PRODUCT: MYOBLOC® (rimabotulinumtoxinB) Injection
PROTOCOL NUMBER / AMENDMENT #: SN-SIAL-351 / 01

SPONSOR:
Solstice Neurosciences, LLC,
a subsidiary of US WorldMeds, LLC
4441 Springdale Rd, Louisville, KY 40241, USA

TITLE:
A Phase 3, Long-Term, Open-Label and Single-Arm Study of MYOBLOC®
in the Treatment of Troublesome Sialorrhea in Adult Subjects

DOCUMENT DATE: July 23, 2015
IND NUMBER: 100,454
NCT NUMBER: NCT02610868

CLINICAL STUDY PROTOCOL

A Phase 3, Long-Term, Open-Label and Single-Arm Study of MYOBLOC® in the Treatment of Troublesome Sialorrhea in Adult Subjects

Protocol Number:	SN-SIAL-351
Product:	MYOBLOC® (rimabotulinumtoxinB) Injection
Investigational New Drug (IND) Number:	IND 100,454
Development Phase of Study:	Phase 3
Medical Monitor:	
Sponsor:	Solstice Neurosciences, LLC, a subsidiary of US WorldMeds, LLC 4010 Dupont Circle, Suite L-07 Louisville, KY 40207
Protocol Date:	February 12, 2015
Amendment No. 01 Date:	July 23, 2015

1 PROTOCOL AMENDMENT SUMMARY

This section provides a summary of major changes made to the protocol for Study SN-SIAL-351 in this current amendment (No. 01). Section 25 provides a detailed accounting of all amendment changes.

- Protocol was revised by changing applicable inclusion/exclusion criteria to allow enrollment of subjects who have had prior botulinum toxin A or B injections to the salivary glands, provided that last administration was at least 24 weeks before screening, and previous botulinum toxin A or B exposure to other anatomical locations provided that last administration was at least 12 weeks before screening. Further, enrollment of subjects who previously received botulinum toxin injections would require that prior toxin exposure was well tolerated and without any significant long-term side effects, and subjects, in the Investigator's opinion, must not have failed to respond to previous treatment with botulinum toxin. This change was implemented in order to improve enrollment and to facilitate the collection safety data on subjects who would be likely candidates for treatment with MYOBLOC for sialorrhea in clinical practice.

- Revised exclusion criteria to remove specific exclusion of subjects with moderate to severe dysphagia and moderate to severe choking, and have revised exclusion criteria related to risk of aspiration (moderate to high risk of aspiration is exclusionary). Specific considerations have been provided which should be taken into account when the Investigator determines the subject's level of risk of aspiration. Moderate to high risk of aspiration is defined by any one of the following
    - History of aspiration pneumonia in the last 6 months before screening
    - Speech pathologist and/or formal swallowing test (e.g., with barium, endoscopy, dynamic swallowing study, imaging study, fiber-optic endoscopic swallowing evaluation or other imaging scan) that concludes that a moderate to severe risk of aspiration exists
    - Due to perceived risk of aspiration, a health care professional has recommended PEG or G-tube but subject declined
    - In the investigator's clinical judgment, the subject is at moderate to high risk of aspiration

  Subjects whose risk of aspiration are judged by the investigator to be satisfactorily controlled by placement of PEG or G-tube for nutritional support are eligible to participate. Specific criteria excluding subjects with moderate to severe dysphagia or choking within the last 6 months prior to screening have been removed, and instead the protocol focuses solely on the risk of aspiration, taking into consideration that those with a PEG or G-tube (in whom placement of either would mitigate the risk of aspiration associated with a moderate to severe risk dysphagia or choking) may participate. The previous exclusion criteria could be considered too vague or restrictive as it focused on a symptom (dysphagia or difficulty with swallowing) that is common to many neurological disorders and especially frequent in ALS. The

revised inclusion/exclusion criteria now focus on the baseline risk of aspiration because it is aspiration that can lead to significant morbidity and even mortality.

- The requirement to administer the Visual Analog Scale (VAS) to subjects in order to rate severity for dysphagia and dry mouth at every clinic visit has been removed. Administering the scale at every visit, regardless of a reported event of dysphagia or dry mouth, is unnecessary and would result in an overreporting of events. Adverse events of dysphagia and dry mouth will continue to be collected based on subject report and severity will be determined by the Investigator.

  Study drug injections should not be administered if an adverse event of dysphagia or dry mouth of moderate to severe severity persists without prior consultation with the Medical Monitor. If the adverse event has not resolved or has not improved to a mild severity by the end of the per protocol window for injections to occur (every 13 ± 2 weeks), the Medical Monitor should be contacted to discuss whether or not the subject should be dosed, discontinued, etc.

- Administrative updates have been incorporated, including a change in the Medical Monitor information.

2 SIGNATURE PAGE

By signing below, Solstice Neurosciences, LLC and the Investigator indicate approval of this protocol as well as assurance that this study will be conducted according to the procedures described in the protocol, Good Clinical Practices, and all applicable regulatory requirements.

Protocol Approval:

Signature: **Date:** July 23, 2015

Name (print):

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ **Date:** _____

Name (print): _____

3 PROCEDURES IN CASE OF EMERGENCY

Table 1. Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Lead		Solstice Neurosciences, LLC a subsidiary of US WorldMeds, LLC 4010 Dupont Circle, Suite L-07 Louisville, KY 40207
Sr. Medical Monitor/ Safety Physician		
Back-up Medical Monitor/Safety Physician		
SAE Reporting		

4 SYNOPSIS

Title	A Phase 3, Long-Term, Open-Label and Single-Arm Study of MYOBLOC® in the Treatment of Troublesome Sialorrhea in Adult Subjects
Objectives	**Primary** • To determine the long-term safety and tolerability of MYOBLOC (administered intraglandularly as a single total dose of 3,500 Units) treatments every 13 weeks over a maximum possible duration of 1 year in adult subjects with troublesome sialorrhea. **Secondary** • To assess the magnitude of therapeutic response of MYOBLOC (administered intraglandularly as a single total dose of 3,500 Units) using effectiveness assessments performed at intervals after treatments every 13 weeks over a maximum possible duration of 1 year.
Study Design	Multicenter, open-label, outpatient study of the safety and effectiveness of repeated doses (3,500 Units every 13 weeks) of MYOBLOC over a 1-year duration in adult subjects with troublesome sialorrhea. The study population will be comprised of a mixture of patient populations including, but not limited to, subjects with Parkinson's Disease (PD)-related sialorrhea, sialorrhea secondary to other non-PD conditions (e.g., adult cerebral palsy, amyotrophic lateral sclerosis [ALS], stroke, traumatic brain injury), or sialorrhea secondary to oral cancer or medications (e.g., neuroleptics). All MYOBLOC injections will be performed by Investigators who have prior experience or have been appropriately trained with injecting botulinum toxin. Injections will be guided by external anatomical landmarks or by external anatomical landmarks with ultrasound-guided confirmation. Sites designated as "ultrasound" sites will perform all their injections with ultrasound-guidance. After a screening period (up to 21 days), those subjects who satisfy all eligibility criteria may receive single dose injections of 3,500 Units of MYOBLOC every 13 weeks (±2 weeks) for a total of 4 treatments via injections into the submandibular and parotid glands. Repeat injections at each treatment session will be done when subjects return to baseline status as determined by the Investigator, with a minimum interval of 11 weeks from the prior injection. If after the first treatment of 3,500 Units the subject develops intolerable side effects, but still wishes to remain in the study, the Investigator has the discretion to decrease subsequent doses, but to no less than a total dose of 2,500 Units.

