of 80 years of age, inclusive.
3. Upper limb spasticity due to stroke, or traumatic brain injury, or spinal cord injury that occurred ≥ 6 months prior to randomization. Eligible subjects may have upper limb monoplegia or hemiplegia. Subjects with cerebral palsy are eligible for study enrollment.
4. Modified Ashworth Scale (MAS) scores of ≥2 in at least two muscle groups inclusive of the elbow, wrist, and finger flexors at screening and baseline.
5. In the Investigator's opinion, the subject will be available and able to comply with the study requirements for at least 1 year, based on the subject's overall health and disease prognosis.
6. In the Investigator's opinion, the subject will be willing and able to comply with all requirements of the protocol, including completion of study questionnaires. A caregiver may be designated to assist with the physical completion of questionnaires/scales.

5.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be allowed to participate:

1. Quadriplegia/tetraplegia, or triplegia with both upper limbs affected.
2. Uncontrolled epilepsy or any type of seizure disorder with a seizure(s) within the previous year.
3. Neuromuscular disorders including, but not limited to, amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), multiple sclerosis (MS), myasthenia gravis, or muscular dystrophy.
4. History of major joint contracture(s), in which, based on the Investigator's assessment, the contracture(s) significantly contributes to joint immobility in the affected upper limb.
5. Unresolved fracture(s) in the affected upper limb.
6. Severe atrophy in the affected upper limb.
7. Known hypersensitivity to botulinum toxins type A or B or to any MYOBLOC solution components.

8. Concomitant use or exposure within 5 half-lives of randomization of the following: aminoglycoside antibiotics, curare-like agents, or other agents that may interfere with neuromuscular function.
9. Treatment with a neurolytic agent (e.g., phenol, alcohol blocks) to the affected upper limb within 1 year before randomization.
10. Presence of a spinal stimulator or intrathecal baclofen pump that has not been turned off within 30 days prior to screening.
11. Changes to treatment regimen or any new treatment with oral antispasmodics and/or muscle relaxants within 30 days prior to randomization.
12. Initiation of physical and/or occupational therapy <30 days before randomization. Subjects receiving physical and/or occupational therapy ≥30 days before randomization must be willing to maintain their therapy regimen through Week 4 of the DBP.
13. Prior botulinum toxin type A (BoNT/A) or B (BoNT/B) treatment in the affected upper limb within 24 weeks before screening. Prior BoNT/A or BoNT/B treatment in areas other than the affected upper limb is not exclusionary but must have occurred at least 12 weeks before screening. Prior toxin exposure must have been well tolerated and without any significant long-term side effects in the case of repeated prior exposure.
14. Subjects should not receive nor have any plans to receive any botulinum toxin treatment, other than the study drug (MYOBLOC), from the time that informed consent is obtained until participation in the study is complete.
15. Severe dysphagia (i.e., inability to swallow liquids, solids or both without choking or medical intervention), or dysphagia with a history of aspiration pneumonia, within 6 months before screening.
16. Prior surgery to treat spasticity in the affected upper limb (i.e., tendon lengthening or tendon transfer).
17. Any anticipated or scheduled surgery during the study period, with the exception of dermatological procedures performed under local anesthesia for the purposes of removing precancerous and cancerous lesions.
18. Major surgery within 30 days before screening.
19. Pregnancy or breastfeeding.
20. Females of childbearing potential must agree to practice a medically acceptable method of contraception (e.g., intrauterine device, hormonal contraception started at least one full cycle before study enrollment, or barrier method in conjunction with spermicide) for the duration of the study (including 2 months after study completion). For the purposes of this study, all females are considered to be of childbearing potential unless they are confirmed by the Investigator to be post-menopausal (at least 1 year since last menses and laboratory test confirmation), biologically sterile, or surgically sterile (e.g., hysterectomy with bilateral oophorectomy, tubal ligation).
21. History of drug or alcohol abuse within 6 months before screening.

22. Obstructive pulmonary disease with forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <70%.
23. Slow vital capacity (SVC) <60% of predicted.
24. Chronic or current use of inhaled corticosteroids.
25. Ventilator dependence (i.e., 24-hour ventilator dependence when intubated, or due to a failure to wean the subject from the ventilator while hospitalized in the intensive care unit or respiratory care center). Subjects who use oxygen on an as-needed basis or during sleeping hours only via a nasal cannula are eligible for the study.
26. Infection at the planned sites of injection.
27. Treatment with an investigational drug, device, or biological agent within 30 days before screening or while participating in this study.
28. Malignancy diagnosed 3 months before screening.
29. Has one or more screening clinical laboratory test values outside the reference range that, in the opinion of the Investigator, are clinically significant, or any of the following :
    - Serum creatinine >1.5 times the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 times ULN;
    - Serum alanine aminotransferase or aspartate aminotransferase >2 times ULN.
30. Has any of the following cardiac findings at screening:
    - Abnormal ECG that is, in the Investigator's opinion/evaluation, clinically significant;
    - PR interval >220 ms;
    - QRS interval >130 ms;
    - QTcF interval >450 ms (for men), or >470 ms (for women) (QT corrected using Fridericia's method);
    - Second-or third-degree atrioventricular block;
    - Any rhythm, other than sinus rhythm, that is interpreted or assessed by the Investigator to be clinically significant.
31. Any other medical illness, condition, or clinical finding that, in the opinion of the Investigator and/or the Sponsor, would put the subject at undue risk.

5.3. Screen Failures

Screen failures are potential study subjects who provide written informed consent and HIPAA authorization, complete some screening procedures but are not subsequently enrolled. A screening log for all subjects who are screened will be maintained. The screening log will uniquely identify each subject and report whether the subject failed screening and the reason(s) for the screening failure. An enrolled subject is defined as one for which appropriate written informed consent has been obtained, who meets all eligibility criteria and is randomized or scheduled to receive study drug. Subjects who fail to meet entry criteria may be eligible to re-screen at a later time, subject to approval of the Medical Monitor. Subjects who are re-screened will receive a new subject identification number and are required to sign a new informed consent form (ICF).

5.4. Subject Discontinuation Criteria

Once a subject is enrolled, any subject not completing the DBP or OLE for any reason will be considered a premature discontinuation, and the Investigator must record the reason(s) for discontinuation in the subject's source document and eCRF. Any subject that is discontinued or withdraws prematurely, regardless of the reason, will be asked to complete all early discontinuation assessments and procedures (Section 8.4). Those subjects may not re-enter the study, nor will they be replaced.

The Investigator or Sponsor may discontinue subjects from the study at any time if it is deemed clinically appropriate for any reason, which may include the following:

- An intolerable or unmanageable AE or SAE (the relationship to study drug must be recorded in source and entered into the electronic data capture [EDC] system)
- A subject who had an initial pre-treatment SVC of ≥80% of their predicted value, has their SVC fall to <60% of their predicted value (Section 10.1.7)
- Does not meet the re-treatment criterion at 20 weeks post-injection
- Is unable to tolerate an upper limb dose of 10,000 Units
- Insufficient therapeutic response
- Requires a medication or procedure that is prohibited (Section 6.4) per protocol
- Is noncompliant with the protocol
- Is lost to follow-up.
  If a subject is lost to follow-up, repeated attempts will be made to reach the subject or caregiver (defined as a minimum of 3 telephone calls, followed by sending a letter). If repeated attempts are unsuccessful, a status of lost to follow-up will be recorded in the subject's source document and eCRF as the reason for early discontinuation.
- Withdrawal of consent.
  Subjects are free to withdraw from the study at any time, regardless of their reasons, and without prejudice to further treatment. In such cases, the subject or caregiver will be asked about the reason(s) for the decision to withdraw consent and the reasons(s) clearly documented in the subject's source document and eCRF. Subjects withdrawing consent will be asked to complete early discontinuation procedures (Section 8.4) but have the option to refuse.

The Medical Monitor for the study should be contacted if study drug discontinuation is considered for any reason. If the reason for discontinuation is due to an AE that is at least possibly related to study drug, the clinical course of each AE should be followed until the event has resolved, stabilized or is otherwise explained or subject is lost to follow-up. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome (Section 10.5.3).

Subjects discontinuing prematurely due to lack of effect or loss of effect will be encouraged to return to the study site to complete early discontinuation study procedures.

6. TREATMENT OF SUBJECTS

6.1. Randomization and Blinding

6.1.1. Randomization

Double-Blind Period

Subjects [redacted] will be randomized on Day 1 of the DBP after eligibility has been confirmed but prior to study drug administration.

- **Phase 2:** 90 subjects will be randomized 1:1:1 to 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo. The volume-matched placebo group will consist of 15 subjects assigned to the low-dose group and 15 subjects assigned to the high-dose group, combined to form the final placebo group of 30 total subjects.

[redacted]

Subject randomization will be performed according to a computer-generated randomization schedule loaded into an Interactive Response Technology (IRT) system to assure subjects are centrally randomized. Randomization will be stratified by the PTMG (elbow, wrist, or finger flexors). Site staff will connect to the IRT system to enter the subject's information after confirming eligibility. The IRT system will provide site staff with a kit number linked to the randomized study drug to be administered.

Hard copies of the study drug randomization schedule will be stored securely. Only medically necessary unblinding(s) will be allowed (Section 6.1.2 describes the unblinding procedures).

Open-Label Extension

This phase of the study is open-label.

6.1.2. Maintaining and Breaking the Blind

All subjects (and caregivers), study personnel (including the Investigator, study coordinator(s), pharmacist/designee), and the Sponsor, will be blinded to the identity of the study drug (active or placebo) administered in the DBP until after the last Phase 3 subject completes the last visit of the DBP (including any reevaluation visits, if applicable) and the database is locked.

Following injection on Day 1 of the DBP, the dosing/injection records will be maintained separately from the rest of the study documentation (e.g., with the pharmacy source records) and may be accessed only by a study site pharmacist/designee for the duration of the study. The pharmacist/designee may not administer, record, or interpret protocol safety and efficacy assessments.

Study site personnel should not discuss the dose, volume of study drug administered, or treatment assignment from the DBP with subjects (or caregivers) enrolled in the study for the duration of their participation (i.e., through the OLE).

Although there is no specific known antidote for MYOBLOC, if an Investigator believes it is necessary to break the blind for reasons of subject safety, the Investigator must call the Sponsor's Medical Monitor (or designee) for consultation before unblinding. The decision to break the study blind should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management. If, after discussion with the Medical Monitor, it is determined that

the study treatment should be disclosed, medical personnel will be able to access this information via IRT. Circumstances surrounding unblinding of subjects must be documented in writing. Patient Completion and Withdrawal Causality should be assessed by the Investigator before unblinding of treatment assignment but must not delay treatment in an emergency situation. The date and reason for the unblinding must be recorded in the subject's source record and eCRF. Contact information for the Sponsor's Medical Monitor can be found in Table 1.

See Section 11.7.5 for details regarding the DMC.

6.2. Treatments Administered

6.2.1. Study Drug Preparation

During the DBP, the Investigator may prepare or oversee preparation of the syringes in order to properly plan for the selection of doses per muscle to be administered. Following injection on Day 1 of the DBP, the injection records will be maintained separately from the rest of the study documentation (e.g., with the pharmacy source records) and accessed only by a pharmacist/designee. The OLE doses may also be prepared by the Investigator, but the injection records are not required to be maintained separate from the rest of the study documentation.

6.2.2. Study Drug Administration

Throughout the study, the Investigator must use guidance when performing injections, but the type of guidance (electromyography [EMG], electrical stimulation, or sonography) will be per Investigator discretion.

6.2.2.1. Double-Blind Period: Treatment Session 1

Phase 2

Phase 2 subjects will be randomized to receive a total limb dose of 10,000 Units of MYOBLOC, 15,000 Units of MYOBLOC, or volume-matched placebo via IM injection into the affected upper limb on Day 1 of the DBP. Prior to randomization on Day 1, the Investigator will select two muscle groups inclusive of the elbow, wrist, and finger flexors to target for treatment. Both selected muscle groups must have a MAS score ≥2 but only one will be designated as the PTMG; the other muscle group will be designated the npTMG. The designation of the PTMG will be made at the discretion of the Investigator. On Day 1, a fixed dose will be administered to the PTMG per the dose-per-muscle ranges outlined for each treatment group in Table 3.

Table 3: Required PTMG Muscles and Dose-Per-Muscle Ranges During the Double-Blind Period

PTMG	Upper Limb Muscle	MYOBLOC or Placebo (volume matched)						Number of Injection Sites
		Low-Dose Group 10,000 Units			High-Dose Group 15,000 Units			
		Min (Units)	Max (Units)	Total Dose (Units)	Min (Units)	Max (Units)	Total Dose (Units)	
Elbow Flexors*	Biceps brachii	2,500	3,500	5,000	5,000	7,000	10,000	3
	Brachioradialis	1,500	2,500		3,000	5,000		2
Wrist Flexors †	Flexor carpi radialis	1,000	1,500	2,500	2,000	3,000	5,000	2
	Flexor carpi ulnaris	1,000	1,500		2,000	3,000		2
Finger Flexors ǂ	Flexor digitorum profundus	1,000	1,500	2,500	2,000	3,000	5,000	2
	Flexor digitorum superficialis	1,000	1,500		2,000	3,000		2
Required Total Limb Dose #,∞		**10,000 Units**			**15,000 Units**			

Max = maximum, Min = minimum, PTMG = primary target muscle group

* If the elbow flexors are selected as the PTMG, both the biceps brachii and brachioradialis muscles are required to be injected within the specified ranges so that the total dose administered to the elbow flexors equals 5,000 Units or 10,000 Units (or volume-matched placebo) if assigned to the low-dose or high-dose group, respectively.

† If the wrist flexors are selected as the PTMG, both the flexor carpi radialis and the flexor carpi ulnaris muscles are required to be injected within the specified ranges so that the total dose administered to the wrist flexors equals 2,500 Units or 5,000 Units (or volume-matched placebo) if assigned to the low-dose or high-dose group, respectively.

ǂ If the finger flexors are selected as the PTMG, both the flexor digitorum profundus and the flexor digitorum superficialis muscles are required to be injected within the specified ranges so that the total dose administered to the finger flexors equals 2,500 Units or 5,000 Units (or volume-matched placebo) if assigned to the low-dose or high-dose group, respectively.

\# Total Limb Dose includes PTMG and npTMG injections

∞ The total body maximum dose should not exceed 32,500 Units.

The npTMG selected for treatment will be injected on Day 1 in accordance with the dose-per-muscle ranges listed in Table 4.

Table 4: Required npTMG Muscles and Dose-Per-Muscle Ranges During the Double-Blind Period

Muscle Group	Muscle	MYOBLOC or Placebo (volume matched)		Number of Injection Sites
		Minimum (Units)	Maximum (Units)	
Elbow flexors*	Biceps brachii	2,500	7,000	3
	Brachioradialis	1,500	5,000	2
Wrist flexors †	Flexor carpi radialis	1,000	3,000	2
	Flexor carpi ulnaris	1,000	3,000	2
Finger flexors ǂ	Flexor digitorum profundus	1,000	3,000	2
	Flexor digitorum superficialis	1,000	3,000	2
Thumb#	Flexor pollicis longus	1,000	2,500	1-2
	Adductor pollicis	1,000	2,500	1-2
Forearm	Pronator teres	1,000	3,000	1-2

npTMG = non-primary target muscle group

* If the elbow flexors are selected as the npTMG, both the biceps brachii and brachioradialis muscles are required to be injected within the specified ranges.

† If the wrist flexor muscles are selected as the npTMG, both the flexor carpi radialis and the flexor carpi ulnaris muscles are required to be injected within the specified ranges.

ǂ If the finger flexor muscles are selected as the npTMG, both the flexor digitorum profundus and the flexor digitorum superficialis muscles are required to be injected within the specified ranges.

If the thumb muscles are selected as the npTMG, both the flexor pollicis longus and the adductor pollicis muscles are required to be injected within the specified ranges.

If there is study drug remaining after injecting the required muscles of both the PTMG and the npTMG, additional muscles must be selected for treatment but only those listed in Table 4 are eligible, and the dose administered must be in accordance with the dose-per-muscle ranges outlined in Table 4. Under these circumstances, both muscles of a muscle group are **not** required to be injected.

Note that subjects assigned to the low-dose group or to the high-dose group must be administered a total limb dose that equals 10,000 Units or 15,000 Units (or volume-matched placebo), respectively.

[redacted]

6.2.2.2. Open-Label Extension: Treatment Sessions 2, 3, 4 and 5

All [redacted] subjects who complete Treatment Session 1 of the DBP will be allowed to participate in the OLE provided that the re-treatment criterion is met no later than 20 weeks post-injection on Day 1 of the DBP.

Phase 2 Subjects Entering the Open-Label Extension

Phase 2 subjects entering the OLE will receive MYOBLOC via IM injection once every 13 weeks (±2 weeks) over 4 treatment sessions (Treatment Sessions 2, 3, 4, and 5), provided that the retreatment criterion is met at the end of each session (not to exceed a treatment session interval of 20 weeks). The start of a new treatment session will begin the day that the retreatment criterion is met and study drug is administered. Section 4.1.4 outlines the retreatment criterion and the procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session. The affected upper limb that was injected on Day 1 of the DBP must be injected at each treatment session throughout the OLE. The selection of muscles to inject in the affected upper limb will be at the discretion of the Investigator; however, only those listed in Table 5 are eligible for injection, and the dose administered to the selected muscles must be in accordance with the dose-per-muscle ranges listed in Table 5.

At Treatment Session 2, the dose administered to the affected upper limb will be 15,000 Units in accordance with Table 5. Section 6.3 outlines the dose reductions permitted during the OLE.

Table 5: Eligible Upper Limb Muscles and Dose-per-Muscle Ranges During the Open-Label Extension

Muscle	MYOBLOC Dose (Units)		Number of Injection Sites
	Minimum	Maximum	
Biceps brachii	2,500	7,000	1-3
Brachioradialis	1,500	5,000	1-2
Flexor carpi radialis	1,000	3,000	1-2
Flexor carpi ulnaris	1,000	3,000	1-2
Flexor digitorum superficialis	1,000	3,000	1-2
Flexor digitorum profundus	1,000	3,000	1-2
Flexor pollicis longus	1,000	2,500	1-2
Adductor pollicis	1,000	2,500	1-2
Pronator teres	1,000	3,000	1-2

Beginning at Treatment Session 3, the dose administered to the affected upper limb may be increased to a maximum of 20,000 Units provided that a 15,000 Unit dose administered at a previous session was well tolerated. Also beginning at Treatment Session 3, if a subject has spasticity in a lower limb that warrants treatment, then, at the discretion of the Investigator and in consultation with the Medical Monitor and Sponsor, muscles in that lower limb may also receive study drug injections provided a minimum 10,000 Unit single upper limb dose administered at a previous treatment session was well tolerated. The selection of muscles to inject in the affected upper limb will be at the discretion of the Investigator and in the lower limb will be at the discretion of the Investigator in consultation with the Medical Monitor and Sponsor, but only the muscles listed in Table 5 and Table 6 are eligible, and the dose administered to the selected muscles must be in accordance with the dose-per-muscle ranges listed in Table 5 and Table 6. The minimum and maximum single limb doses and total body dose permitted to be administered to Phase 2 subjects at each treatment session of the OLE are outlined in Table 7. If the lower limb is injected, the MAS, CGI-C, [redacted] must also be completed.

Table 6: Eligible Lower Limb Muscles and Dose-per-Muscle Ranges During the Open-Label Extension

Muscle	MYOBLOC Dose (Units)		Number of Injection Sites
	Minimum	Maximum	
Medial gastrocnemius	3,000	5,000	2-3
Lateral gastrocnemius	3,000	5,000	2-3
Soleus	2,500	4,000	2-3
Tibialis posterior	2,000	4,000	2-3
Flexor digitorum longus	1,500	3,000	1-2
Flexor hallicus longus	1,500	3,000	1-2
Semimembranosus	1,500	3,000	2-3
Semitendinosus	1,500	3,000	2-3

Table 7: Total Limb and Total Body Dose Administered at Each Treatment Session During the Open-Label Extension for Phase 2 Subjects [redacted]

	Upper Limb Dose (Units)		Lower Limb Dose (Units)		Total Body Dose (Units)	
	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
Session 3	15,000	20,000 (a)	0	7,500	15,000	22,500 (a)
Session 4	15,000	20,000 (a)	0	12,500	15,000	27,500 (b)
Session 5	15,000	20,000 (a)	0	17,500	15,000	32,500 (b)

(a) Subject must have demonstrated tolerability at the 15,000 Unit single limb dose administered at a previous session.

(b) Total body dose administered may be increased by a maximum of 5,000 Units from the previous session, provided that the total body dose administered at the previous session was well tolerated

[redacted]

[redacted]

6.3. Dose Adjustment Criteria

Upon entering the OLE after completion of Phase 2, [redacted] a single upper limb dose less than 15,000 Units may be considered if AEs that may be indicative of distant toxin spread (DSOT) are observed, or due to Investigator/subject preference. A dose reduction may be permitted after discussion with the Medical Monitor. The reason for the dose reduction and the actual dose administered must be recorded in the subject's eCRF. The lowest upper limb dose permitted to be administered to any subject at any treatment session during the OLE is 10,000 Units; therefore, if at any point during the OLE, a subject experiences AEs that may be indicative of DSOT that would prevent him or her from receiving a single upper limb dose of at least 10,000 Units, the subject must be discontinued.

Adjusting or stopping doses due to results observed on PFTs are outlined in Section 10.1.7 and are as follows:

- For subjects who require repeat PFTs following a 4-week post-injection visit, the Medical Monitor and the Sponsor must be contacted if dose escalation at the next treatment session is being considered.
- If at any 13-week post-injection visit, or if applicable, at a reevaluation visits(s) when the retreatment criterion (Section 4.1.4) is met, a subject experiences a ≥10% decrease in SVC relative to their pretreatment value measured on Day 1 of the DBP, the Medical Monitor must be contacted before administration of study drug in order to determine whether additional investigations are warranted and whether the subject can safely receive additional study drug injections at the next treatment session.
- If at any time during the study, a subject who had an initial pretreatment SVC of ≥80% of their predicted value, has their SVC fall to <60% of their predicted value, study drug should be discontinued and consultation with the Medical Monitor and the Sponsor is required.

6.4. Concomitant Medications and Therapies

Concomitant medications will be assessed on Day 1 and at each subsequent study visit. In general, concomitant medications that interfere with neuromuscular function or the conduct of this study will not be allowed during the study, including:

- Aminoglycoside antibiotics
- Curare-like agents
- BoNT/A
- BoNT/B, except that provided as study drug
- Phenol or alcohol blocks to any limb treated during the study
- Intrathecal baclofen
- Oral antispasmodics and muscle relaxants:
    - Double-Blind Period: Antispasmodics and/or muscle relaxant treatment prior to Day 1 is not excluded, but subjects must be on a stable dose and frequency for at least 30 days prior to randomization. Initiation of antispasmodic and/or muscle relaxant treatment during the DBP is prohibited. After completion of the DBP, initiation of treatment with antispasmodics and/or muscle relaxant treatment is permitted.
    - Open-Label Extension: Initiation (or continuation) of antispasmodic and/or muscle relaxant treatment is permitted.

Other medications not listed above, either specifically or by category, that do not interfere with neuromuscular function may be used by subjects in this study, at the discretion of the Investigator. All concomitant medications taken by the subject will be recorded in the Concomitant Medication eCRF along with dose, dates of administration, and reason for use.

Subjects who have been on a physical and/or occupational therapy regimen for at least 30 days prior to randomization must continue their therapy through Week 4 of the DBP of the trial. Subjects may initiate physical and/or occupational therapy at any point during the OLE; however, such treatment is independent and separate from this study. All such therapy must be documented in the source and eCRF.

6.5. Treatment Compliance

All study drug will be administered at the investigative site by the Investigator.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Description of Study Drug

7.1.1. MYOBLOC

MYOBLOC (rimabotulinumtoxinB) is a clear and colorless to light-yellow sterile injection solution of a purified neurotoxin. Each single-use vial of formulated MYOBLOC contains:

- 5,000 Units of BoNT/B per 1.0 mL in 0.05% human serum albumin
- 0.01 M sodium succinate
- 0.1 M sodium chloride at approximately pH 5.6

7.1.2. Placebo

Placebo solution, 0.9% NaCl injectable saline formulation, pH 5.4-5.8, will be identical to MYOBLOC in appearance. Placebo will be provided by the Sponsor in single-use vials identical to those containing active MYOBLOC and at the same fill volumes. Study personnel will not know whether study vials contain active MYOBLOC or placebo.

7.2. Study Drug Packaging and Labeling

MYOBLOC and placebo will be provided by the Sponsor in identically appearing 3.5-mL glass vials, each vial containing either MYOBLOC at 5,000 Units per 1 mL or volume-matched placebo. Study drug will be supplied in study drug kits; high-dose kits will contain a sufficient number of vials to achieve 15,000 Unit dosing, low-dose kits will contain a sufficient number of vials to achieve 10,000 Unit dosing. All study drug kits and vials will be labeled as investigational drug for research purposes only, in compliance with federal regulations.

Section 6.1.2 provides details on unblinding of study drug should breaking of the blind become necessary for subject safety. For the OLE, each study drug vial kit will be associated with a unique identification number for purposes of accountability.

7.3. Study Drug Storage

Study drug will be stored in a secure refrigerator at 36°F to 46°F (2°C to 8°C) with access restricted to authorized personnel.

7.4. Study Drug Accountability

Upon receipt of investigational drug supplies, study site personnel will call/log into the IRT to confirm receipt and verify the allocation/study drug vial kit numbers contained in the shipment. Accurate recording of all investigational agents received, dispensed, administered, and returned will be maintained by study site personnel. The investigational agents are to be used only as described by this study protocol by appropriately licensed Investigators named in Form FDA 1572.

Study staff should retain the original individual vial cartons, as well as all vials, including those empty, partially empty, or full. All used and unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Used and unused investigational agents will be retained at the participating sites to enable a full investigational drug

inventory by the sites' respective monitors. The Sponsor will provide instructions to return the unused study drug to the Sponsor or Sponsor's designee for proper destruction in accordance with local and federal regulations.

7.5. Study Drug Handling and Disposal

Any spills/leaks of MYOBLOC should be decontaminated with 10% caustic solution or 0.5% sodium hypochlorite (2 mL household chlorine bleach per liter of water). Soak up the liquid with an appropriate absorbent, seal the absorbed toxin in an autoclave bag and process as Medical Biohazardous Waste in accordance with local regulations. Water-proof gloves and other appropriate protective garments should be worn while cleaning up spills/leaks; these garments should be destroyed or cleaned as per local regulations.

8. STUDY PROCEDURES

8.1. Schedules of Assessments

8.1.1. Schedule of Assessments for the Double-Blind Period

Table 9: Schedule of Assessments for Screening and the Double-Blind Period (Phase 2 [redacted] Subjects)

Activity	Screening (Day -21 to -1)	Treatment Session 1				
		Baseline Day 1 (a)	Week 2 (b) (± 3 days)	Week 4 (b) (± 3 days)	Week 8 (b) (± 1 week)	Week 13 (c) (±2 weeks) and Reevaluation Visits
Written Informed Consent and HIPAA Authorization (d)	X					
Inclusion/Exclusion Criteria	X					
Demographics	X					
Medical/Surgical/Medication History	X					
Complete Physical Examination	X					X (p)
Identify primary target muscle group (PTMG)		X				
Brief Physical Examination		X	X	X	X	
Weight	X	X	X	X	X	X
Height	X					
Neurologic Examination	X	X	X	X	X	X (p)
Pulmonary Function Tests (e)	X	X		X		X
Clinical Laboratory Tests (f)	X			X		X
Urine Pregnancy Test (g)	X	X	X	X	X	X (p)
Vital Signs (h): BP and Pulse (i); RR, Temperature	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)	X	X				X
Adverse Events/Serious Adverse Events Assessment		X	X	X	X	X
C-SSRS Baseline Version (j)	X	X				
C-SSRS Since Last Visit Version (j)			X	X	X	X
Concomitant Medications Assessment		X	X	X	X	X
[redacted]						
Clinical Global Impression-Change (CGI-C) (k)			X	X	X	X

Activity	Screening (Day -21 to -1)	Treatment Session 1				
		Baseline Day 1 (a)	Week 2 (b) (± 3 days)	Week 4 (b) (± 3 days)	Week 8 (b) (± 1 week)	Week 13 (c) (±2 weeks) and Reevaluation Visits
Modified Ashworth Scale (MAS)	X	X	X	X	X	X
[redacted]						
Administration of Study Drug (o)		X (1st)				X (2nd) (p)

BP = blood pressure, C-SSRS = Columbia Suicide Severity Rating Scale; HIPAA = Health Insurance Portability and Accountability Act; OLE = open-label extension; RR = respiration rate

(a) All assessments and results must be available prior to randomization and study drug administration. AEs will only be recorded if they occur after study drug administration.
(b) Office visit.
(c) Office visit: If the subject meets the retreatment criterion (Section 4.1.4) and study drug is administered, the Week 13 (±2 weeks) visit of the DBP is the same visit as Day 1 of Treatment Session 2 in the OLE. If the subject does not meet the retreatment criterion, then study drug will not be administered, and the subject will return for a maximum of 2 reevaluation visits until the retreatment criterion is met: the first of which must occur no later than 16 weeks post-injection on Day 1; and the second of which must occur no later than 20 weeks post-injection on Day 1. The reevaluation visit, at which the subject meets the retreatment criterion will be the same visit as Day 1 of Treatment Session 2 in the OLE. If the retreatment criterion is still not met after 20 weeks post-injection, then the subject will be discontinued from the study, and the assessments for the End-of-Study/Early Discontinuation visit will apply (Section 8.4).
(d) Must be obtained before conducting any study procedure.
(e) Pulmonary function tests will be performed via spirometry (Section 10.1.7).
(f) Hematology, Chemistry, and Urinalysis (see Section 10.1.8).
(g) Females of childbearing potential only. Negative pregnancy test must be confirmed prior to administration of study drug.
(h) Vital signs will be taken before spirometry assessments.
(i) BP and pulse will be obtained after the subject sits quietly for at least 5 minutes.
(j) If the subject does not have the mental capacity to reliably (per Investigator judgment) provide a self-assessment, the C-SSRS will be omitted, and the reason for omission will be carefully documented. The scale is administered by trained study personnel, and the subject's responses are recorded by the trained study personnel (i.e., the subject does not complete the scale directly). Results obtained at screening will be confirmed on Day 1 prior to dosing.
(k) CGI assessments are to be completed prior to performing the MAS. Both scales are to be completed by the same assessor.

[redacted]

[redacted]

(o) Subject must not be randomized and study drug must not be administered until all required assessments are complete.
(p) Assessments only to be performed if the retreatment criterion is met and must be completed prior to 2nd administration of study drug.

8.1.2. Schedule of Assessments for the Open-Label Extension

Table 10: Schedule of Assessments for the Open-Label Extension (All Eligible Subjects)

Activity	Treatment Session 2 (Weeks 17, 21 and 26); Treatment Session 3 (Weeks 30, 34 and 39) Treatment Session 4 (Weeks 43, 47 and 52); and Treatment Session 5 (Weeks 56, 60 and 65)			
	4-Week Visit Weeks 17/30/43/56 (a) (± 5 days)	**8-Week Telephone Contact Weeks 21/34/47/60 (b) (± 1 week)**	**13-Week Visit Week 26/39/52 (c) (± 2 weeks) and Reevaluation Visits (m)**	**End-of-Study/Week 65 (± 2 weeks) or Early Discontinuation Visit**
Complete Physical Examination			X (n)	X
Brief Physical Examination	X			
Weight	X		X	X
Neurologic Examination	X		X (n)	X
Pulmonary Function Tests (d)	X		X	X
Clinical Laboratory Tests (e)	X		X	X
Urine Pregnancy Test (f)	X		X (n)	X
Vital Signs (g): BP and Pulse (h); RR, Temperature	X		X	X
12-Lead ECG			X	X
Adverse Events/Serious Adverse Events Assessment	X	X	X	X
C-SSRS Since Last Visit Version (i)	X		X	X
Concomitant Medications Assessment	X	X	X	X
Modified Ashworth Scale (MAS) (o)	X		X	X
[redacted]				
Clinical Global Impression-Change (CGI-C) (o)	X		X	X
[redacted]				

Activity	Treatment Session 2 (Weeks 17, 21 and 26); Treatment Session 3 (Weeks 30, 34 and 39) Treatment Session 4 (Weeks 43, 47 and 52); and Treatment Session 5 (Weeks 56, 60 and 65)			
	4-Week Visit Weeks 17/30/43/56 (a) (± 5 days)	**8-Week Telephone Contact Weeks 21/34/47/60 (b) (± 1 week)**	**13-Week Visit Week 26/39/52 (c) (± 2 weeks) and Reevaluation Visits (m)**	**End-of-Study/Week 65 (± 2 weeks) or Early Discontinuation Visit**
[redacted]				
Administration of Study Drug (m)			X (3^{rd}, 4^{th}, 5^{th})	

BP = blood pressure, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = Electrocardiogram; OLE = Open-Label Extension, RR = respiration rate

(a) Office visit.

(b) Telephone follow-up.