Study Design *(continued)*	Subjects will undergo safety and effectiveness assessments at Weeks 4, 8, 13, 17, 26, 30, 39, 43, and 52 as detailed below, and telephone follow up will occur at Weeks 21, 34, and 47.
Sites	20 or more (Target: up to 1 subject/site/month. Recruitment time: 6 to 12 months)
Inclusion Criteria	1. Able to read and provide written informed consent before enrollment into the study, or the subject's caregiver (Legally Authorized Representative) can provide written informed consent. 2. Male or female, 18 to 85 years of age (inclusive). 3. Seeking treatment for troublesome sialorrhea for at least 3 months that is occurring secondary to any disorder or related to any cause, including, but not limited to, Parkinson's Disease (PD), adult cerebral palsy, amyotrophic lateral sclerosis (ALS), stroke, traumatic brain injury, oral cancer, and side effects of other medications. Note: A diagnosis of Parkinson's Disease fulfills the UK Parkinson's Disease Society Brain Bank diagnostic criteria. A diagnosis of ALS fulfills the El Escorial World Federation of Neurology criteria. 4. Minimum unstimulated salivary flow rate of 0.2 g/min at screening (unstimulated normal rate is 0.3 g/min) [Wang 1998]. 5. Minimum Investigator's Drooling Frequency and Severity Scale (DFSS) score of 4 (range 2-9, a score of 2 = "never drools") at screening. 6. Ability and availability to participate in the study for up to 1 year (ALS subjects: ability and availability to participate in the study for at least 6 months), based on overall health of the subject and disease prognosis, as applicable, in the opinion of the Investigator, and able to comply with all requirements of the protocol, including completion of study questionnaires. A caregiver may be designated to assist with assessments.
Exclusion Criteria	1. A moderate to high risk of aspiration will exclude participation in this study. Moderate to high risk of aspiration is defined by any one of the following: • History of aspiration pneumonia in the last 6 months before screening • Speech pathologist and/or formal swallowing test (e.g., with barium, endoscopy, dynamic swallowing study, imaging study, fiber-optic endoscopic swallowing evaluation or other imaging scan) that concludes that a moderate to severe risk of aspiration exists • Due to perceived risk of aspiration, a health care professional has recommended PEG or G-tube but subject declined • In the Investigator's clinical judgment, the subject is at moderate to

	high risk of aspiration. Subjects whose risk of aspiration are judged by the Investigator to be satisfactorily controlled by placement of PEG tube or G-tube for nutritional support are eligible to participate. 2. Respiratory forced vital capacity (FVC) of <20% of predicted. FVC will be tested in all ALS subjects, and also in other subjects at Investigator discretion if warranted. 3. Prior botulinum toxin type A or B treatment in the salivary gland(s) identified for treatment in this study within 24 weeks before screening. Prior botulinum toxin type A or B treatment into other anatomical regions not selected for treatment in this study is not exclusionary, but must have occurred at least 12 weeks before screening. • In the Investigator's assessment, prior toxin exposure must have been well tolerated and without any significant long-term side effects in the case of repeated prior exposure. Subjects should be excluded if, in the Investigator's opinion, the subject failed to respond to previous treatment with botulinum toxin. Subjects should not receive nor have any plans for receiving any botulinum toxin treatment, other than the study drug (MYOBLOC), during the entire course of the study (from the point the informed consent is signed until subject's participation is complete). 4. Prior salivary gland surgery. 5. Concomitant use, or exposure within 5 half-lives of screening, of aminoglycoside antibiotics, curare-like agents, or other agents that interfere with neuromuscular function.
Exclusion Criteria *(continued)*	6. Current treatment or treatment at any time during the study with Coumadin® (warfarin) or similar anti-coagulant medications. Anti-platelet medications are not specifically exclusionary. 7. Anticipated or scheduled surgery during the study period. A PEG tube/G tube may be placed for nutritional support at any time during the study and will not exclude the subject from continued study participation. 8. Major surgery (requiring general anesthesia, except PEG tube/G tube placement) within the previous 6 months before screening. If surgery occurred more recently than 6 months before screening, Investigator must have sufficient documentation to demonstrate the subject has fully recovered and stabilized. Prior movement disorder-related surgery (e.g., pallidotomy, thalamic/subthalamic/pallidal deep brain stimulation) will not exclude the subject, provided the surgery was performed at least 6 months before screening. 9. Anticholinergic and antihistamine medication eligibility restrictions: • Oral/transdermal pharmacologic treatment (specifically

	antihistamines and those medications with anticholinergic properties) ***for troublesome sialorrhea*** must be discontinued during the 30-day period before screening and are not allowed in the entire duration of the study, except ALS subjects as allowed herein. For ALS subjects only: such medications for the treatment of sialorrhea are allowed; however, conversion to, or continuation of, a short-acting medication (duration of action of approximately 8 hours or less) is required at a stable dose/regimen at least 2 weeks before the first injection of study drug (i.e., Day 1 of Treatment Session 1). The short-acting anti-cholinergic medication for the treatment of sialorrhea may be continued throughout screening and study participation provided that the ALS subject agrees to hold the medication for at least 8 hours before the screening, baseline, and all subsequent study visits, so that the effectiveness and safety of the study drug can be properly evaluated. • Antihistamines and anticholinergic medications taken ***for a non-sialorrhea condition*** should be avoided as much as possible, but are not exclusionary.
Exclusion Criteria *(continued)*	10. Evidence of any clinically significant neurologic disease (e.g., myasthenia gravis, Lambert-Eaton syndrome), cardiovascular, hematologic (including bleeding diathesis), hepatic, renal, gastrointestinal, endocrine, pulmonary, musculoskeletal, psychiatric disease or condition, or dental condition, which in the judgment of the Investigator or screening dentist would put the subject at risk while in the study, could influence the results of the study, or negatively impact the subject's ability to participate in the study 11. Pregnancy or lactation • As assessed by the Investigator, 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), biologically sterile, or surgically sterile (e.g., s/p hysterectomy, bilateral oophorectomy, tubal ligation). 12. History of drug or alcohol abuse currently or within the previous 6 months, as determined by the Investigator. 13. Current infection at the sialorrhea treatment injection site(s). 14. Participation in another clinical drug, device, or biological agent study

	within 30 days of screening or while participating in this study. 15. Any other condition or clinical finding that, in the opinion of the Investigator and/or the Sponsor, is determined to be unsuitable for enrollment into this study.
Number of Subjects	Approximately 120 to 200 subjects or until requirements of safety database are met.
Safety Endpoints	• Occurrence, seriousness, severity, and causality assessment of adverse events at each study visit; • Occurrence of adverse events of special interest (i.e., aspiration, aspiration pneumonia, choking, dysphagia) at each study visit as assessed by the Investigator; • Columbia Suicide Severity Rating Scale (C-SSRS) at each study visit; and • Occurrence of dental adverse events.
Effectiveness Endpoints	• Unstimulated salivary flow rate (USFR) (Assessor) at each study visit; • Clinical Global Impression of Severity (CGI-S) and Change (CGI-C) (Assessor) at each study visit; • DFSS-I (Assessor) at each study visit; • DFSS-S as assessed via subject's diary at each assessment time point; • Patient Global Impression of Severity (PGI-S) and Change (PGI-S) at each study visit; and • Drooling Impact Score (DIS) (Subject) at each study visit.
Duration	The planned duration of participation for each subject is a minimum of 26 weeks and a maximum of 52 weeks (excluding up to a 21-day screening period), including: • Up to four 13-week (±2 weeks) treatment sessions over a 1-year period. Note that Treatment Sessions 3 and 4 are likely, but may not be necessary as the study progresses because the study may be stopped early once enough subjects have completed the study to meet FDA safety database requirements. Any subject that enters the study, however, is required to participate at least through 6 months (i.e., complete Treatment Sessions 1 and 2).
Study Visits	<u>Screening Period:</u> up to 21 days <u>Treatment Session 1</u> Day 1 (day of injection of study drug) and 4 weeks (±3 days), 8 weeks (±3 days), and 13 weeks (±2 weeks) post-injection, and a telephone follow up 24 hours (±1 day) post-injection. <u>Treatment Sessions 2, 3, and 4</u> For each 13-week treatment session:

	• 4 weeks (±5 days) and 13 weeks (±2 weeks) after each treatment, with a telephone follow up 1 week (±1 day) and 8 weeks (±5 days) after each treatment. Note that the last visit of a prior treatment session will serve as the first day of the next treatment session.
Safety Assessments	The following safety assessments will be performed as follows: • Occurrence, seriousness, severity, and causality assessment of adverse events at each study visit or, if applicable, at discontinuation from the study; • Occurrence of adverse events of special interest (i.e., aspiration, aspiration pneumonia, choking, dysphagia) at each study visit or, if applicable, at discontinuation from the study; • Occurrence of dental-related adverse events; • Vital signs at each study visit or, if applicable, at discontinuation from the study; • Complete physical exam at Weeks 4, 13, 26, 39, and 52 (brief at other study visits) or, if applicable, at discontinuation from the study; • FVC in all ALS subjects, and in other subjects if warranted at the discretion of the Investigator, at screening, before the first injection of study drug on Day 1, and at Weeks 4, 8 (as clinically warranted), and 13. Thereafter, FVC will be checked as clinically warranted. • Clinical laboratory safety tests (fasting) at screening and Weeks 13, 26, and 52 or, if applicable, at discontinuation from the study. Laboratory testing will also be done as clinically warranted throughout the study. • Neurologic exam at screening, Day 1 (before first injection of study drug), and Weeks 13 and 52 or, if applicable, at discontinuation from the study. Additional neurologic exams will be performed as clinically warranted. • Dental exam by a licensed dentist at screening and Weeks 4, 13, 26, and 52 or, if applicable, at discontinuation from the study. Four bite-wing radiographs or panoramic imaging (if edentulous or if bite-wing x-rays are difficult due to limited teeth) will be obtained at screening and Weeks 26 and 52 or, if applicable, at discontinuation from the study. Additional dental exams will be performed as clinically warranted based on predefined safety criteria (e.g., persistent severe dry mouth). • Oral exam by the Investigator at each study visit where a dental exam is not required. • Columbia Suicide Severity Rating Scale (C-SSRS) on Day 1 (before first injection of study drug) and each subsequent study visit or, if applicable, at discontinuation from the study.
Effectiveness Assessments	The following effectiveness assessments will be performed at each study

	visit: • USFR (Assessor); • CGI-S and CGI-C (Assessor); • DFSS-I; • PGI-S and PGI-C (Subject); and • DIS (Subject). In addition, DFSS will be assessed daily via the subject's diary the first 2 weeks after each injection, then weekly for the remainder of each treatment session.

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TABLES

APPENDICES

6 ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of Daily Living
AESI	Adverse Events of Special Interest
ALS	Amyotrophic Lateral Sclerosis
BP	Blood Pressure
CAP	College of American Pathologist
CD	Cervical Dystonia
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CIB	Clinical Investigator's Brochure
CLIA	Clinical Laboratory Improvement Act of 1988
C-SSRS	Columbia Suicide Severity Rate Scale
CRA	Clinical Research Associate
CRO	Clinical Research Organization
DFSS	Drooling Frequency and Severity Score
DIS	Drooling Impact Score
eCRF(s)	Electronic Case Report Form(s)
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB(s)	Institutional Review Board(s)
LAR	Legally Authorized Representative
LD_{50}	Median Lethal Dose
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
n	Number
NG	Nasogastric
PD	Parkinson's Disease
PEG	Percutaneous Endoscopic Gastrostomy
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
RR	Respiration Rate
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
SAP	Statistical Analysis Plan
TEAE(s)	Treatment-Emergent Adverse Event(s)

Temp	Temperature
ULN	Upper Limit of Normal
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
USFR	Unstimulated Salivary Flow Rate
VAS	Visual Analog Scale
WBC	White Blood Cell
Wk	Week

7 BACKGROUND AND SIGNIFICANCE

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine the long-term safety and tolerability of MYOBLOC (administered intraglandularly as a single total dose of 3,500 Units) treatments every 13 weeks over a maximum possible duration of 1 year in adult subjects with troublesome sialorrhea.

8.2 Secondary Objective

The secondary objective of this study is:

- To assess the magnitude of therapeutic responses of MYOBLOC (administered intraglandularly as a single total dose of 3,500 Units) using effectiveness assessments performed at intervals after treatments every 13 weeks over a maximum possible duration of 1 year.

9 STUDY ENDPOINTS

9.1 Safety Endpoints

- Occurrence, seriousness, severity, and causality assessment of adverse events at each study visit;
- Occurrence of adverse events of special interest (i.e., aspiration, aspiration pneumonia, choking, dysphagia) at each study visit as assessed by the Investigator;
- Columbia Suicide Severity Scale (C-SSRS) at each study visit; and
- Occurrence of dental adverse events.

9.2 Effectiveness Endpoints

- Unstimulated salivary flow rate (USFR) (Assessor) at each study visit;
- Clinical Global Impression of Severity (CGI-S) and Change (CGI-C) (Assessor) at each study visit;
- DFSS-I (Assessor) at each study visit;
- DFSS as assessed via subject's diary at each assessment time point;
- Patient Global Impression of Severity (PGI-S) and Change (PGI-C) at each study visit; and
- Drooling Impact Score (DIS) (Subject) at each study visit.