(c) Office visit. If the subject meets the retreatment criterion (Section 4.1.4) and study drug is administered, the 13-week (±2 weeks) visit is the last visit of the current treatment session and Day 1 of the subsequent treatment session. If the subject does not meet the re-treatment criterion, then study drug will not be administered, and the subject will return for a maximum of two reevaluation visits until the retreatment criterion is met: the first of which must occur no later than 16 weeks post-injection on Day 1; and the second of which must occur no later than 20 weeks post-injection on Day 1 of the current treatment session. The reevaluation visit at which the subject meets the retreatment criterion is both the end visit of the current treatment session and the Day 1 visit of the subsequent treatment session. If the retreatment criterion is still not met after 20 weeks post-injection, then the subject will be discontinued from the study, and the assessments for the End of Study/Early Discontinuation visit will apply (Section 8.4).

(d) Pulmonary function tests will be performed via spirometry (Section 10.1.7).

(e) Hematology, Chemistry, and Urinalysis will be performed at Weeks 17, 26, 30, 39, 43, 52, 56, and 65 (or, if applicable, at the Early Discontinuation visit). See Section 10.1.8 for blood and urine laboratory tests. Clinical laboratory tests do not need to be repeated at reevaluation visits.

(f) Females of childbearing potential only. Negative pregnancy test must be confirmed prior to administration of study drug.

(g) Vital signs will be taken before spirometry assessments.

(h) BP and pulse will be obtained after the subject sits quietly for at least 5 minutes.

(i) If the subject does not have the mental capacity to reliably (per Investigator judgment) provide a self-assessment, the C-SSRS will be omitted, and the reason for omission will be carefully documented. The scale is administered by trained study personnel, and the subject's responses are recorded by the trained study personnel (i.e., the subject does not complete the scale directly).

[redacted]

(m) All assessments must be performed prior to administration of study drug.

(n) Assessments only to be performed if the retreatment criterion is met.

(o) Assessment to be performed for the affected upper limb. If a lower limb is injected starting at Treatment Session 3 or later, the assessment should also be performed for that lower limb prior to study drug administration on Day 1 of that treatment session, and for subsequent study visits post-injection as indicated.

8.2. Screening (Day -21 to Day -1)

Subjects who provide written consent to participate and HIPAA authorization to use their personal health information will be screened for inclusion in the study. A screening window of up to 21 days is provided to ensure the Investigator has adequate time to evaluate the subject's medical history, screening laboratory tests, and other eligibility criteria.

The following activities will be completed:

- Review of inclusion and exclusion criteria
- Demographics and medical/surgical/medication history
- Complete physical examination (including height and weight)
- Neurologic examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- 12-Lead Electrocardiogram (ECG)
- PFTs (via spirometry)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Urine pregnancy test (females of childbearing potential only)
- C-SSRS Baseline Version
- MAS (Qualified Assessor)

8.3. Double-Blind Period: Treatment Session 1

The following sections apply to all subjects [redacted] enrolled in the DBP.

8.3.1. Day 1

The following assessments will be completed on Day 1 prior to administration of study drug:

- Brief physical examination
- PTMG designation (study physician)
- Neurologic examination
- 12-Lead Electrocardiogram (ECG)
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- PFTs (via spirometry)
- Urine pregnancy test (females of childbearing potential only; negative test must be confirmed prior to injection)
- Weight
- Review of concomitant medications
- C-SSRS Baseline version (confirm results have not changed since screening visit)

[redacted]

- MAS (Qualified Assessor)

[redacted]

The assessor performing the MAS and the CGI scales must be the same for each subject. Then the CGI scales must be completed prior to performing the MAS. Section 9.1 and Section 9.2 define qualified assessors permitted to administer the MAS and CGI scales, respectively.

Once all assessments have been completed, evaluated, and eligibility is confirmed, qualified subjects will be randomized and receive their initial treatment with MYOBLOC or volume-matched placebo via injection into muscles in the affected upper limb as detailed in Section 6.2.2.1.

8.3.2. Weeks 2 (±3 days), 4 (±3 days), and 8 (±1 week)

Subjects will return at Weeks 2 (±3 days), 4 (±3 days), and 8 (±1 week), and the assessments/procedures listed below will be completed. Visit windows are provided to allow flexibility in scheduling subjects for appointments.

Efficacy Assessments:

All efficacy assessments should be completed prior to any safety assessments. Efficacy assessments completed by a qualified assessor(s) include:

- [redacted] CGI-C
- MAS

The assessor performing the MAS and CGI scales must be the same for each subject. The CGI scales must be completed prior to performing the MAS. Section 9.1 and Section 9.2 define qualified assessors permitted to administer the MAS and CGI scales, respectively. The study physician should not refer to any previously recorded efficacy assessments ([redacted] CGI-C, [redacted] when making current assessments. [redacted] The CGI assessments will be recorded in the site's source documents and the results will be transferred to the eCRF.

[redacted]

Safety Assessments:

Safety assessments should be conducted following the completion of all efficacy assessments. Evaluation of AEs/SAEs should occur prior to all other safety assessments. After the evaluation of AEs/SAEs, the

remaining safety assessments may be completed in any order. All of the safety assessments listed below must be completed:

- Evaluation of AEs/SAEs (first)
- Review of concomitant medications
- Brief physical examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight
- Neurologic examination (Week 2, Week 4, and Week 8)
- Clinical laboratory tests (serum chemistry, hematology, urinalysis) (Week 4)
- Urine pregnancy test (females of childbearing potential only; Week 2, Week 4 and Week 8)
- PFTs (via spirometry; Week 4)
- C-SSRS (Since Last Visit version)

If a subject withdraws or is discontinued from the study prior to completion of the Week 13 (±2 weeks) visit, the reason must be documented in the subject's source document and eCRF. Whenever a subject is discontinued, the procedures/assessments listed in Section 8.4 for the Early Discontinuation visit should be followed.

8.3.3. Week 13 (±2 weeks) and Reevaluation Visits

Subjects will return at Week 13 (±2 weeks) post-injection. If the subject meets the retreatment criterion (Section 4.1.4) and study drug is administered, then the Week 13 (±2 weeks) visit will serve as both the end visit of the DBP and the Day 1 visit of Treatment Session 2 in the OLE (Figure 1). If the subject does not meet the retreatment criterion, then study drug will not be administered, and the subject will return for a maximum of 2 reevaluation visits until the retreatment criterion is met. Section 4.1.4.1 outlines the procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session.

The assessments/procedures listed below will be completed at the Week 13 (±2 weeks) visit, and at reevaluation visits (if applicable) as follows:

Efficacy Assessments:

All efficacy assessments should be completed prior to any safety assessments. Efficacy assessments completed by a qualified assessor(s) include:

- [redacted] CGI-C
- MAS

The assessor performing the MAS and the CGI scales must be the same for each subject. Then the CGI scales must be completed prior to performing the MAS. Section 9.1 and Section 9.2 define qualified assessors permitted to administer the MAS and CGI scales, respectively.

Safety Assessments:

Safety assessments should be conducted following the completion of all efficacy assessments. Evaluation of AEs/SAEs should occur prior to all other safety assessments. After the evaluation of AEs/SAEs, the remaining safety assessments may be completed in any order. All of the safety assessments listed below must be completed:

- Evaluation of AEs/SAEs
- Review of concomitant medications
- C-SSRS (Since Last Visit version)
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- 12-Lead ECG
- PFTs (via spirometry)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Weight

If the subject meets the retreatment criterion at the Week 13 (±2 weeks) visit, or if applicable, at a reevaluation visit(s) when the subject meets the retreatment criterion, then in addition to the assessments listed above, the assessments/procedures listed below must also be completed before administration of study drug (note that clinical laboratory tests do not need to be repeated at reevaluation visits):

- Complete physical examination
- Urine pregnancy test (females of childbearing potential only: negative test must be confirmed prior to injection)
- Neurologic examination

If at the second reevaluation visit (maximum 20 weeks post-injection on Day 1), the subject still does not meet the retreatment criterion, then the subject will be discontinued, and the assessments/procedures listed in Section 8.4 will apply.

8.3.4. Open-Label Extension: Treatment Sessions 2, 3, 4, and 5

Phase 2 [redacted] subjects who meet the retreatment criterion (Section 4.1.4) no later than 20 weeks post-injection on Day 1 of the DBP may participate in up to 4 additional 13-week (±2 weeks) open-label treatment sessions (not to exceed a treatment session interval of 20 weeks). During the OLE, the start of a new treatment session will begin on the day the subject meets the retreatment criterion and study drug is administered (Figure 2). Thus, if the subject meets the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session and study drug is administered, then that visit will serve as both the end visit of the current treatment session as well as the Day 1 visit of the next treatment session. Section 4.1.4.1 outlines the procedures should the subject not meet the retreatment criterion at the Week 13 (±2 weeks) visit of a treatment session.

8.3.5. Day 1 (Injection Visits of Treatment Sessions 2, 3, 4 and 5)

On Day 1 of Treatment Session 2 (same day as the Week 13 [±2 weeks] visit of the DBP, or if applicable the reevaluation visit when the retreatment criterion is met), subjects will receive MYOBLOC (as detailed in Section 6.2.2.2) after the double-blind assessments/procedures outlined in Section 8.3.3 have been completed.

Similarly, on Day 1 of Treatment Sessions 3, 4, and 5 (same day as Week 26 [±2 weeks], Week 39 [±2 weeks], and Week 52 [±2 weeks] visits of Treatment Session 2, 3, and 4, respectively, or if applicable the reevaluation visit when the retreatment criterion is met). Subjects will receive MYOBLOC (as detailed in Section 6.2.2.2) after the 13-week (±2 weeks) post-injection assessments/procedures listed in Section 8.3.3 have been completed.

8.3.6. 4-Week (±5 Days) Post-Injection Visits (Week 17, Week 30, Week 43, and Week 56 of Treatment Sessions 2, 3, 4, and 5, Respectively)

Subjects will return at 4 weeks (±5 days) after each injection during each treatment session (i.e., Week 17 [±5 days], Week 30 [±5 days], Week 43 [±5 days], and Week 56 [±5 days] of Treatment Sessions 2, 3, 4, and 5, respectively), and the assessments/procedures listed below will be completed:

- [redacted] CGI-C (Qualified Assessor)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Evaluation of AEs/SAEs
- Review of concomitant medications
- Brief physical examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight
- Neurologic examination
- PFTs (via spirometry)
- C-SSRS (Since Last Visit version)
- Clinical laboratory tests (biochemistry, hematology, and urinalysis)
- Urine pregnancy test (females of childbearing potential only)
- MAS (Qualified Assessor)

8.3.7. 8-Week (±1 Week) Post-Injection Telephone Contacts (Week 21, Week 34, Week 47, and Week 60 of Treatment Sessions 2, 3, 4, and 5, Respectively)

A telephone follow-up will be made at 8 weeks (±1 week) post-injection for each treatment session (i.e., Week 21 [±1 week], Week 34 [±1 week], Week 47 [±1 week], and Week 60 [±1 week]) of Treatment Sessions 2, 3, 4, and 5, respectively, to assess:

- Adverse Events/Serious Adverse Events
- Concomitant Medications

8.3.8. 13-Week (±2 Weeks) Post-Injection Visits (Week 26, Week 39, Week 52, and Week 65 of Treatment Sessions 2, 3, 4, and 5, Respectively), and Reevaluation Visits

Subjects will return at 13 weeks (±2 weeks) post-injection for each treatment session (i.e., Week 26 [±2 weeks], Week 39 [±2 weeks], Week 52 [±2 weeks], and Week 65 [±2 weeks] of Treatment Sessions 2, 3, 4, and 5, respectively), and if applicable, at reevaluation visits of Treatment Sessions 2, 3, and/or 4, and the assessments/procedures listed below will be completed:

- [redacted] CGI-C (Qualified Assessor) (any order)
- MAS (Qualified Assessor)
- [redacted]
- [redacted]
- [redacted]
- Evaluation of AEs
- Review of concomitant medications
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- 12-Lead ECG
- PFTs (via spirometry)
- Clinical laboratory tests (biochemistry, hematology, urinalysis)
- Weight
- C-SSRS (Since Last Visit version)

If the subject meets the retreatment criterion (Section 4.1.4) at the Week 26 (±2 weeks), Week 39 (±2 weeks), and Week 52 (±2 weeks) visits of Treatment Sessions 2, 3, and 4, respectively, or if applicable, at a reevaluation visit(s) of Treatment Sessions 2, 3, and/or 4 when the subject meets the retreatment criterion, then in addition to the assessments listed above, the assessments/procedures listed below must also be completed prior to administration of study drug. Clinical laboratory tests do not need to be repeated at reevaluation visits. These same procedures also will be conducted at the last End-of-Study visit of Treatment Session 5 (i.e., Week 65 [±2 weeks]).

- Complete physical examination
- Neurologic examination
- Urine pregnancy test (females of childbearing potential only; negative test must be confirmed prior to injection)
- [redacted]

If at the second reevaluation visit of a treatment session (maximum 20 weeks post-injection on Day 1 of the previous session), the subject still does not meet the retreatment criterion, then the subject will be discontinued, and the assessments/procedures listed in Section 8.4 will apply.

8.4. Early Discontinuation Visit

If the subject withdraws or is discontinued from the study before completion, regardless of whether they have received study drug, the reason for discontinuation must be documented in the subject's source document and eCRF. If a subject discontinues the study due to an AE, the AE should be indicated as the reason for study discontinuation, even if the Investigator would not have considered discontinuation of treatment because of the AE. When a subject is discontinued from the study, the procedures/assessments listed for the End-of-Study visit should be performed. If a subject discontinues the study while at a scheduled visit, assessments completed at that visit should be entered into the EDC system for that scheduled visit, and any additional assessments required specifically for the End-of-Study visit.

8.4.1. Post-Study Telephone Contact

If a subject discontinues from the study, the subject will be contacted 13 weeks (±3 days) after the last injection of study drug, unless the subject withdraws consent and refuses post-study contact. If a subject discontinues participation due to an AE/SAE that is at least possibly related to study drug, the subject will be followed until the event has resolved, stabilized or is otherwise explained/subject is lost to follow-up.

This telephone contact will be documented in the subject's source document and eCRF.

9. ASSESSMENT OF EFFICACY

Assessors/Raters

In order to maintain consistency in the administration and rating of the scales, all assessors (i.e., Investigators, sub-Investigators, physical therapists, occupational therapists, or other study personnel named on Form FDA 1572) will be trained, and this same assessor must administer/rate a given assessment for a subject throughout that subject's participation in the DBP. During the OLE, the assessor completing scales on Day 1 of each treatment session should consistently rate scales at subsequent study visits as in the DBP, when possible; however, an alternate, qualified and trained assessor (named on Form FDA 1572) may serve as back-up if necessary. Note that when the assessors complete/rate efficacy assessments, they should not refer to any previously recorded assessments (CGI-C,) through the subject's participation in the DBP.

9.1. Modified Ashworth Scale (MAS)

The MAS is an internationally accepted and validated instrument used to measure resistance during passive soft-tissue stretching.[21] Resistance will be measured and recorded using a 6-point scale ranging from 0 (no increase in muscle tone) to 4 (affected part[s] rigid in flexion or extension) (Appendix A; also see MAS in Assessor's Workbook). Qualified assessors permitted to administer the MAS include physicians, physical therapists and occupational therapists, but any assessor administering the scale must be trained and listed on Form FDA 1572. The MAS will be administered at screening, prior to administration of study drug on Day 1 of each treatment session, at each subsequent study visit, and if applicable, at discontinuation from the study.

The qualified assessor who administers the MAS on Day 1 of the DBP must also administer the MAS at each subsequent study visit throughout the DBP for each subject. Then the CGI scales must be completed prior to the administration of the MAS as to reduce potential bias that MAS scores could have on CGI ratings. During the OLE, the qualified assessor administering the MAS on Day 1 of each treatment session must administer the MAS at each subsequent study; however, an alternate, qualified and trained assessor (named on Form FDA 1572) may serve as a back-up assessor if necessary. The assessor will record the subject's MAS score in the site's source documents and the results will be transferred to the eCRF.

9.2. Clinical Global Impression of Change (CGI-C)

The CGI-C scale will be used to rate the physician's global impression of change in the subject's ability to function on a 7-point scale ranging from "very much improved" to "very much worse" (Appendix B). The CGI-C will be completed at each visit subsequent to the first administration of study drug on Day 1 of the DBP, at each visit during the OLE, and if applicable, at discontinuation from the study. Note that change in the subject's ability to function will be compared to the subject's functionality prior to the subject's receipt of

his/her most recent injection of study drug (Appendix B). The qualified assessor who is permitted to complete the CGI scales will be a study physician (Investigator named on Form FDA 1572) who administers the assessment only after training on the scale has been completed.

During the DBP, the study physician completing the CGI [redacted] scale on Day 1 must also complete the [redacted] CGI [redacted] scales at each subsequent study visit through the Week 13 (±2 weeks) visit and if applicable, at reevaluation visits. The study physician must not refer to any previously recorded efficacy assessments ([redacted] CGI-C, [redacted]) when making current assessments. The study physician completing the CGI scales is to also administer the MAS. The CGI scales must be completed prior to the administration of the MAS at each study visit.