10 STUDY DESIGN

This is a Phase 3, multicenter, open-label, outpatient study of safety/tolerability and effectiveness of repeated doses (3,500 Units) of MYOBLOC in adult subjects with troublesome sialorrhea over a maximum 1-year duration. The study population will be comprised of a mixture of patient populations including, but not limited to, subjects with PD-related sialorrhea, subjects with sialorrhea secondary to other non-PD conditions (e.g., cerebral palsy, ALS, stroke, traumatic brain injury), or sialorrhea secondary to oral cancer or medications (e.g., neuroleptics). The study is planned to be conducted at 20 or

more study sites and include approximately 120 to 200 male and female subjects (or until enough subjects have completed to meet FDA safety database requirements; see further details in Section 11.1). A diagnosis of PD fulfills the UK Parkinson's Disease Society Brain Bank diagnostic criteria, and a diagnosis of ALS fulfills the El Escorial World Federation of Neurology criteria.

The planned duration of participation for each subject is a minimum of 26 weeks and a maximum of 52 weeks, excluding the screening period, which can last up to 21 days, with study drug injected at approximately 13-week (±2 weeks) intervals for a maximum of 4 treatments over this 1-year period.

During the screening period, the following will be assessed to evaluate the subject's eligibility to participate in the study: inclusion and exclusion criteria; medical, surgical, and medication history; presence or prior history of aspiration, aspiration pneumonia, choking, and/or dysphagia; complete physical exam (including vital signs, height, and weight); neurologic exam; dental exam; clinical laboratory testing; urine pregnancy testing (females of childbearing potential only); and forced vital capacity (FVC) (if warranted, such as in ALS patients). All subjects successfully completing screening will have the following procedures/ assessments conducted at baseline (Day 1) before the first injection of MYOBLOC: brief physical exam (including vital signs); FVC (if warranted); neurologic exam; Columbia Suicide Severity Rate Scale (C-SSRS); oral exam; saliva production quantitatively determined via USFR; qualitative assessments by the Investigator including CGI-S and DFSS-I; subject assessments including PGI-S, DFSS, DIS; and urine pregnancy test (result must be negative to proceed with the injection). Those subjects who satisfy all eligibility criteria may receive a dose of MYOBLOC (3,500 Units) via injections into the submandibular and parotid glands on Day 1. Subjects will be contacted by telephone 24 hours post-injection to inquire about their health status.

Subsequent study visits will occur at Weeks 4 (±3 days), 8 (±3 days), 13 (±2 weeks), 17 (±5 days), 26 (±2 weeks), 30 (±5 days), 39 (±2 weeks), 43 (±5 days), and 52 (±2 weeks), with safety and effectiveness assessments made as detailed in the Schedule of Assessments in Table 2 in Section 14.1; telephone follow up will be done at Weeks 14 (±1 day), 21 (±5 days), 27 (±1 day), 34 (±5 days), 40 (±1 day), and 47 (±5 days)

Injections at each treatment session will be done when the subject returns to baseline status as determined by the Principal Investigator, with a minimum interval of 11 weeks from the prior injection but no later than 15 weeks from the prior injection. If after the first treatment of 3,500 Units the subject develops intolerable side effects, but still wishes to remain in the

study, the Investigator has the discretion to decrease subsequent doses, but to no less than a total dose of 2,500 Units.

11 SELECTION OF SUBJECTS

11.1 Population Base

Adult subjects with troublesome sialorrhea and a minimum USFR (as defined in Section 11.1.1) are eligible for the study. Enrollment will continue until a minimum total of 300 subjects (across this protocol and the prior MYOBLOC clinical trial in sialorrhea expected to meet FDA safety database requirements) have been treated with clinically relevant doses (≥2,500 Units) of MYOBLOC for a minimum of 6 months and 100 subjects treated with MYOBLOC at clinically relevant doses for a minimum of 1 year. Sixty of the 100 subjects must be treated with 3,500 Units for the minimum period of 6 months. It is estimated that approximately 120 to 200 subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation. The study population should be comprised of a mixture of patient populations including, but not limited to, subjects with PD-related sialorrhea, subjects with sialorrhea secondary to other non-PD conditions (e.g., cerebral palsy, ALS, stroke, traumatic brain injury), or sialorrhea secondary to oral cancer or medications (e.g., neuroleptics). Entry into the study is open to both men and women and to all racial and ethnic subgroups.

11.1.1 Inclusion Criteria

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

1. Able to read and provide written informed consent before enrollment into the study, or the subject's caregiver (Legally Authorized Representative) can provide written informed consent.
2. Male or female, 18 to 85 years of age (inclusive).
3. Seeking treatment for troublesome sialorrhea for at least 3 months that is occurring secondary to any disorder or related to any cause, including, but not limited to, PD, adult cerebral palsy, ALS, stroke, traumatic brain injury, oral cancer, and side effects of other medications. Note: A diagnosis of PD fulfills the UK Parkinson's Disease Society Brain Bank diagnostic criteria. A diagnosis of ALS fulfills the El Escorial World Federation of Neurology criteria.
4. Minimum USFR of 0.2 g/min at screening (unstimulated normal rate is 0.3 g/min) [Wang 1998].
5. Minimum Investigator's DFSS score of 4 (range 2-9, a score of 2 = "never drools") at screening.

6. Ability and availability to participate in the study for up to 1 year (ALS subjects: ability and availability to participate in the study for at least 6 months), based on overall health of the subject and disease prognosis, as applicable, in the opinion of the Investigator, and able to comply with all requirements of the protocol, including completion of study questionnaires. A caregiver may be designated to assist with assessments.

11.1.2 Exclusion Criteria

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

1. A moderate to high risk of aspiration will exclude participation in this study. Moderate to high risk of aspiration is defined by any one of the following:

   - History of aspiration pneumonia in the last 6 months before screening
   - Speech pathologist and/or formal swallowing test (e.g., with barium, endoscopy, dynamic swallowing study, imaging study, fiber-optic endoscopic swallowing evaluation or other imaging scan) that concludes that a moderate to severe risk of aspiration exists
   - Due to perceived risk of aspiration, a health care professional has recommended PEG or G-tube but subject declined
   - In the Investigator's clinical judgment, the subject is at moderate to high risk of aspiration.

   Subjects whose risk of aspiration are judged by the Investigator to be satisfactorily controlled by placement of PEG tube or G-tube for nutritional support are eligible to participate.

2. Respiratory FVC of <20% of predicted. FVC will be tested in all ALS subjects, and also in other subjects at Investigator discretion if warranted.

3. Prior botulinum toxin type A or B treatment in the salivary gland(s) identified for treatment in this study within 24 weeks before screening. Prior botulinum toxin type A or B treatment into other anatomical regions not selected for treatment in this study is not exclusionary, but must have occurred at least 12 weeks before screening.

   - In the Investigator's assessment, prior toxin exposure must have been well tolerated and without any significant long-term side effects in the case of repeated prior exposure. Subjects should be excluded if, in the Investigator's opinion, the subject failed to respond to previous treatment with botulinum toxin. Subjects should not receive nor have any plans for receiving any botulinum toxin treatment, other than the study drug (MYOBLOC), during the entire course of the study (from the point the informed consent is signed until subject's participation is complete).

4. Prior salivary gland surgery.

5. Concomitant use, or exposure within 5 half lives of screening, of aminoglycoside antibiotics, curare-like agents, or other agents that interfere with neuromuscular function.

6. Current treatment or treatment at any time during the study with Coumadin® (warfarin) or similar anti-coagulant medications. Anti-platelet medications are not specifically exclusionary.
7. Anticipated or scheduled surgery during the study period. A PEG tube/G tube may be placed for nutritional support at any time during the study and will not exclude the subject from continued study participation.
8. Major surgery (requiring general anesthesia, except PEG tube/G-tube placement) within the previous 6 months before screening. If surgery occurred more recently than 6 months before screening, Investigator must have sufficient documentation to demonstrate the subject has fully recovered and stabilized. Prior movement disorder-related surgery (e.g., pallidotomy, thalamic/subthalamic/pallidal deep brain stimulation) will not exclude the subject, provided the surgery was performed at least 6 months before screening.
9. Anticholinergic and antihistamine medication eligibility restrictions (see also Section 16.10):
    - Oral/transdermal pharmacologic treatment (specifically antihistamines and those medications with anticholinergic properties) ***for troublesome sialorrhea*** must be discontinued during the 30-day period before screening and are not allowed in the entire duration of the study, except ALS subjects as allowed herein. For ALS subjects only: such medications for the treatment of sialorrhea are allowed; however, conversion to, or continuation of, a short-acting medication (duration of action of approximately 8 hours or less) is required at a stable dose/regimen at least 2 weeks before the first injection of study drug (i.e., Day 1 of Treatment Session 1). The short-acting anti-cholinergic medication for the treatment of sialorrhea may be continued throughout screening and study participation provided that the ALS subject agrees to hold the medication for at least 8 hours before the screening, baseline, and all subsequent study visits, so that the effectiveness and safety of the study drug can be properly evaluated.
    - Antihistamines and anticholinergic medications taken ***for a non-sialorrhea condition*** should be avoided as much as possible, but are not exclusionary.
10. Evidence of any clinically significant neurologic disease (e.g., myasthenia gravis, Lambert-Eaton syndrome), cardiovascular, hematologic (including bleeding diathesis), hepatic, renal, gastrointestinal, endocrine, pulmonary, musculoskeletal, psychiatric disease or condition, or dental condition, which in the judgment of the Investigator or screening dentist would put the subject at risk while in the study, could influence the results of the study, or negatively impact the subject's ability to participate in the study
11. Pregnancy or lactation
    - As assessed by the Investigator, 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), biologically sterile, or surgically sterile (e.g., s/p hysterectomy, bilateral oophorectomy, tubal ligation).

12. History of drug or alcohol abuse currently or within the previous 6 months, as determined by the Investigator.
13. Current infection at the sialorrhea treatment injection site(s).
14. Participation in another clinical drug, device, or biological agent study within 30 days of screening or while participating in this study.
15. Any other condition or clinical finding that, in the opinion of the Investigator and/or the Sponsor, is determined to be unsuitable for enrollment into this study.

12 ENROLLMENT PROCEDURES AND SUBJECT WITHDRAWAL

12.1 Screening Failures

Screening failures are potential study subjects who provide written informed consent and HIPAA authorization, complete some screening procedures but are determined to be ineligible for treatment with study drug. A screening log for all subjects who are screened will be maintained. The screening log will uniquely identify each subject and report whether he/she passed or failed screening, and, if he/she did not pass, the reason(s) for the screening failure. Subjects who fail screening may rescreen at a later time as long as at least 30 days have passed since screen fail per Investigator discretion.

12.2 Randomization and Blinding

This is an open-label study.

12.3 Subject Withdrawal Criteria

Once a subject starts study treatment, any subject not completing the study for any reason will be considered a premature termination and the Investigator must record the reason(s) for withdrawal in the subject's source document and electronic case report form (eCRF). Any subject that discontinues prematurely, regardless of the reason, will be requested to complete all early discontinuation assessments and procedures (see Section 14.7). Once withdrawn, subjects may not re-enter the study, nor will they be replaced.

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. In such cases, the subject/caregiver will be queried as to the reason(s) for the decision to withdraw consent and the reasons(s) clearly documented in the subject's source document and eCRF to ensure the decision was not due to an adverse event (if due to an adverse event, the adverse event should be indicated as the reason for discontinuation even if the Investigator would not have considered discontinuation of treatment because of the adverse event).

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

- An intolerable adverse event or serious adverse event (SAE);
- Insufficient therapeutic response, including:
  - Lack of effectiveness – no improvement in USFR or CGI-C after the subject's initial treatment when comparing scores at Week 4 versus respective scores at baseline (Day 1);
  - Loss of effectiveness – after demonstrating some improvement in USFR and CGI-C scores post-injection on the subject's initial treatment, 1 or both of these assessments is not improved on subsequent injections at Week 4 versus the respective score at baseline (Day 1);
- Requires a medication that was prohibited (see Sections 11.1.2 and 16.10) by the protocol;
- Does not follow guidelines specified in the protocol;
- Is lost to follow up; and
- In the Investigator's opinion, does not continue to meet entry criteria.

The clinical course of each adverse event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome (see Section 16.2.7).

Subjects prematurely discontinuing due to lack of effectiveness or loss of effectiveness will be encouraged to return to the study site to complete early termination study procedures to evaluate safety and saliva production.

In cases where a subject fails to return for required visits, repeated attempts will be made to reach the subject/caregiver

If repeated attempts are unsuccessful, lost to follow up will be recorded in the subject's source document and eCRF as the reason for early termination.

13 STUDY DRUG MATERIALS AND MANAGEMENT

13.1 Study Drug

MYOBLOC® (rimabotulinumtoxinB) Injection is a clear and colorless to light-yellow sterile injection solution of a purified neurotoxin. Each single-use vial of formulated MYOBLOC (supplied by the Sponsor, Solstice Neurosciences, LLC) contains 5,000 Units of botulinum toxin type B per 1.0 mL in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at approximately pH 5.6.

13.2 Study Drug Administration and Compliance

Subjects will receive single dose injections of MYOBLOC every 13 weeks (±2 weeks) for a maximum total of 4 treatments. MYOBLOC will be injected first into the submandibular glands (right and then left) followed by the parotid glands (right and then left)

- Total dose of 3,500 Units (0.7 mL) of MYOBLOC with 1,500 Units (0.3 mL) injected into each parotid gland and 250 Units (0.05 mL) injected into each submandibular gland.