[redacted]

During the OLE, an alternate study physician (Investigator named on Form FDA 1572) may complete the CGI scales if necessary, but only after training on the scale has been completed. Note that the study physician completing the CGI scales on Day 1 of each treatment session throughout the OLE must also complete the scales at the subsequent study visits of that given treatment session.

All CGI ratings will be recorded in the site's source documents, and the results will be transferred to the eCRF.

[redacted]

[redacted]

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

10.1.1. Demographic/Medical History

The medical history should include: demographic information (age, gender, and race); spasticity history (with date of onset); past treatment(s) for spasticity; current co-morbidities; relevant past illnesses; prior surgical procedures; and all current medications (including those taken within 30 days before screening).

10.1.2. Vital Signs

Resting vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured after sitting quietly for at least 5 minutes at screening and each study visit or, if applicable, at discontinuation from the study. Vital signs will be taken before spirometry assessments.

10.1.3. Electrocardiogram

A 12-lead ECG will be obtained as per the Schedules of Assessments (Table 9 and Table 10). Additional ECGs may be performed at other times if deemed necessary by the Investigator. The ECG will be recorded while the subject is resting in a supine position for at least 10 minutes and will electronically measure the PR, QRS, QT, and QTc intervals, and heart rate. All ECG tracings will be reviewed within 24 hours by the Investigator or qualified sub-Investigator. PR intervals will be determined for each of these ECGs from a single reading. Invalid measurements will be repeated. QTc will be reported as QTcF (QT corrected using Fridericia's method).

10.1.4. Weight and Height

Weight will be recorded at each study visit. Height will be recorded at screening only.

10.1.5. Physical Examination

A complete physical examination will be performed by the Investigator or designee at screening, at Weeks 13, 26, 39, and 52 (or at reevaluation visits once the subject meets the retreatment criterion), or if applicable, at discontinuation from the study. The complete examination will involve gross examination of general appearance; head, ears, eyes, nose and throat; skin; extremities; chest; abdomen; and lymph nodes. Cardiac and pulmonary auscultation will also be recorded as part of the complete physical examination.

The individual performing the physical examination will characterize findings as either normal or abnormal. Any clinically significant findings before the first injection of the study drug will be recorded in the subject's Medical History eCRF, and any clinically significant findings post-first study drug injection will be recorded as AEs if newly occurring or worsening from baseline.

A brief physical examination consisting of cardiac and pulmonary auscultation will be performed on Day 1 (prior to administration of study drug), at Weeks 2, 4, and 8 of the DBP, and at Weeks 17, 30, 43, and 56 of the OLE.

10.1.6. Neurologic Examination

A neurologic examination will be performed at screening, Day 1 (prior to administration of study drug), at Weeks 2, 4, 8, and 13 of the DBP, at Weeks 17, 26, 30, 39, 43, 52, and 56 of the OLE, at Week 65, or if applicable/feasible, at discontinuation from the study. At Weeks 13, 26, 39, and 52, the neurologic

examination will only be performed once the subject meets the retreatment criterion. The neurologic examination will consist of 9 sections to evaluate: 1) level of consciousness; 2) speech; 3) cranial nerves; 4) motor; 5) sensory; 6) coordination; 7) gait; 8) reflexes; and 9) Romberg test (Appendix G).

10.1.7. Pulmonary Function Tests

Pulmonary function tests (PFTs) will be administered via spirometry by a trained technician and will include the following:

- SVC, including inspiratory capacity (IC), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), expiratory vital capacity (VCex), and percent predicted VCex (VCex %pred)
- FVC
- FEV_1
- FEV_1/FVC

During the DBP, PFTs will be administered at screening, prior to administration of the study drug on Day 1, at Weeks 4 and 13 of the DBP, and if applicable, at reevaluation visits. During the OLE, PFTs will be administered at Weeks 4 and 13 of each treatment session, at reevaluation visits if applicable, or if applicable/feasible, at discontinuation from the study.

At each 4-week post-injection visit, any subject who experiences a ≥20% decrease in SVC relative to their pretreatment value (i.e., the value measured prior to the first administration of study drug on Day 1 of the DBP) will be required to have PFTs repeated at 1 week (±3 days) following the visit during which the ≥20% in SVC decrease was obtained. If at that visit the subject's SVC has not returned to ≥90% of their pretreatment value, then the subject will be required to have PFTs repeated again 1 week (±3 days) later. If this second repeat of PFTs fails to demonstrate recovery to an SVC value of ≥90% of their pretreatment SVC, the Medical Monitor must be contacted in order to determine whether additional investigations are warranted and whether the subject is eligible to receive study drug injections at the next treatment session.

For subjects who require repeat PFTs following a 4-week post-injection visit, the Medical Monitor must be contacted and provide approval if dose escalation at the next treatment session is being considered.

If prior to administration of study drug at any 13-week post-injection visit, or if applicable, prior to administration of study drug at a reevaluation visits(s) when the retreatment criterion (Section 4.1.4) is met, a subject experiences a ≥10% decrease in SVC relative to their pretreatment value measured on Day 1 of the DBP, the Medical Monitor must be contacted prior to administration of further study drug in order to determine whether additional investigations are warranted and whether the subject can safely receive additional study drug injections at the next treatment session.

If at any time during the study a subject who had an initial pretreatment SVC of ≥80% of their predicted value has their SVC fall to <60% of their predicted value, study drug should be discontinued and consultation with the Medical Monitor is required.

10.1.8. Laboratory Assessments

10.1.8.1. Standard Laboratory Tests

Safety blood and urine specimens (Table 11) will be collected from all subjects at screening, Week 4, and Week 13 of the DBP; and at Week 17, 26, 30, 39, 43, 52, 56, and 65 of the OLE, or if applicable, at

discontinuation from the study. Subjects are not required to fast prior to collection of laboratory samples, but fasting status should be captured in source.

For this multicenter study, a central laboratory (to be determined) will be used that is directly accredited by the College of American Pathologists (CAP) and licensed by the Clinical Laboratory Improvement Act of 1988 (CLIA); both certification and accreditation must be renewed every 2 years. The laboratory will need to provide a copy of current certification and the Laboratory Normal Ranges for their laboratory values to determine the upper limit of normal (ULN).

Table 11: Hematology, Chemistry, and Urinalysis Tests

Hematology	Chemistry	Urinalysis
Hemoglobin	Cholesterol	Specific gravity
Hematocrit	Phosphorus	pH
Platelet count	Sodium	Glucose
Red blood cell count	Potassium	Blood
MCV	Calcium	Protein
MCH	Urea nitrogen	Color
MCHC	Creatinine	Nitrites
White blood cell (WBC) count	Albumin	Ketones
WBC differential (%)	Total protein	Bilirubin
bands	Aspartate aminotransferase	Urobilinogen
neutrophils	Alanine aminotransferase	Leukocyte esterase
lymphocytes	Alkaline phosphatase	
monocytes	Gamma-glutamyl transferase	
eosinophils	Uric acid	
basophils	Total bilirubin	
	Glucose	
	Lactate dehydrogenase	
	Chloride	
	Bicarbonate	

MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume

The Investigator must review the laboratory report, document the evaluation/assessment, and record any clinically significant laboratory abnormality during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, or if due to an underlying disease, judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered abnormally clinically significant during participation in the study or within 13 weeks (±3 days) after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedules of Assessments. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or dose modification), the results must be recorded in the eCRF.

10.1.8.2. Pregnancy Test

A "dip-stick" urine pregnancy test will be performed for all female subjects of childbearing potential at screening, on Day 1 (prior to administration of study drug), at Weeks 4, 8, and 13; and Weeks 17, 26, 30, 39, 43, 52, and 56 of the OLE once the subject meets the retreatment criterion; and at Week 65, or if applicable, at discontinuation from the study. A negative pregnancy test must be confirmed prior to each administration of study drug. Sites are encouraged to use any FDA-approved urine pregnancy test.

10.1.9. Columbia Suicide Severity Rating Scale

The C-SSRS[25] measures both suicidal ideation and suicidal behavior and will be completed at screening, reassessed on Day 1 (before the first injection of study drug), at each subsequent study visit or, if applicable/feasible, at discontinuation from the study. The scale is administered by trained study personnel, and the subject's responses are recorded by the trained study personnel (i.e., the subject does not complete the scale directly). The Baseline version of the C-SSRS (Appendix H) will be used to assess lifetime suicidality at screening and confirmed on Day 1 prior to dosing. At all other protocol-specified time points, the C-SSRS – Since Last Visit version (Appendix I) will be used to assess the subject's suicidality since the last assessment. After enrollment, if the subject does not have the mental capacity to reliably provide a self-assessment (per Investigator judgment), the C-SSRS will be omitted, and the reason will be carefully documented.

The C-SSRS has three subscales: suicidal ideation, suicidal behavior, and intensity of suicidal ideation. Both suicidal ideation subscale and suicidal behavior subscale have 5 yes/no items each, with a sum score ranging from 0 to 5 and higher score indicating greater severity. The intensity of suicidal ideation has 5 items, with a sum score ranging from 2 to 25 and higher score indicating greater risk.

If any item(s) on the C-SSRS are answered with "yes", a physician Investigator must review the subject's responses in order to determine the subject's study eligibility or continued participation and potential need for referral to a mental health professional. A significant risk of suicide is defined as a "yes" in answer to: a) questions 4 or 5 on the suicidal ideation section; or b) any questions on any item in the suicidal behavior section. This must be reported as an SAE and followed up accordingly. Additionally, if a subject responds "yes" to any of the suicidal ideation questions 1 to 3, the Investigator should apply clinical judgment to determine the need for reporting as an AE or SAE and the need for any referral.

10.2. Adverse and Serious Adverse Events

10.2.1. Definitions of Adverse Events

10.2.1.1. Adverse Event

Per 21 Code of Federal Regulations (CFR) 312.32, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, such an occurrence is considered an AE if it occurs after study drug has been administered. An AE includes any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes.

Examples include an exacerbation of pre-existing conditions or events or intercurrent illnesses. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

In clinical studies, an AE can include an undesirable medical condition occurring at any time during study participation, including run-in or wash-out periods, even if no study treatment has been administered. Events occurring after signing informed consent but prior to study drug administration are to be documented in the subject's medical history (source and eCRF) but are not to be considered AEs.

10.2.1.2. Serious Adverse Event

Per 21CFR.312.32, an SAE is an AE occurring after administration of study drug at any dose, comparator or placebo, that fulfils one or more of the following:

- Results in death during the period of protocol-defined surveillance
- Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject, in the view of the Investigator, was at immediate 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)
- Requires inpatient hospitalization or prolongation of existing hospitalization*
- Results in a persistent or significant disability or incapacity, or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect

*Hospitalization: Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it might be (e.g., bronchospasms, laryngeal edema). Hospital admission and/or surgical operations planned before or during a study are not considered SAEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. It should be noted that for this study, subjects with planned or anticipated surgery (with the exception noted in the exclusion criteria) should not be enrolled into the study.

Important Medical Events: Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the subject or may require medical or surgical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious, and examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasms
- Development of drug dependency or drug abuse

All SAEs will be assessed by the Investigator as detailed in Section 10.4.

10.2.1.3. Adverse Events that may be Indicative of Distant Toxin Spread

The effects of MYOBLOC (and all botulinum toxin products) may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. Adverse event terms for DSOT are listed in Table 12.

Table 12: Adverse Events that may be Indicative of Distant Spread of Toxin

Accommodation disorder	Areflexia	Aspiration
Asthenia	Botulism	Bradycardia
Bulbar palsy	Constipation	Cranial nerve palsies multiple
Cranial nerve paralysis	Diaphragmatic paralysis (of any magnitude)	Diplopia
Dry mouth	Dysarthria	Dysphagia
Dysphonia	Dyspnea	Extraocular muscle paresis
Eyelid function disorder	Eyelid ptosis	Facial palsy
Facial paresis	Hemiparesis	Hypoglossal nerve paresis
Hyporeflexia	Hypotonia	IIIrd cranial nerve paresis
Ileus paralytic	IVth cranial nerve paresis	Monoparesis
Muscular weakness	Paralysis	Paralysis flaccid
Paraparesis	Paresis	Paresis cranial nerve
Peripheral nerve palsy	Peripheral paralysis	Pelvic floor muscle weakness
Pneumonia aspiration	Pupillary reflex impaired	Quadriparesis
Respiratory arrest	Respiratory depression	Respiratory failure
Speech disorder	Trigeminal nerve paresis	Urinary retention
Vision blurred	Vocal cord paralysis	Vocal cord paresis

All such occurrences will be recorded in the subject's source document and eCRF, and will be assessed by the Investigator as detailed in Section 10.4.

10.3. Relationship of Adverse Events to Study Drug

For each AE, the Investigator must assess the attribution of the study drug to the AE, and determine whether the AE is or is not related to the study or test drug as defined below. When in doubt, the AE should be considered at least "possibly related" until further evidence becomes available to refute this assessment.

Definitely Not Related

- Subject did not receive the test drug, the temporal sequence of the AE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE.

Possibly Related

- There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, but the AE could have been due to another equally likely cause.

Probably Related

- There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, and the AE is more likely explained by the test drug than by any other cause.

Definitely Related

- There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, and the AE is more likely explained by the test drug than by any other cause, and the AE shows a pattern consistent with previous knowledge of the test drug or test drug class.

10.4. Recording Adverse Events

All AEs and details for the events will be recorded in the subject's source document and Adverse Event eCRF. An AE should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed or reported. It is important that the Investigator only record 1 AE per line on the eCRF. Combination events (e.g., nausea/vomiting), should not be entered as 1 event, but 2 events.

Adverse events can be collected by either the Investigator or the Study Coordinator; however, the Investigator must determine the intensity of the AE (Section 10.5), assess whether or not the study drug caused the AE (Section 10.4), record whether the AE led to discontinuation of the subject from the study (Section 10.5), record the outcome of the AE (Section 10.5), and determine if the AE is serious (Section 10.2.1.2).

For this study, AEs will be collected beginning with the start of dosing on Day 1 and will end at study completion (Week 65 [±2 weeks]). Serious adverse events are to be reported upon signing of the informed consent.

10.5. Reporting Adverse Events

The Investigator must assess the intensity of each AE as mild, moderate, or severe as defined below.

- Mild: no medical interventions required, short lasting discomfort, and does not interfere with subject's daily activities

- Moderate: activity may be limited, and subject may require minimal medical therapy, intervention, or assistance
- Severe: definitely limits subject's daily activity that may require hospitalization and or intervention/therapy

For each AE, the Investigator must indicate whether or not the AE caused the subject to discontinue from the study (more than 1 AE may be associated with the decision to discontinue a subject).

The Investigator must assess the outcome of each AE as: unresolved, resolved, resolved with sequelae, death, or unknown.

For each AE, the Investigator must determine if the AE meets the criteria for a SAE as defined in Section 10.2.1.2.

10.5.1. Adverse Events Requiring Expedited Reporting to the Sponsor's Designated Pharmacovigilance Group

The following events should be forwarded to the Sponsor's Designated Pharmacovigilance group within 24 hours of becoming aware of the event:

- All SAEs, regardless of causality
- Overdose (with or without an AE)
- Inadvertent or accidental exposure
- Pregnancy (Section 10.6)
- Unexpected therapeutic benefit

SAEs should be reported on SAE form and within the EDC system by checking 'serious' on the AE eCRF. For emergency situations when access to the EDC is unavailable, SAEs may be reported on the SAE stand-alone SAE form provided to sites, by sending directly to the Sponsor's Pharmacovigilance group via email, fax, or phone (see Table 1 for contact information). All SAEs reported using the stand-alone SAE form must be entered into the EDC system as soon as access is available.

Events of Overdose, Accidental exposure, and Unexpected benefit should be reported using the stand-alone SAE form sent directly to the Sponsor's Designated Synteract Pharmacovigilance group, indicating (Synteract) on the form which type of event is being reported, and if the event is/is not also considered an SAE.

Events of Pregnancy must be reported using the stand-alone Pregnancy form provided to sites, by sending to Synteract/the Sponsor's Designated Pharmacovigilance group via email, fax, or phone (see Table 1 for contact information).

When submitting directly to the Sponsor's Pharmacovigilance group, a confirmation of receipt email will be provided. If no confirmation email is provided, double check the contact information used and resend. For any issues with SAE reporting, contact the Sponsor's Designated Pharmacovigilance Group (Synteract) per the contact information in Table 1.

10.5.2. Timeframe for Collecting and Reporting Serious Adverse Events and Other Immediately Reportable Events

Serious AEs and other events as noted in Section 10.5.1 requiring expedited reporting occurring from the time of signing the informed consent form up until study completion (or within 13 weeks ±3 days of last study drug injection for subjects discontinuing participation prematurely), must be reported to the Sponsor's Pharmacovigilance group (Synteract) ***within 24 hours*** of the time any study staff member is made aware of the event. Additional eCRF and/or paper documentation may also need to be provided.

10.5.3. Follow-up of All Adverse Events/Serious Adverse Events

The clinical course of each AE that is at least possibly related to study drug should be followed until the event has resolved, stabilized or is otherwise explained or subject is lost to follow-up. Serious adverse events that are still ongoing at the end of the study period must be followed to determine the final outcome. The Investigator must provide the Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug or placebo. Subjects who discontinue because of an AE before Week 65 will be evaluated as soon as possible and contacted 13 weeks (±3 days) after their last injection of study drug to determine if the AE has resolved, continues unabated, or has reached a new baseline. This telephone contact will be documented in the subject's source document and eCRF.

10.5.4. Regulatory Notification

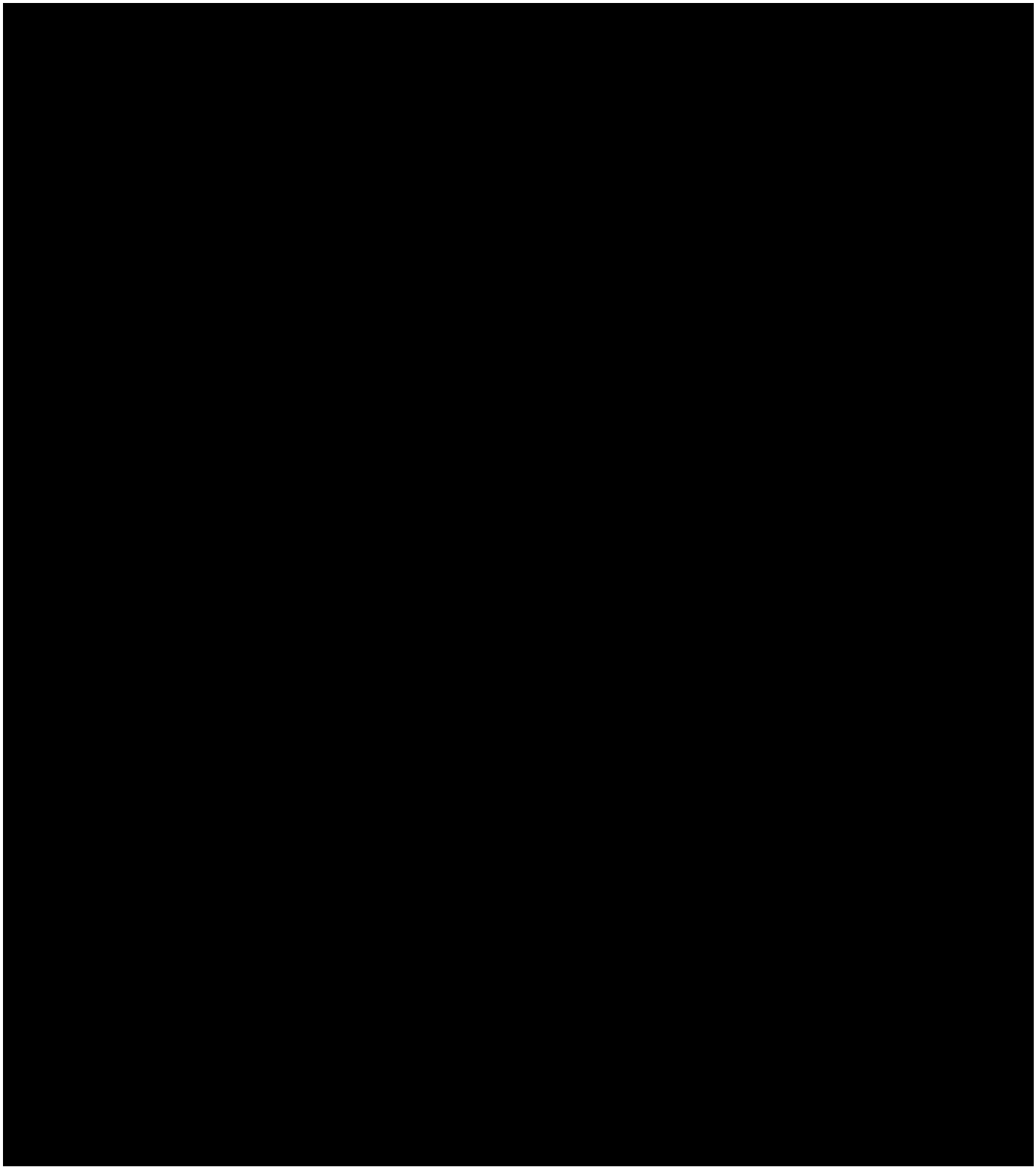
The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious drug-related events that occur during the clinical trial. Each site is responsible for notifying his or her IRB or IEC of these events.

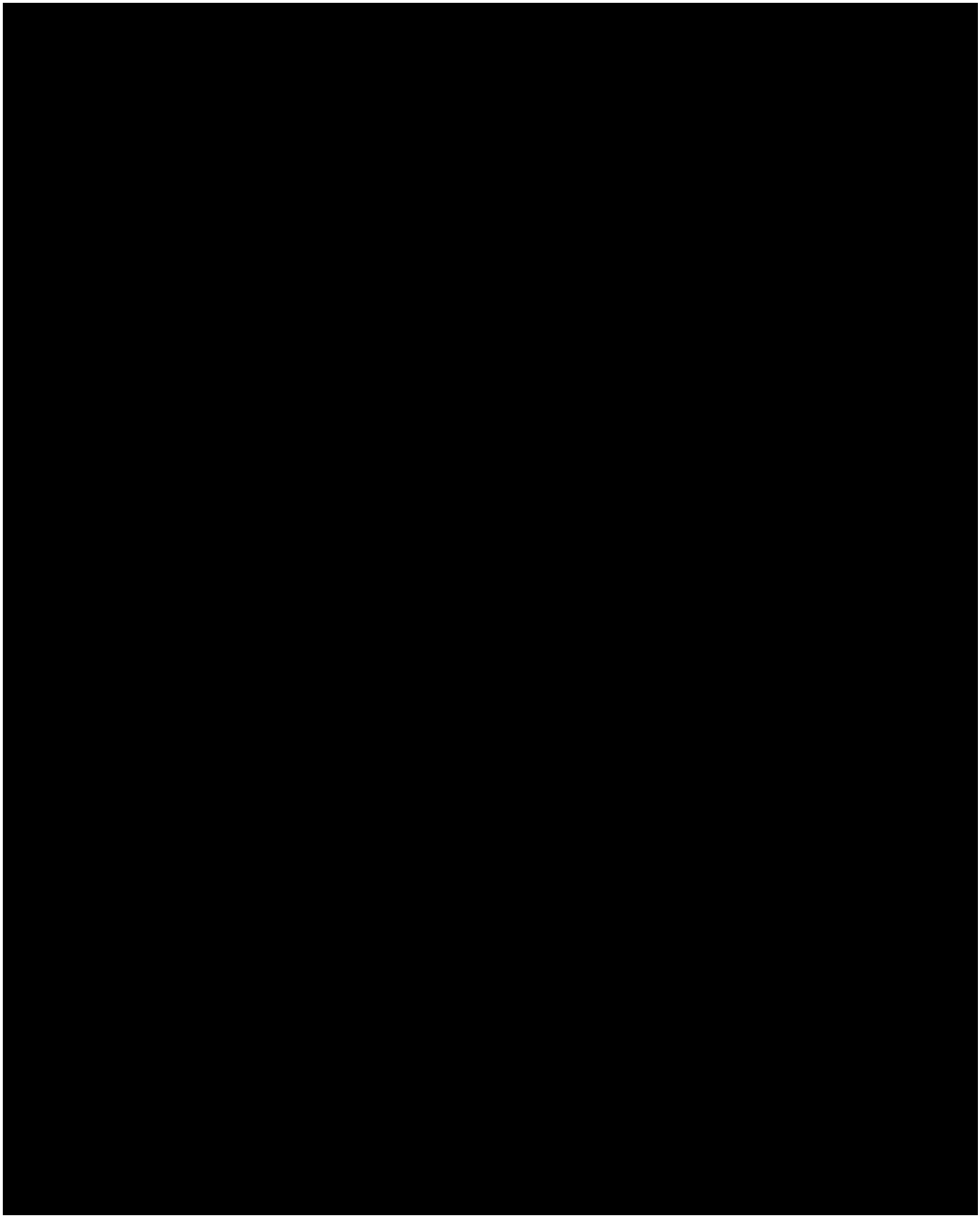
10.6. Pregnancy

It is the responsibility of the Investigator to report any pregnancy in a subject (spontaneously reported to them or discovered during a protocol-defined pregnancy test) that occurs during the study or within 13 weeks after the last injection of study drug to the Sponsor's Pharmacovigilance group within 24 hours of first becoming aware of the event. Pregnancy must be reported on a Pregnancy Report Form. The Investigator should discuss the case with the Medical Monitor; the Investigator must follow any pregnant subject for 3 months after the child is born. Any AEs concerning the pregnancy of the subject during pregnancy or the child after birth must be documented and reported to the Sponsor.

11. STATISTICS

Details for statistical methods are provided in the Statistical Analysis Plan (SAP). Information in the SAP supersedes descriptions provided in this protocol.





11.3. Analysis Populations

All subjects who return on Day 1 of the DBP (i.e., Baseline) and have all required baseline assessments/procedures completed (prior to randomization and injection of study drug) will be considered study participants. Study populations, identified and finalized before database lock, are described below.

11.3.1. All Randomized Population (DBP Only)

All subjects randomized to an active treatment or placebo will be included in the All Randomized population for [redacted] DBP. Subjects in the All Randomized population will be analyzed according to their randomized treatment group. The OLE part of the study will not include an All Randomized population.

11.3.2. Safety Population

For the DBP, subjects in the All Randomized population who actually receive an active treatment or placebo will be included in the Double-Blind Safety population. For the OLE, subjects in the Double-Blind Safety Population who receive any treatment in the open-label part of the study will be in the Open-Label Safety population. The Safety Population, analyzed as treated, will be used for all double-blind and open-label safety analyses.

11.3.3. Intent-to-Treat (ITT) Population

For the DBP, the Double-Blind ITT population is defined as all subjects who are randomized to active treatment or placebo (same as All Randomized population). For the OLE, the Open-Label ITT population is defined as all subjects who receive any treatment in the open-label part of the study (same as Open-Label Safety population).

11.3.4. Modified Intent-to-Treat (MITT) Population

For the DBP, the Double-Blind MITT population is defined as all subjects who are injected with study drug and have at least one valid post-baseline measurement recorded in the eCRF for both co-primary endpoints at Baseline (Day 1), Week 2 or Week 4 in the DBP of the study. The MITT population is the primary efficacy population.

For the OLE, the Open-Label MITT population is defined as all subjects in the Open-Label Safety population who have a measurement recorded in the eCRF for any primary or secondary efficacy endpoint at any visit after Week 13.

11.3.5. Per-Protocol Population

For DBP, the Double-Blind Per-Protocol (PP) population is defined as all subjects in the Double-Blind MITT population who do not have major protocol deviations during the DBP. Subjects with major protocol deviations will be defined before any data unblinding. This population will be used for efficacy as a supplementary analysis.

The open-label extension part of the study will not include a PP population.

11.4. Demographic and Baseline Characteristics

All baseline summaries for the double-blind part of the study will be based on the All Randomized and MITT populations. Baseline summaries for the OLE part of the study will be based on the Open-Label Safety population, and subjects will be summarized by the treatment received at Week 13 of the DBP.

Sex and race will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum). Age may be summarized by decades using number and percent.

The number and percent of subjects with abnormal physical examination findings at screening will be summarized. The number and percent of subjects with medical history events will be summarized. Vital signs collected at screening will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum).

No inferential statistics will be made on these characteristics.

11.5. Subject Disposition

A disposition of subjects will include the number and percentage of subjects in each of the analysis populations. Within each of these categories, the number and percentage of subjects who completed and discontinued from the study and the primary reason for early discontinuation will be summarized.

[redacted]

11.7. Analytical Methods

[redacted]

11.7.1. Efficacy

[redacted]

[redacted]

11.7.2. Analysis of Safety

11.7.2.1. Extent of Exposure

The duration of subject exposure to study treatment will be quantified as the number of weeks post-injection of study drug and measured from the time the subject received study treatment to the time the subject completed or discontinued from the study. The duration of dosing (weeks) will be summarized using descriptive statistics and ranges, with ranges of 0 to <2 weeks, 2 to <4 weeks, and 4 to <13 weeks for the double-blind part of the study and 1 to <13 weeks, 13 to <26 weeks, 26 to <39 weeks, 39 to ≤52 weeks, and 52 to ≤65 weeks for the OLE part of the study. Duration of exposure will be listed and summarized for all subjects in the Safety population by treatment group and by study part (DBP/OLE).

11.7.2.2. Treatment Compliance

Overall percent compliance will be summarized by treatment group for the Double-Blind Safety population. Percent compliance will also be summarized in the categories of <80% and ≥80%.

The number of subjects treated at each visit will be summarized by treatment group. Subjects who missed each visit will be identified and summarized by treatment group. For the OLE, treatment group will be determined by the treatment the subject received before the scheduled visit.

A summary of dose modifications (increase/decrease) at each post-baseline injection visit will also be presented. Total average dose will be summarized by treatment group in the All Randomized population.

11.7.2.3. Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs), including those that may be indicative of the DSOT (Table 12), will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment. Subject counts and percentages and event counts will be presented for each treatment group and totaled for all treatment groups for the following:

- All TEAEs, DSOT
- All TEAEs, DSOT by severity
- All SAEs
- TEAEs leading to discontinuation of study participation

Listings will be presented by subject for all AEs, as well as SAEs, AEs with outcome of death, AEs that may be indicative of DSOT, and AEs leading to discontinuation from the study.

For double-blind visits, treatment group will be determined by the treatment the subject received at the start of the double-blind part of the study. For OLE visits, treatment group will be determined by the treatment the subject received before the occurrence of the AE.

11.7.2.4. Vital Signs

Pre-injection values, post-injection values, and the change from baseline in vital signs' measurements (systolic and diastolic blood pressure, pulse, respiration rate, and temperature) will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each time point by treatment group. The baseline value will be value just before injection of study drug. For double-blind visits, treatment group will be determined by the treatment the subject received at the start of the double-blind part of the study. For OLE visits, treatment group will be determined by the treatment the subject received before the collection of the vital signs.

11.7.2.5. Electrocardiograms

ECG results will be summarized by visit by treatment group using descriptive statistics (for quantitative ECG parameters) and frequency tables (for qualitative ECG parameters, including the overall ECG finding). Change from baseline will be summarized, and individual ECG parameters will be provided in listings

11.7.2.6. Neurologic Examination

The number and percentage of subjects with new abnormal findings on the neurologic examination will be summarized by visit. For study visits during the DBP, treatment group will be determined by the treatment the subject received at Day 1 of the double-blind part of the study. For study visits during the OLE, treatment group will be determined by the treatment the subject received before the collection of the neurologic examination data.

11.7.2.7. Pulmonary Function Tests

The number and percentage of subjects with a SVC decrease of ≥20% will be summarized by visit. For double-blind visits, treatment group will be determined by the treatment the subject received on Day 1 of the DBP. For OLE visits, treatment group will be determined by the treatment the subject received before the collection of the pulmonary function data.

Pre-injection values, post-injection values, and the change from baseline in pulmonary function (SVC, IC, IRV, ERV, VCex, VCex %pred, FVC, FEV_1, and FEV_1/FVC) will be summarized with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each time point by treatment group. The baseline value will be value just before injection of study drug (Day 1).

11.7.2.8. Clinical Laboratory Evaluations

Clinical laboratory results at each time point and for change from baseline will be displayed using descriptive statistics (n, mean, SD, median, minimum, and maximum).

All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified time-point. Baseline is defined as the latest result obtained before the injection of study drug. For double-blind visits, treatment group will be determined by the treatment the subject received at the start of the double-blind part of the study. For OLE visits, treatment group will be determined by the treatment the subject received before the collection of the lab data.

11.7.2.9. Columbia Suicide Severity Rating Scale

The number and percentage of subjects with worsening (increasing in change from baseline) scores on the C-SSRS will be summarized by subscale and visit. For double-blind visits, treatment group will be determined by the treatment the subject received at the start of the double-blind part of the study. For OLE visits, treatment group will be determined by the treatment the subject received before the collection of the C-SSRS data.

11.7.3. Statistical Analytical Issues

[redacted]

[redacted]

11.7.3.3. Handling of Dropouts and Missing Data

It is anticipated that 10% of subjects will dropout before Week 4. For the primary efficacy analysis, all available data up to Week 4 will be used in the analysis. Missing data up to and including Week 4 will not be imputed for the primary efficacy analysis but will be imputed for sensitivity analyses. Details of missing data imputation will be described in the SAP.

[redacted]

[redacted]

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines
- US CFRs dealing with Protection of Human Subjects (US 21 CFR Part 50), Financial Disclosure (US 21 CFR Part 54), IRBs (US 21 CFR Part 56) and INDs (US 21 CFR Part 312)
- The Nuremberg Code
- The Declaration of Helsinki, revised version of Seoul, October 2008 (in compliance with FDA guidance)
- Applicable laws and regulations

The purpose of these regulations, legal obligations, and guidelines is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research. Copies of these materials can be downloaded from the FDA website at www.fda.gov.