Subsequent injections at each treatment session will be done when subjects return to baseline status as determined by the Investigator, with a minimum interval of 11 weeks from the prior injection. Study drug injections should not be administered if an adverse event of dysphagia or dry mouth of moderate to severe severity persists without prior consultation with the Medical Monitor. If the adverse event has not resolved or has not improved to a mild severity by the end of the per protocol window for injections to occur (every 13 ± 2 weeks), the Medical Monitor should be contacted to discuss whether or not the subject should be dosed, discontinued, etc.

If after the first treatment of 3,500 Units the subject develops intolerable side effects, but still wishes to remain in the study, the Investigator has the discretion to decrease subsequent doses, but to no less than a total dose of 2,500 Units. If this does occur, the total dose can therefore be 2,500 Units to 3,500 Units of MYOBLOC. The Investigator must clearly indicate the adjusted dose given. MYOBLOC will be injected first into the submandibular glands (right then left) followed by the parotid glands (right then left) as follows:

- Total dose of 2,500 to 3,500 Units (0.5 mL to 0.7 mL) of MYOBLOC with 1,000 to 1,500 Units (0.2 mL to 0.3 mL) injected equally into each parotid gland and 250 Units (0.05 mL) injected into each submandibular gland.

All MYOBLOC injections will be performed by Investigators who have prior experience or have been appropriately trained with injecting botulinum toxin and such experience/training will be documented in the study records. Injections will be guided by external anatomical landmarks or by external anatomical landmarks with ultrasound-guided confirmation (Appendix A). Sites designated as “ultrasound” sites will perform all their injections with ultrasound-guidance.

13.3 Study Drug Packaging and Labeling

Study drug will be supplied in a 3.5-mL glass vial containing a volume of 1.0 mL (5,000 Units of MYOBLOC). All study drug will be labeled as investigational drug for research purposes only, in compliance with federal regulations.

13.4 Study Drug Storage

Study drug must be stored in a secure refrigerator (2°C to 8°C) with access restricted to authorized personnel only.

13.5 Study Drug Accountability

Accurate recording of all investigational agent received, dispensed, administered, and returned will be maintained by study site personnel. The investigational agent is to be used only as described by this study protocol by an appropriately licensed Investigator 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 agent 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.

14 STUDY PROCEDURES

14.1 Schedule of Assessments

A schedule of assessments is shown in Table 2. No protocol related procedures should be performed before subjects provide written informed consent and HIPAA authorization.

Table 2. Schedule of Study Assessments

Activity	Screening (Day -21 to -1)	Treatment Session 1				Treatment Session 2			
		Day 1 (a)	Wk 4 (c) (± 3 days)	Wk 8 (c) (± 3 days)	Wk 13 (d) (± 2 wks)	Wk 14 (b) (± 1 day)	Wk 17 (c) (± 5 days)	Wk 21 (b) (± 5 days)	Wk 26 (d) (± 2 wks)
Written Informed Consent and HIPAA Authorization (e)	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Medical/Surgical/Medication History (f)	X								
Complete Physical Examination	X		X		X				X
Brief Physical Examination		X		X			X		
Weight	X	X	X	X	X		X		X
Height	X								
Neurologic Examination	X	X	As needed		X		As needed		As needed
Dental Questionnaire (Subject or Caregiver)	X								
Dental Exam by Licensed Dentist (DDS, DMB)	X (g)		X	As needed	X		As needed		X (g)
Oral Examination by Investigator		X		X			X		
Clinical Laboratory Tests (hematology, full chemistry panel including glucose and alkaline phosphatase, urinalysis) (fasting)	X		As needed		X		As needed		X
Urine Pregnancy Test (h)	X	X	As needed				As needed		As needed
Vital Signs (sitting BP and pulse after 5 minutes rest, RR, Temp)	X	X	X	X	X		X		X
Forced Vital Capacity (i)	X	X	X	As needed	X		As needed		As needed
Adverse Events Assessment		X	X	X	X	X	X	X	X
C-SSRS Baseline Version		X							
C-SSRS Since Last Visit Version			X	X	X		X		X
Concomitant Medications Assessment	X		X	X	X	X	X	X	X
Subject Diary Training	X								
Subject Diary Review			X	X	X		X		X
Salivary Flow Rate Collection (USFR) (j)	X	X	X	X	X		X		X
Clinical Global Impression-Severity (CGI-S) (j) (k)		X	X	X	X		X		X
Clinical Global Impression-Change (CGI-C) (j) (k)			X	X	X		X		X
Patient Global Impression of Severity (PGI-S) (k)		X	X	X	X		X		X
Patient Global Impression of Change (PGI-C) (k)			X	X	X		X		X
Drooling Impact Score (DIS) by Subject		X	X	X	X		X		X
DFSS-I (j)	X	X	X	X	X		X		X
DFSS by Subject (DFSS-S) (l)		X	X	X	X		X		X

Table 2. Schedule of Study Assessments

Activity	Screening (Day -21 to -1)	Treatment Session 1				Treatment Session 2			
		Day 1 (a)	Wk 4 (c) (± 3 days)	Wk 8 (c) (± 3 days)	Wk 13 (d) (± 2 wks)	Wk 14 (b) (± 1 day)	Wk 17 (c) (± 5 days)	Wk 21 (b) (± 5 days)	Wk 26 (d) (± 2 wks)
Review of Common Classes of Anticholinergic & Antihistamine Medications	X								
Study Drug Injection (m)		X (1st) (n)			X (2nd)				X (3rd)
Telephone Follow-up						X (o)		X	

Abbreviations: AE = adverse event, BP = blood pressure, C-SSRS = Columbia Suicide Severity Rating Scale, DFSS = Drooling Frequency and Severity Scale, HIPAA = Health Insurance Portability and Accountability Act, RR = respiration rate, Temp = temperature, USFR = unstimulated salivary flow rate, VAS = visual analog scale, wks = weeks

(a) All screening and baseline assessments and results must be available before injection of MYOBLOC.
(b) Telephone follow-up.
(c) Office visit.
(d) Office visit. Serves as last visit of current treatment session and first visit of subsequent treatment session. Study drug injection will occur after the 13-week assessments have been completed for the prior treatment session.
(e) Must be obtained before conducting any study procedure.
(f) Includes baseline history of aspiration, aspiration pneumonia, choking, and dysphagia.
(g) Includes 4 bite-wing radiographs or panoramic imaging (if edentulous or if bite-wing x-rays are difficult due to limited teeth). If the subject has no teeth, then the dentist will determine if panoramic imaging is required at any visit after screening.
(h) Females of childbearing potential only.
(i) Forced vital capacity will be measured in all subjects with amyotrophic lateral sclerosis and in other subjects if warranted at the discretion of the Investigator.
(j) When possible, assessments should be done by the same person in a given subject to ensure consistency throughout the study.
(k) Global measure of effectiveness must be completed before USFR.
(l) Subject-rated via entry in diary (not during study visit), daily for first 2 weeks after study drug injection and then weekly for remainder of treatment session.
(m) Subjects will receive injections guided by external anatomical landmarks or by external anatomical landmarks with ultrasound-guided confirmation. Sites designated as "ultrasound" sites will perform all their injections with ultrasound-guidance.
(n) Subjects will be injected after completion of all assessments and then will be contacted by telephone 24 hours (±1 day) post-injection to inquire about their health status and remind the subject to complete their diary.
(o) Telephone follow-up by the study staff will be conducted 1 week (±1 day) after study drug injection to assess how the subject feels, document adverse events as appropriate, document any new medications the subject may be taking, and remind the subject to complete their diary.