The protocol, protocol amendments, ICF, Investigator Brochure and any other relevant documents must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

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 requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2. Informed Consent

Properly executed informed consent, in compliance with 21 CFR 50, ICH guidelines, and regional/local regulations, shall be obtained from each subject before entering the subject into the study. If a subject has caregiver assistance in the study, and that caregiver is willing to complete caregiver scales, then in addition to the subject, the caregiver must also consent. Attention is directed to the basic elements that are required in the informed consent under US CFR for Protection of Human Subjects (21 CFR 50.25) and/or ICH E6 4.8.10. Where applicable, the consent form or appended document must also include required elements to maintain compliance with 45 CFR Part 164 (HIPAA) and/or 21 CFR Part 50.27/ICH E6 4.8.8.

Informed consent is a process of interaction between the Investigator and a potential subject/LAR in which the Investigator (or appropriate designee) explains the aims, methods, anticipated benefits (or lack thereof), and potential risks of participating in a study, and informs the potential subject of their rights. The subject/LAR will be given ample time and opportunity to inquire about details of the study so the subject can voluntarily make an informed decision about whether or not to participate in the study. All potential subjects will be given a current IRB- and Sponsor-approved copy of the ICF to read to ensure they are given accurate information, and to assist in verifying that consent was obtained. Information provided verbally, as

supplemental explanation and/or answers to questions, must be accurate and consistent with the ICF, and must not be coercive or misleading. No subject will undergo any study procedures before the subject/LAR signs and dates the ICF, which should be signed before screening. A completed, signed copy will be given to the subject/LAR and a signed original shall be maintained in the subject's clinical file. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Potential subjects/LARs are to be consented using an ICF that is written in a language they understand. If the person obtaining consent is not fluent in the language in which the consent is written (i.e., is not able to explain the consent/answer questions to the subject/LAR), the subject's/LAR's consent must be witnessed by someone who is fluent in the language in which the consent is written who also has the ability to translate any questions/explanations during the consent process.

Each subject/LAR must also sign a HIPAA authorization form before his or her participation in the study. A signed copy must be provided to the subject and a signed original shall be maintained in the subject's clinical file.

The Investigator or authorized designee will explain to each subject, the objectives of the exploratory research. Subjects/LARs 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 storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects (or parents, guardians/LARs) who decline to participate in this optional research will not provide this separate signature.

12.3. Source Documents and Retention

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Information recorded on source documents are to be attributable, legible, contemporaneous, original and accurate and allow reconstruction of the trial from start to finish. It is the responsibility of the Investigator to ensure that source documents capture all required information needed for the verification of data required by the protocol and that data captured on the CRF match information recorded in source. The Investigator may need to request previous medical records from the subject's primary care or other relevant physician.

Source documents and site study records including signed ICFs are to be maintained on site during the duration of the study and retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. 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.

12.4. Subject Confidentiality

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and authorized representatives of the Sponsor. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or the pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or

hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records by virtual or onsite review.

Subjects will be assigned a unique identifier by the site. Any subject record or dataset that is transferred to the Sponsor or authorized representative of the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Subject confidentiality will be maintained in any publications or presentations that result from this study.

12.5. Study Monitoring and Data Quality

The Sponsor or a CRO will monitor the study. Study monitors perform ongoing source data verification to confirm that:

- that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents
- that the safety and rights of participants are being protected
- 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

The Study Monitor serves as the investigative site's primary contact. The Investigator should contact the Study Monitor if additional supplies are required, if there are changes to study personnel, or if the Investigator has questions regarding any aspects of the study.

The Study Monitor will visit each study site or perform a virtual review of study records at intervals as defined in the monitoring plan, after which a report on all monitoring activities will be submitted to the Sponsor. The purpose of the periodic visits/virtual monitoring is to verify that the clinical trial is being conducted and data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. The Data Coordinating Center will implement quality control procedures beginning with the data entry system (eCRF) and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site for clarification and resolution. In addition to data quality checks, centralized monitoring checks will be employed with the purpose of reviewing study performance metrics in addition to identifying trends of key data points within and across research centers. Findings of the centralized monitoring review may result in fewer or more onsite visits or virtual reviews, additional site training, corrective action plans or site closure. The purpose of centralized monitoring is to ensure quality data throughout the study.

12.6. Audits and Inspections

The Investigator is required to make all study records promptly available for inspection, review, or audit at the study site upon request by the monitor, Sponsor, its representatives, or any appropriate regulatory agencies.

The Sponsor may also request the Investigator to scan and email source documents with subject identifying information redacted to de-identify subject protected information. Additionally, as part of the informed consent process the Investigator should inform subjects about the potential of an audit by authorized representatives of the Sponsor and/or regulatory authorities and that confidentiality of the subject's data will be maintained in accordance with local laws.

12.7. Publication Policy

The Sponsor recognizes the importance of communicating medical study data and therefore encourages publication of such data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study is described in the Clinical Trial Agreement between the Sponsor and the institution of the Investigator.

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14. APPENDICES

APPENDIX A. MODIFIED ASHWORTH SCALE

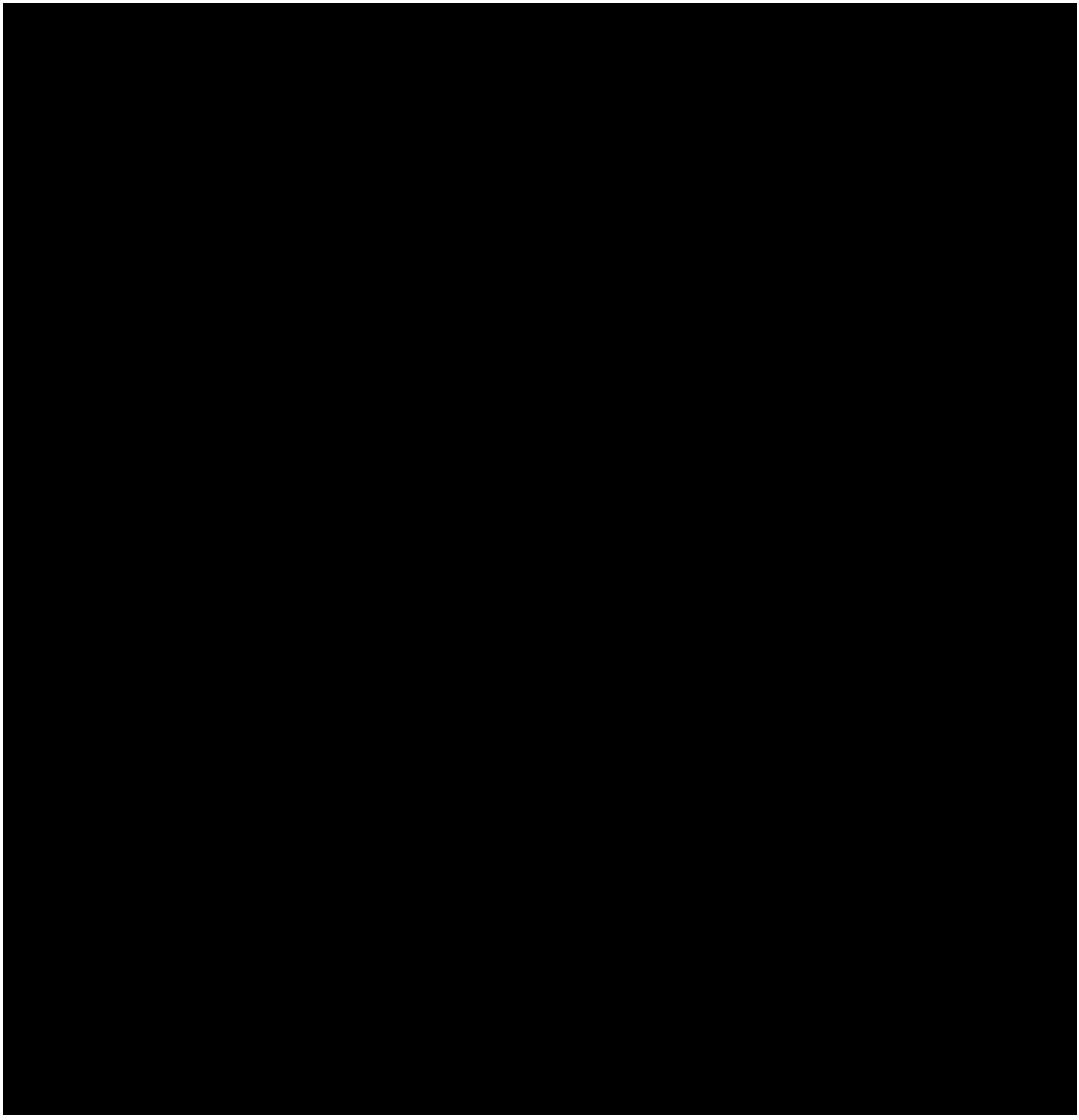
The MAS is an internationally accepted and validated instrument used to measure resistance during passive soft-tissue stretching.[21] Resistance will be measured and recorded using a 6-point scale ranging from 0 (no increase in muscle tone) to 4 (affected part[s] rigid in flexion or extension). Qualified assessors permitted to administer the MAS include physicians, physical therapists and/or occupational therapists, but any assessor administering the scale will be required to be trained and listed on Form FDA 1572. The MAS will be administered at screening, prior to administration of study drug on Day 1 of each treatment session, at each subsequent study visit, and, if applicable, at discontinuation from the study.

The qualified assessor who administers the MAS on Day 1 of the DBP must also administer the MAS at each subsequent study visit throughout the DBP for each subject.

Note that during the DBP, if the assessor administering the MAS is the same assessor completing the CGI scales, the CGI scales must be completed prior to the administration of the MAS as to reduce potential bias that MAS scores could have on CGI ratings. During the OLE, the qualified assessor administering the MAS on Day 1 of each treatment session must administer the MAS at each subsequent study visit; however, an alternate, qualified, and trained assessor (named on Form FDA 1572) may serve as a back-up assessor if absolutely necessary. The assessor will record the subject's MAS score in the site's source documents and the results will be transferred to the eCRF.

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

APPENDIX B. CLINICAL GLOBAL IMPRESSION



Clinical Global Impression of Change (CGI-C)

The CGI-C scale will be used to rate the physician's global impression of change in the subject's ability to function since just before receiving his or her most recent injection of study drug on a 7-point scale ranging from "very much improved" to "very much worse." The CGI-C will be completed at each visit subsequent to the first administration of study drug on Day 1 of the DBP, at each study visit during the OLE, and if applicable/feasible, at discontinuation from the study.

Compared to the subject's ability to function before the subject received his or her most recent injection of study drug, how much has the subject's ability to function changed?

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

The study physician must not refer to any previously recorded efficacy assessments (CGI-S, CGI-C, or any other efficacy assessments) when making current assessments. Additionally, the CGI scales must be completed independent of the subject's self-reported global assessment (PGI-S and PGI-C), and if applicable, independent of caregiver-reported global assessments (GGI-S and GGI-C), so neither party knows how the other has rated the scales. The CGI assessments will be recorded in the site's source documents and the results will be transferred to the eCRF.

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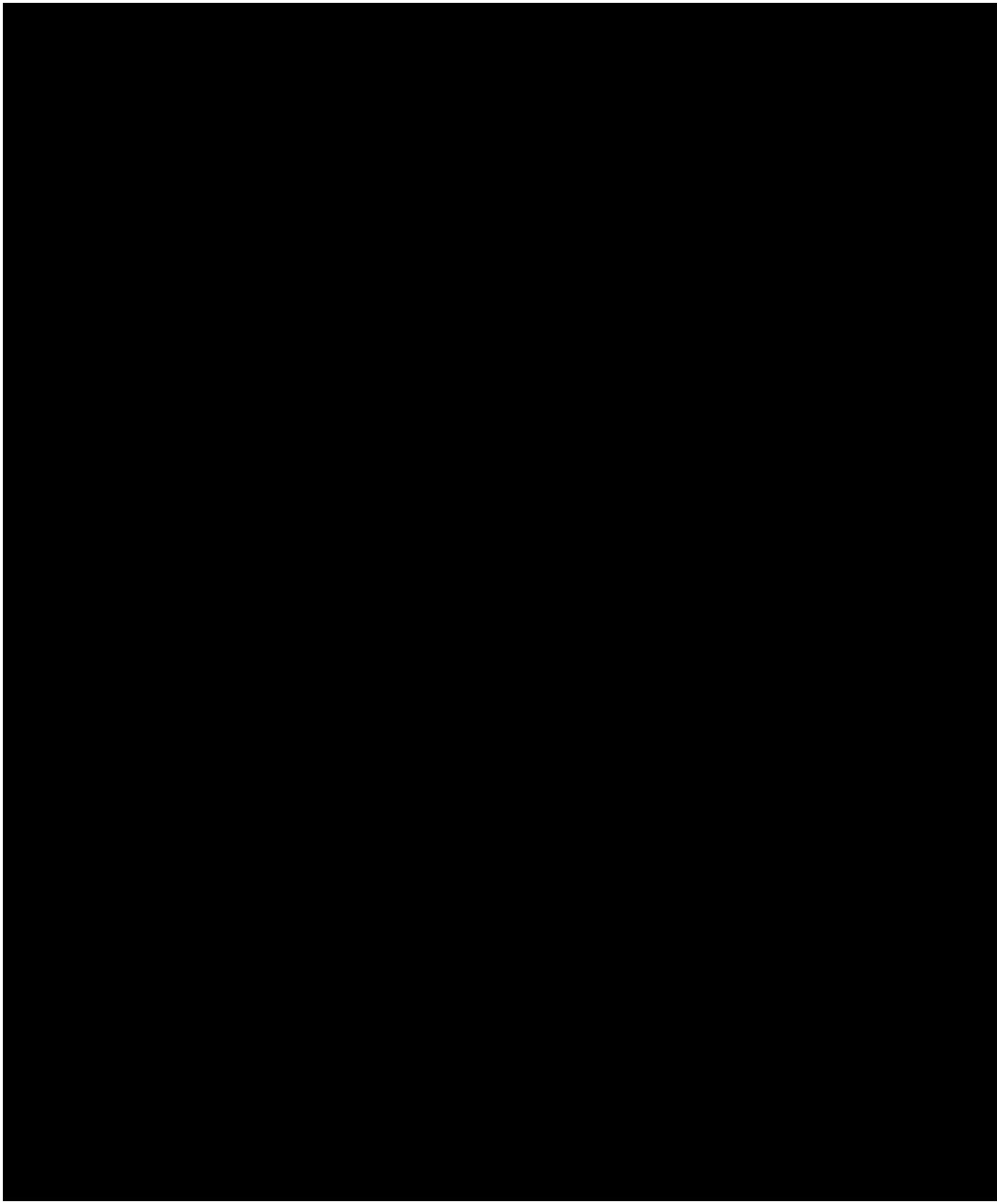