Table 2. Schedule of Study Assessments

Activity	Treatment Session 3 (Optional)*				Treatment Session 4 (Optional)*				Early Discontinuation
	Wk 27 (± 1 day)	Wk 30 (a) (± 5 days)	Wk 34 (b) (± 5 days)	Wk 39 (c) (± 2 wks)	Wk 40 (± 1 day)	Wk 43 (a) (± 5 days)	Wk 47 (b) (± 5 days)	Wk 52 (a) (± 2 wks)	
Complete Physical Examination				X				X	X
Brief Physical Examination		X				X			
Weight		X		X		X		X	X
Neurologic Examination		As needed		As needed		As needed		X	X
Dental Exam by Licensed Dentist (DDS, DMB)		As needed		As needed		As needed		X (d)	X (d)
Oral Examination by Investigator		X		X		X			
Clinical Laboratory Tests (hematology, full chemistry panel including glucose and alkaline phosphatase, urinalysis) (fasting)		As needed		As needed		As needed		X	X
Urine Pregnancy Test (e)		As needed		As needed		As needed		X	X
Vital Signs (sitting BP and pulse after 5 minutes rest, RR, Temp)		X		X		X		X	X
Forced Vital Capacity		As needed		As needed		As needed		As needed	As needed
Adverse Events Assessment	X	X	X	X	X	X	X	X	X (f)
C-SSRS Since Last Visit Version		X		X		X		X	X
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X
Subject Diary Review		X		X		X		X	X
Salivary Flow Rate Collection (USFR) (g)		X		X		X		X	X
Clinical Global Impression-Severity (CGI-S) (g) (h)		X		X		X		X	X
Clinical Global Impression-Change (CGI-C) (g) (h)		X		X		X		X	X
Patient Global Impression of Severity (PGI-S) (h)		X		X		X		X	X
Patient Global Impression of Change (PGI-C) (h)		X		X		X		X	X
Drooling Impact Score by (DIS) Subject		X		X		X		X	X
DFSS-I (g)		X		X		X		X	X
DFSS by Subject (DFSS-S) (i)		X		X		X		X	X
Study Drug Injection (j)				X (4^{th})					
Telephone Follow-up	X (k)		X		X (k)		X		

Abbreviations: AE = adverse event, BP = blood pressure, C-SSRS = Columbia Suicide Severity Rating Scale, DFSS = Drooling Frequency and Severity Scale, RR = respiration rate, Temp = temperature, USFR = unstimulated salivary flow rate, wks = weeks

* Treatment Sessions 3 and 4 are designated as likely, but may not be necessary as the study progresses because the study may be stopped early once enough subjects have completed the study to meet FDA safety database requirements. Any subject that enters the study, however, is required to participate through at least 6 months (i.e., complete Treatment Sessions 1 and 2).

(a) Office visit.
(b) Telephone follow-up.

Table 2. Schedule of Study Assessments

Activity	Treatment Session 3 (Optional)*				Treatment Session 4 (Optional)*				Early Discontinuation
	Wk 27 (± 1 day)	Wk 30 (a) (± 5 days)	Wk 34 (b) (± 5 days)	Wk 39 (c) (± 2 wks)	Wk 40 (± 1 day)	Wk 43 (a) (± 5 days)	Wk 47 (b) (± 5 days)	Wk 52 (a) (± 2 wks)	

(c) Office visit. Serves as last visit of current treatment session and first visit of subsequent treatment session. Study drug injection will occur after the 13-week assessments have been completed for the prior treatment session.
(d) Includes 4 bite-wing radiographs or panoramic imaging (if edentulous or if bite-wing x-rays are difficult due to limited teeth). If the subject has no teeth, then the dentist will determine if panoramic imaging is required at any visit after screening.
(e) Females of childbearing potential only.
(f) Subjects who discontinue because of an AE before completion of the study will be called 13 weeks ± 3 days after his/her last injection to determine if the AE has resolved.

(g) When possible, assessments should be done by the same person in a given subject to ensure consistency throughout the study.
(h) Global measure of effectiveness must be completed before USFR.
(i) Subject-rated via entry in diary (not during study visit), daily for first 2 weeks after study drug injection and then weekly for remainder of treatment session.
(j) Subjects will receive injections guided by external anatomical landmarks or by external anatomical landmarks with ultrasound-guided confirmation. Sites designated as “ultrasound” sites will perform all their injections with ultrasound-guidance.
(k) Telephone follow-up by the study staff will be conducted 1 week (±1 day) after study drug injection to assess how the subject feels, document adverse events as appropriate, document any new medications the subject may be taking, and remind the subject to complete their diary.

14.2 Screening

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/surgical history, screening laboratory tests, and other eligibility criteria.

The following activities will be completed:

- Review of inclusion and exclusion criteria;
- Demographics; medical/surgical/medication history; and baseline history of aspiration, aspiration pneumonia, choking, and dysphagia;
- Salivary flow rate collection (USFR);
- DFSS-I;
- Complete physical examination (including vital signs, height, and weight);
- Neurologic exam;
- Dental exam by a licensed dentist (DDS or DMD), including 4 bite-wing radiographs or panoramic imaging (if edentulous or if bite-wing x-rays are difficult due to limited teeth);
- Dental questionnaire by subject or caregiver;
- Screening laboratory tests (full chemistry panel including glucose and alkaline phosphatase; hematology; urinalysis) in fasting state;
- Urine pregnancy test (females of childbearing potential only); and
- Respiratory function including FVC in all subjects with ALS, and in other subjects if warranted at the discretion of the Investigator.

Subjects will be advised to contact study staff if they require ANY new medication so the Investigator can be consulted on the potential impact to the subject's eligibility in the study (see Section 16.10).

14.3 Treatment Session 1

14.3.1 Day 1

Subjects who are deemed eligible for treatment based on screening assessments/procedures will have the assessments listed below completed on Day 1 (baseline) before injection of MYOBLOC.

- Evaluation of adverse events;
- Brief physical exam (including vital signs and weight);

- FVC in all subjects with ALS, and other subjects if done at screening;
- Neurologic exam;
- Oral exam by the Investigator;
- Columbia Suicide Severity Rating Scale (C-SSRS) Baseline version;
- Urine pregnancy test (females of childbearing potential only, performed just before injection of study drug). Result must be negative to proceed with the injection;
- CGI-S (Assessor) before USFR;
- Saliva production quantitatively determined via USFR collection;
- DFSS-I;
- PGI-S (Subject);
- DIS (Subject); and
- DFSS-S – site personnel will teach the subject how to use the subject diary to complete the DFSS and the subject will perform a practice entry at this visit, with the first real entry to occur that evening.