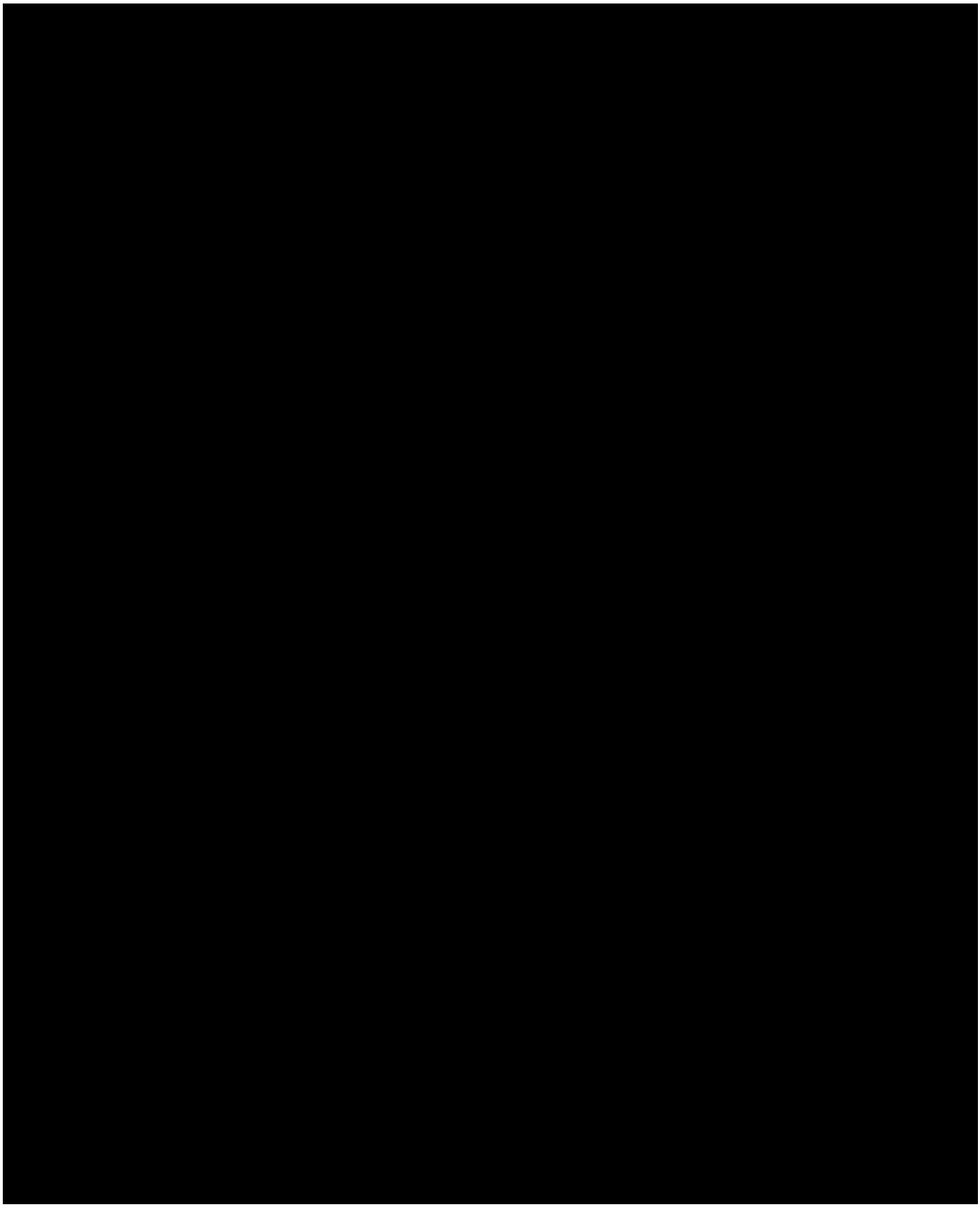

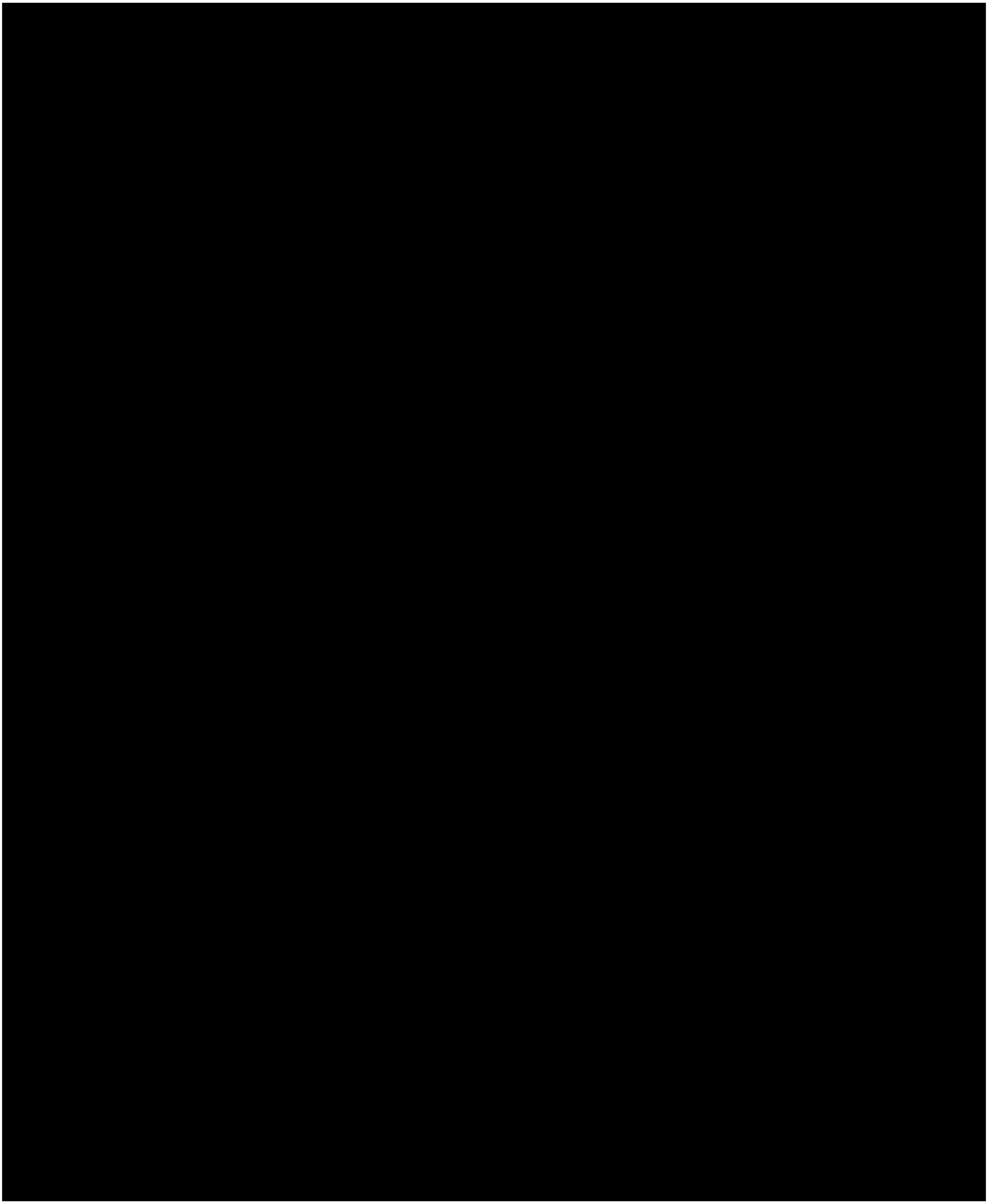

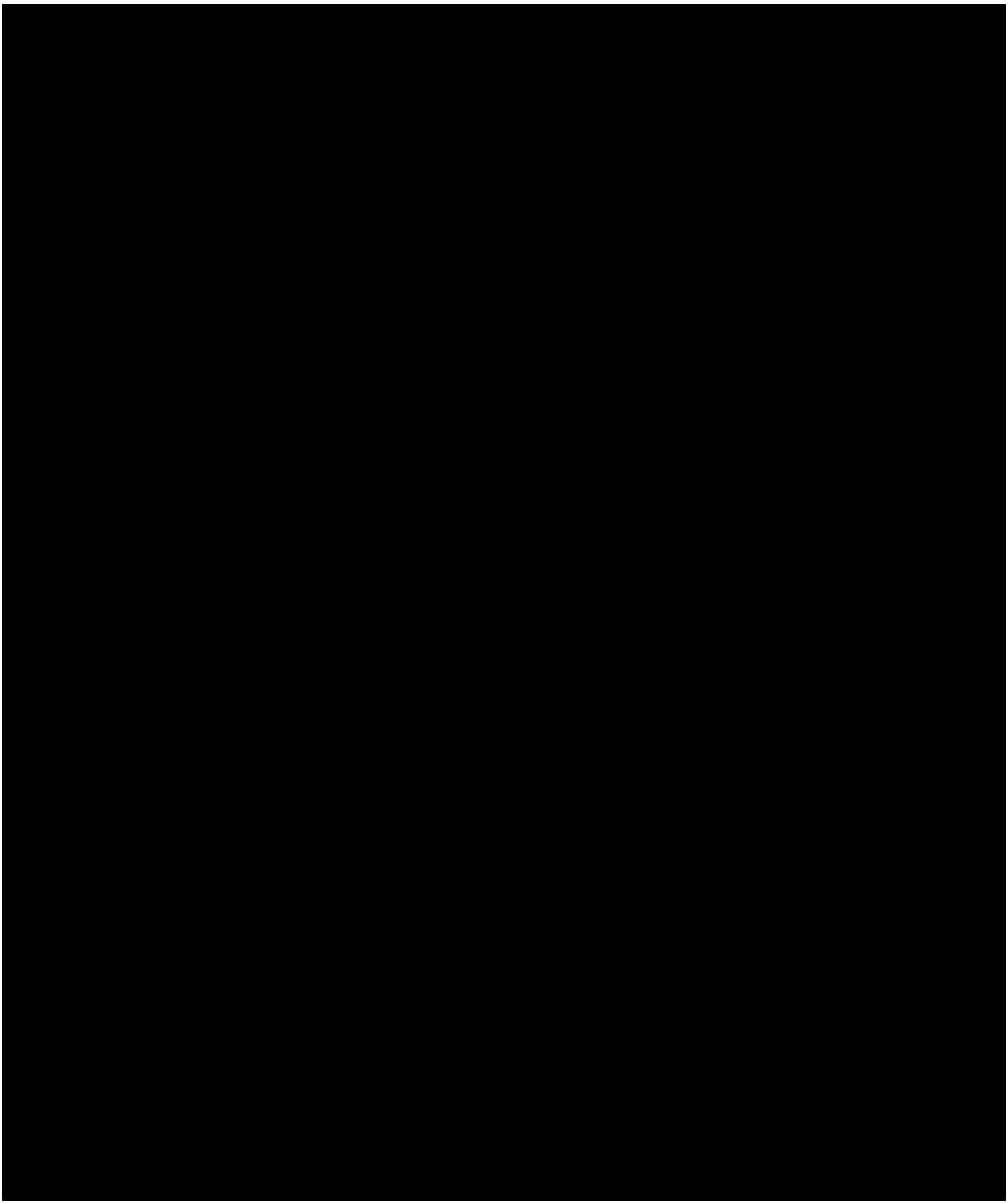

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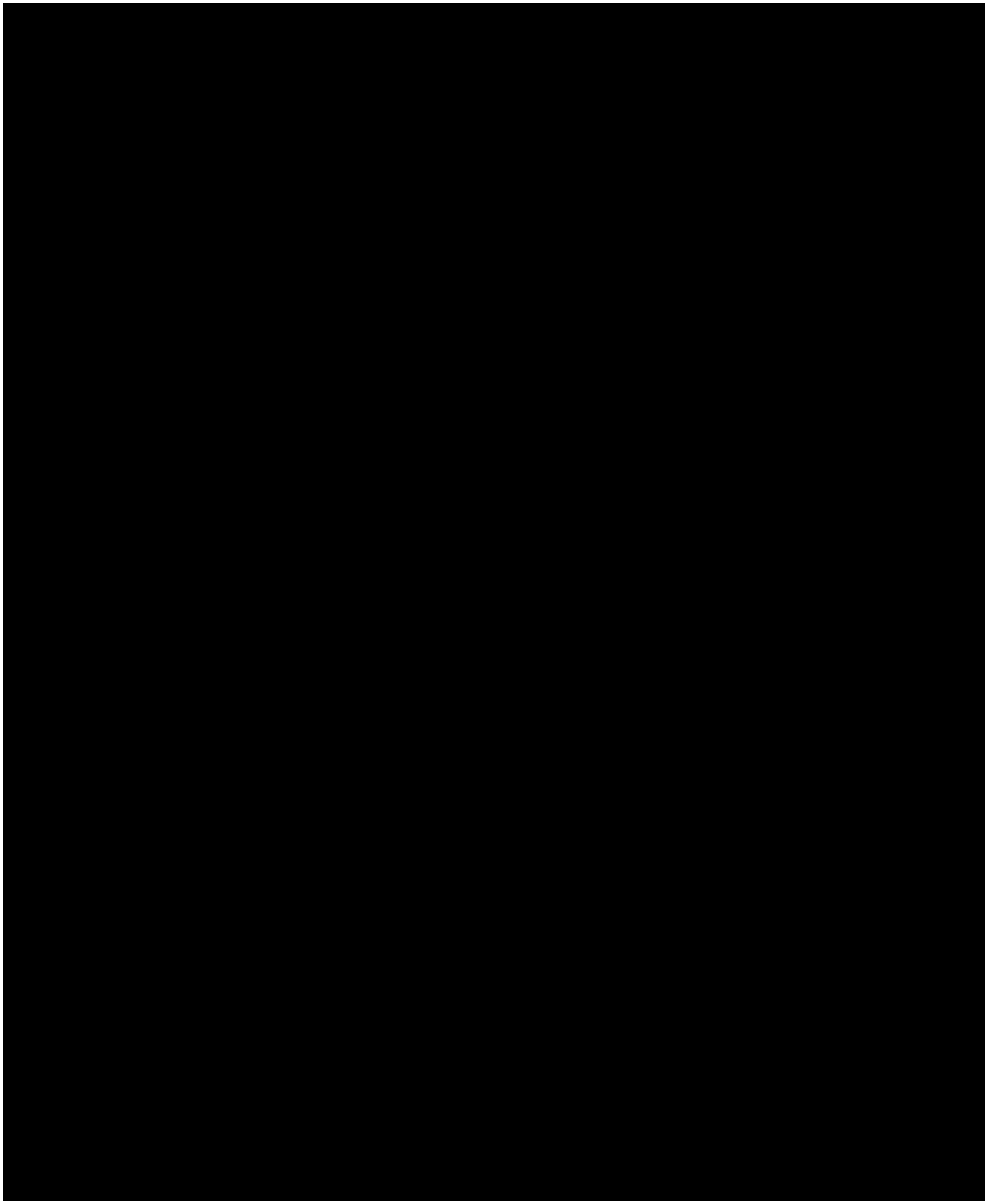
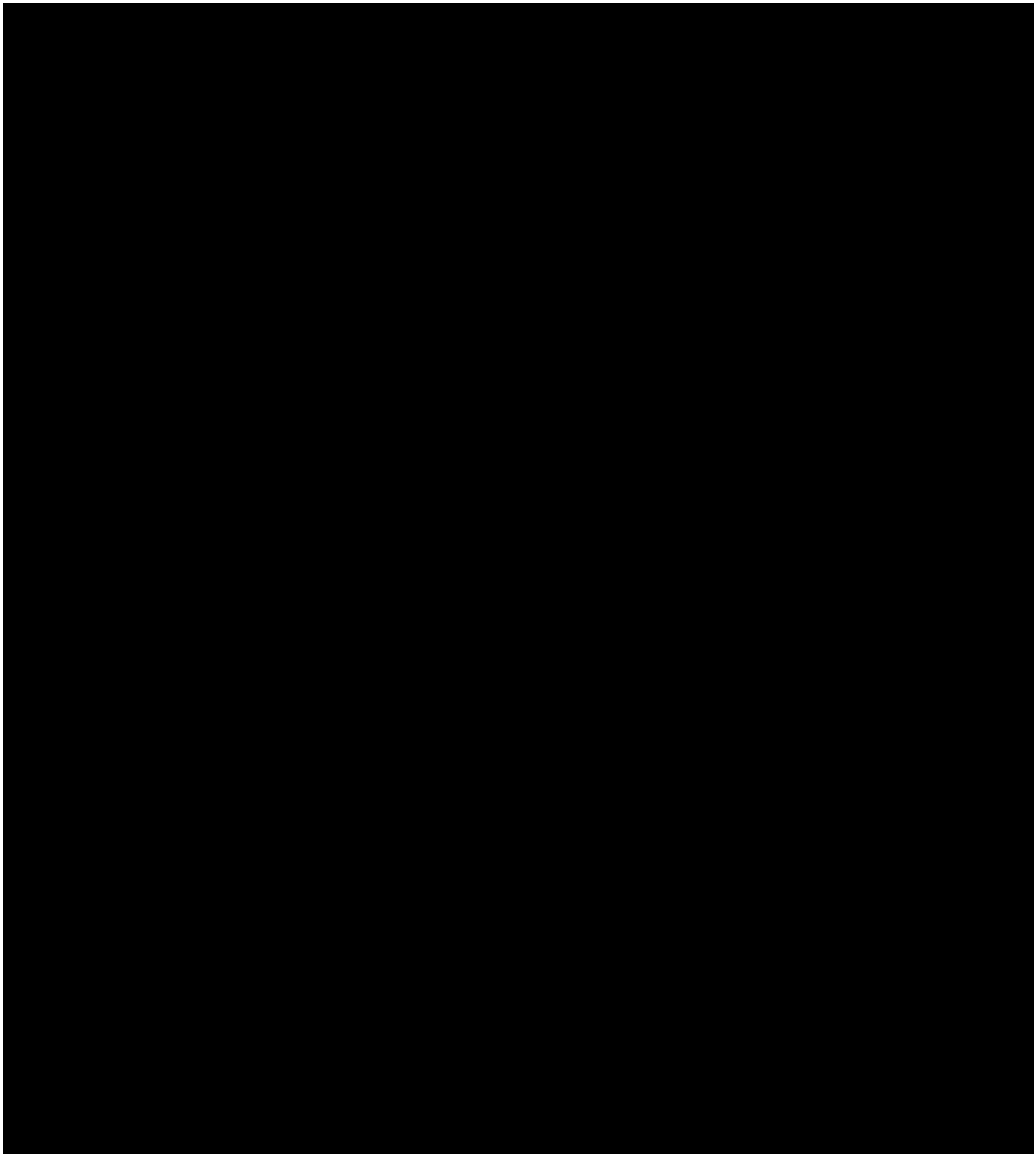
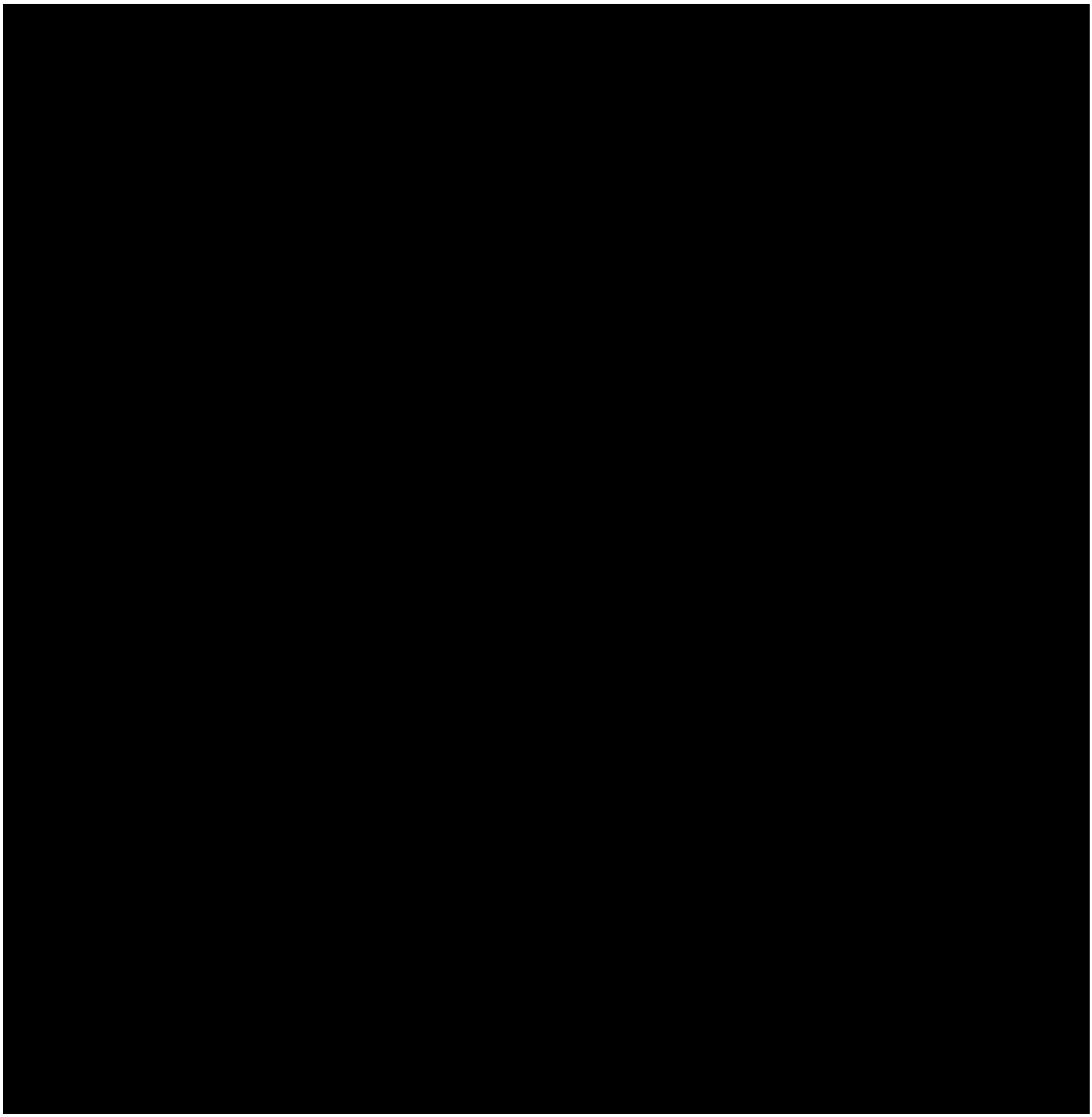






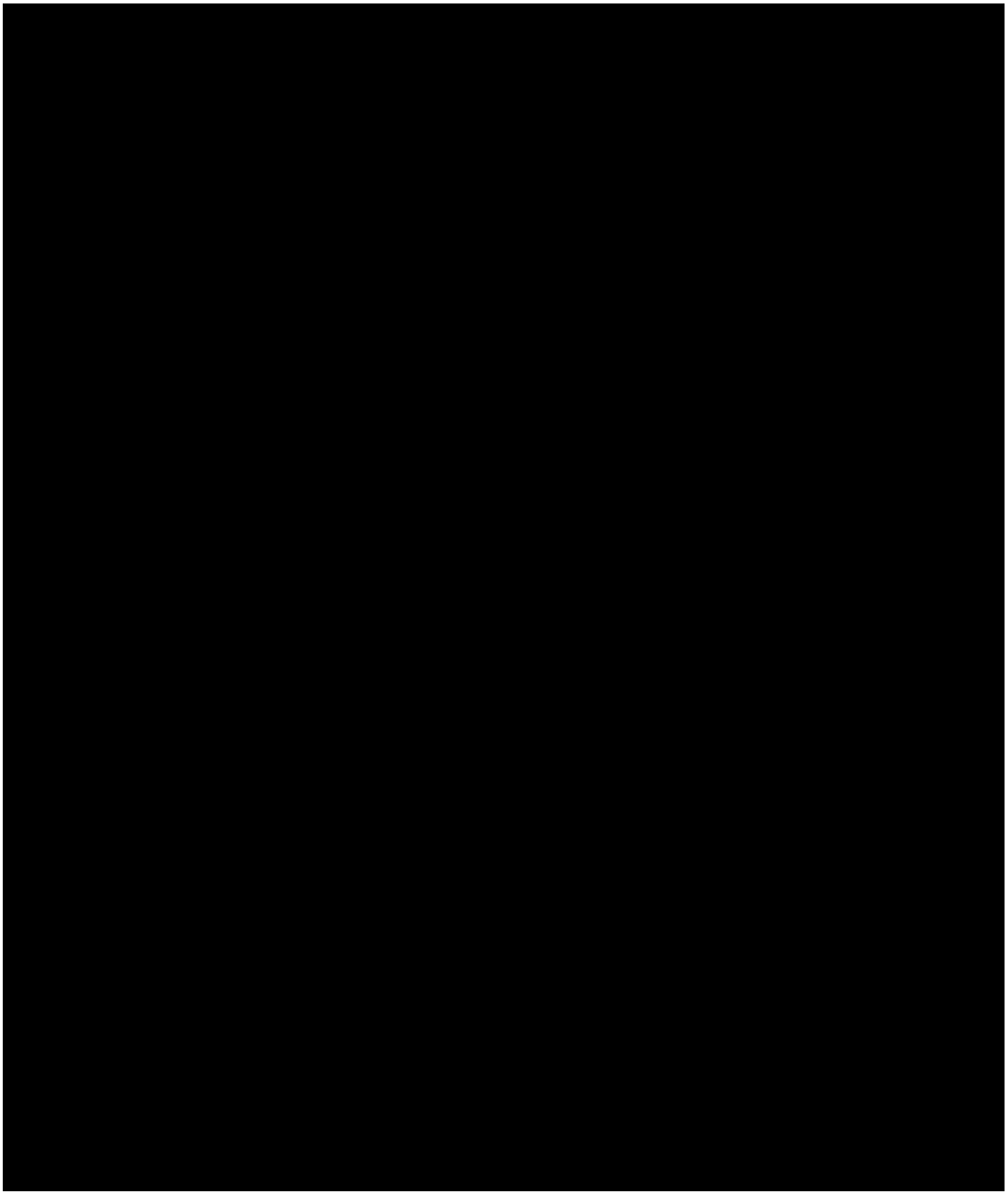
APPENDIX G. NEUROLOGIC EXAMINATION

The neurologic examination consists of 9 sections and evaluates the following: 1) level of consciousness; 2) speech; 3) cranial nerves; 4) motor; 5) sensory; 6) coordination; 7) gait; 8) reflexes, and 9) Romberg test. A description of abnormal findings only will be completed by the Investigator at screening; Day 1 (before injection of study drug); at Weeks 2, 4, 8, and 13 (the DBP of the study); at Weeks 17, 26, 30, 39, 43, 52, and 56 of OLE, at Week 65; or, if applicable, at discontinuation from the study. At Weeks 13, 26, 39, and 52, the neurologic examination will only be performed once the subject meets the retreatment criterion.

Examination		**Rating 0=Normal 1=Abnormal 2=Not Done**	**Description of Abnormal Findings**
1. Level of Consciousness			
2. Speech			
3. Cranial Nerves	II		
	III, IV, & VI		
	VII		
	IX, X		
	XI		
	XII		
4. Motor	RUE		
	RLE		
	LUE		
	LLE		
5. Sensory	RUE		
	RLE		
	LUE		
	LLE		
	Trunk		
6. Coordination	UE		
	LE		
	Other		
7. Gait			
8. Reflexes			
9. Romberg			

RUE (right upper extremity), RLE (right lower extremity), LUE (left upper extremity), LLE (left lower extremity), UE (upper extremity), LE (lower extremity)

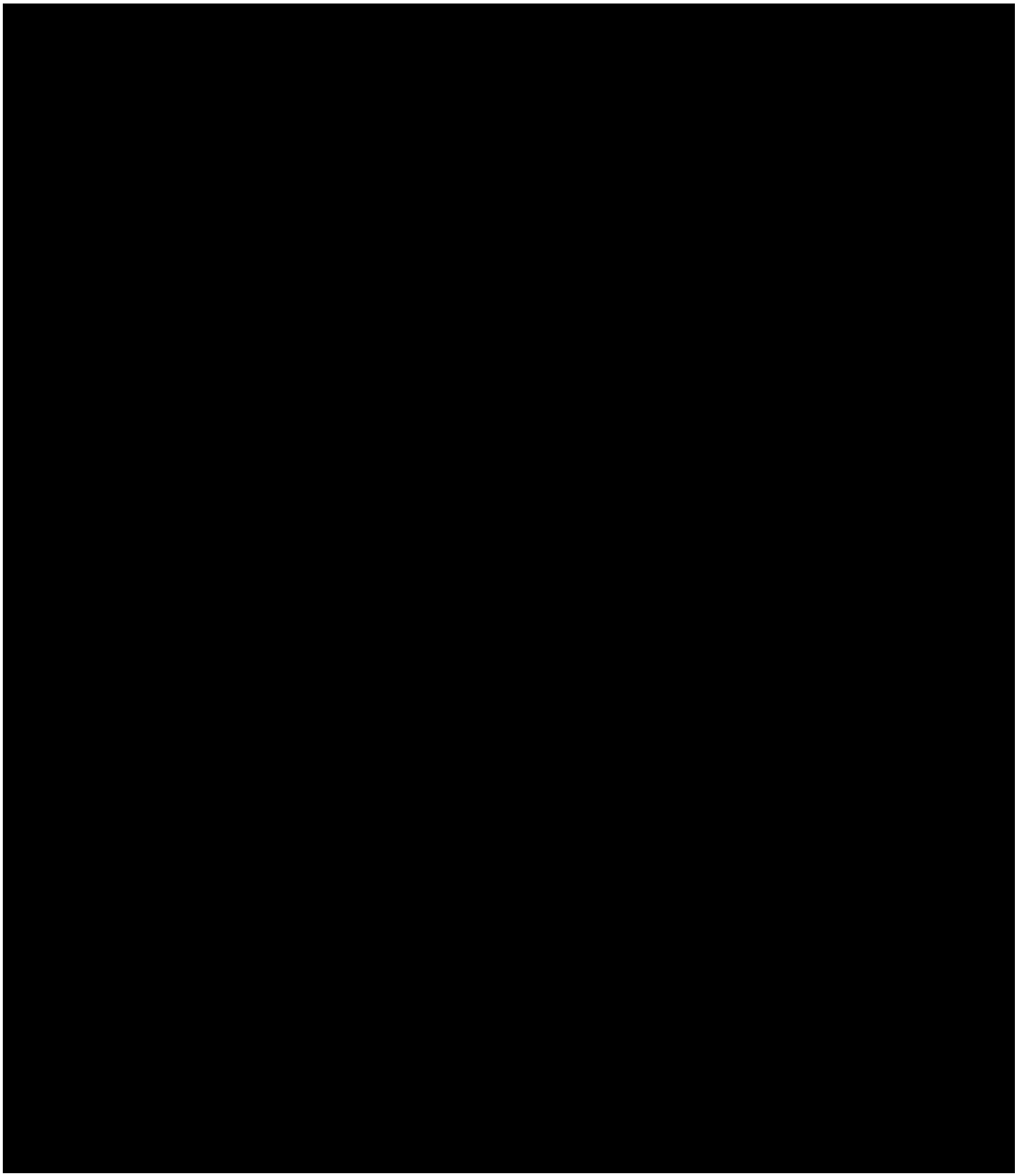
APPENDIX H. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) BASELINE VERSION

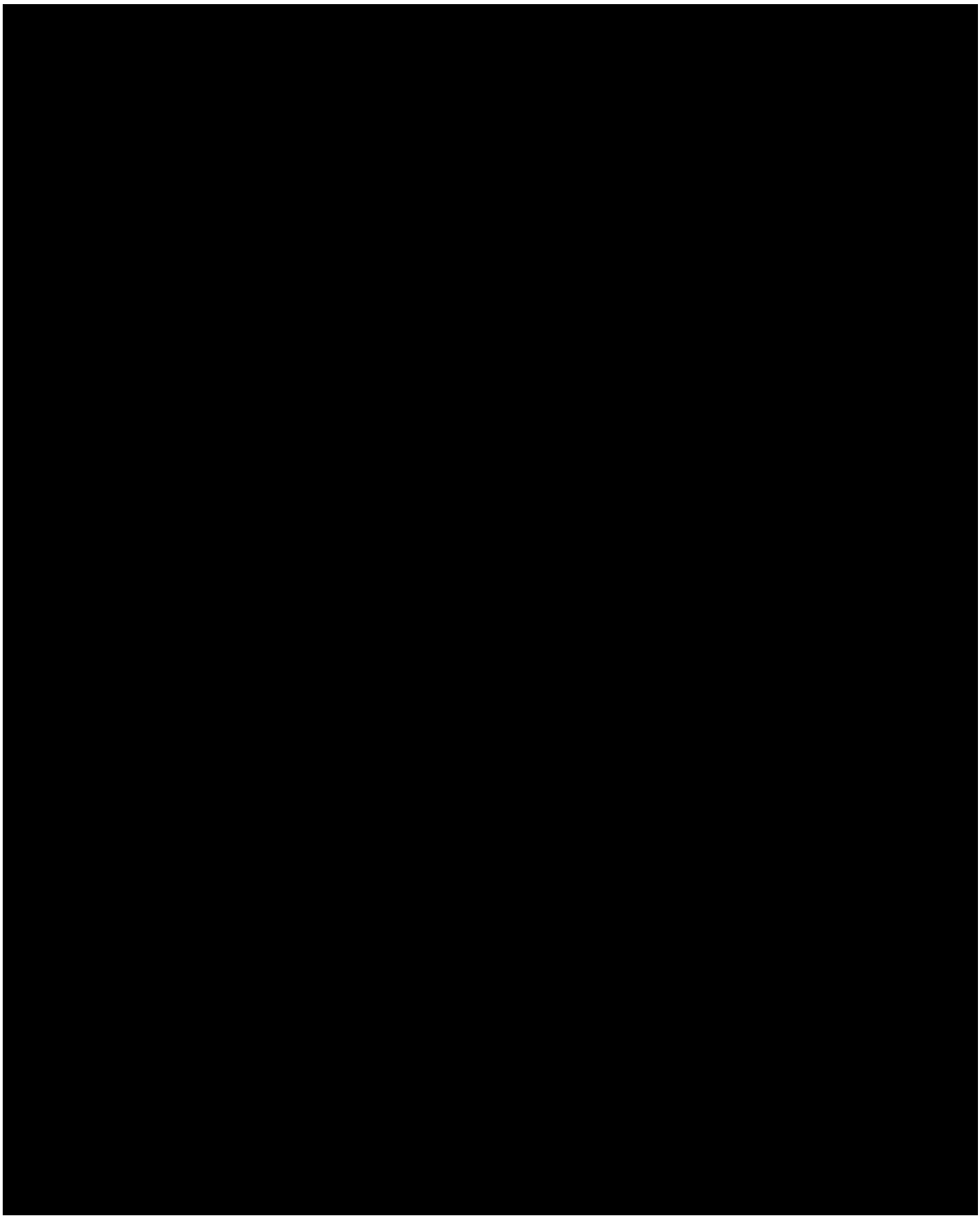


[redacted]

[redacted]

APPENDIX I. COLUMBIA SUICIDE SEVERITY RATE SCALE (C-SSRS) SINCE LAST VISIT VERSION





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