Once all assessments have been completed, evaluated, and eligibility confirmed, the subject will receive a dose of MYOBLOC via injections into the submandibular and parotid glands as detailed in Section 13.2. Subjects will be contacted by telephone 24 hours (±1 day) post-injection to inquire about their health status and to remind the subject to complete their diary.

14.3.2 Weeks 4, 8, and 13

Subjects will return to the clinic for follow-up assessments/procedures at Weeks 4, 8, and 13. Visit windows are provided to allow flexibility in scheduling subjects for appointments: Weeks 4 and 8 have a ±3 day window and Week 13 has a ±2 week window. The following assessments will be completed at each study visit unless otherwise specified:

- Complete (Weeks 4 and 13) and brief (Week 8) physical exam (including vital signs and weight);
- FVC in all subjects with ALS, and other subjects if done at screening, at Weeks 4 and 13 and as needed, per Investigator discretion, at Week 8;
- Clinical laboratory tests (fasting), including full chemistry panel (including glucose and alkaline phosphatase), hematology, and urinalysis at Week 13 and as needed, per Investigator discretion, at Weeks 4 and 8;
- Urine pregnancy test (as clinically warranted);
- Neurologic exam at Week 13 and as clinically warranted at Weeks 4 and 8;

- Dental exam by a licensed dentist at Weeks 4 and 13, and as clinically warranted based on predefined safety criteria;
- Oral exam by Investigator (Week 8);
- Evaluation of adverse events;
- C-SSRS Since Last Visit version;
- Review of concomitant medications;
- Review of subject diary;
- CGI-S and CGI-C (Assessor) before USFR;
- USFR collection;
- DFSS-I;
- PGI-S and PGI-C (Subject);
- DIS (Subject); and
- DFSS-S via entry in the subject's diary, not during study visit, daily for first 2 weeks after injection of MYOBLOC and then weekly for remainder of treatment session.

14.4 Treatment Session 2

14.4.1 Day 1

On Day 1 of treatment session 2 (same day as Week 13 visit), subjects may receive MYOBLOC (as detailed in Section 13.2) after all 13-week assessments have been completed for the prior treatment session.

14.4.2 Weeks 14, 17, 21, and 26

A telephone follow up will be made 1 week (±1 day) after injection of MYOBLOC (Week 14) and at Week 21 (±5 days) to inquire about subjects' health status and to assess adverse events and review concomitant medications (see Section 16.10). Subjects will return to the clinic at Week 17 (±5 days) and Week 26 (±2 weeks) and the assessments listed below will be completed at each visit, unless otherwise specified. Note that the Week 26 visit will serve as the Day 1 visit for the subsequent injection of MYOBLOC (see Section 14.5.1).

- Evaluation of adverse events;
- Brief (Week 17) and complete (Week 26) physical exam (including vital signs and weight);
- FVC (as clinically warranted);
- Clinical laboratory tests (fasting), including full chemistry panel (including glucose and alkaline phosphatase), hematology, and urinalysis at Week 26 and as needed, per Investigator discretion, at Week 17;
- Urine pregnancy test (as clinically warranted);
- Neurologic exam (as clinically warranted);

- Dental exam by a licensed dentist at Week 26 (including 4 bite-wing radiographs or panoramic imaging [if edentulous or if bite-wing x-rays are difficult due to limited teeth]), and as clinically warranted based on predefined safety criteria;
- Oral exam by Investigator (Week 17);
- C-SSRS Since Last Visit version;
- Review of concomitant medications;
- Review of subject diary;
- CGI-S and CGI-C (Assessor) before USFR;
- USFR collection;
- DFSS-I;
- PGI-S and PGI-C (Subject);
- DIS (Subject); and
- DFSS-S via entry in the subject's diary, not during study visit, daily for first 2 weeks after injection of MYOBLOC and then weekly for remainder of treatment session.

14.5 Treatment Session 3

14.5.1 Day 1

On Day 1 of treatment session 3 (same day as Week 26 visit), subjects may receive MYOBLOC (as detailed in Section 13.2) after all 13-week assessments have been completed for the prior treatment session.

14.5.2 Weeks 27, 30, 34, and 39

A telephone follow up will be made 1 week (±1 day) after injection of MYOBLOC (Week 27) and at Week 34 (±5 days) to inquire about subjects' health status and to assess adverse events and review concomitant medications (see Section 16.10). Subjects will return to the clinic at Week 30 (±5 days) and Week 39 (±2 weeks) and the assessments listed below will be completed at each visit, unless otherwise specified. Note that the Week 39 visit will serve as the Day 1 visit for the subsequent injection of MYOBLOC (see Section 14.6.1).

- Evaluation of adverse events;
- Brief (Week 30) and complete (Week 39) physical exam (including vital signs and weight);
- FVC (as clinically warranted);
- Clinical laboratory tests (as clinically warranted);
- Urine pregnancy test (as clinically warranted);
- Neurologic exam (as clinically warranted);
- Dental exam by a licensed dentist (as clinically warranted based on predefined safety criteria);

- Oral exam by Investigator;
- C-SSRS Since Last Visit version;
- Review of concomitant medications;
- Review of subject diary;
- CGI-S and CGI-C (Assessor) before USFR;
- USFR collection;
- DFSS-I;
- PGI-S and PGI-C (Subject);
- DIS (Subject); and
- DFSS-S via entry in the subject's diary, not during study visit, daily for first 2 weeks after injection of MYOBLOC and then weekly for remainder of treatment session.

14.6 Treatment Session 4

14.6.1 Day 1

On Day 1 of treatment session 4 (same day as Week 39 visit), subjects may receive MYOBLOC (as detailed in Section 13.2) after all 13-week assessments have been completed for the prior treatment session.

14.6.2 Weeks 40, 43, 47, and 52

A telephone follow up will be made 1 week (±1 day) after injection of MYOBLOC (Week 40) and at Week 47 (±5 days) to inquire about subjects' health status and to assess adverse events and review concomitant medications (see Section 16.10). Subjects will return to the clinic at Week 43 (±5 days) and Week 52 (±2 weeks) and the assessments listed below will be completed at each visit, unless otherwise specified.

- Evaluation of adverse events;
- Brief (Week 43) and complete (Week 52) physical exam (including vital signs and weight);
- FVC (as clinically warranted);
- Clinical laboratory tests (fasting), including full chemistry panel (including glucose and alkaline phosphatase), hematology, and urinalysis at Week 52 and as clinically warranted at Week 43;
- Urine pregnancy test at Week 52 and as clinically warranted at Week 43;
- Neurologic exam at Week 52 and as clinically warranted at Week 43;
- Dental exam by a licensed dentist at Week 52 (including 4 bite-wing radiographs or panoramic imaging [if edentulous or if bite-wing x-rays are difficult due to limited teeth]) and as clinically warranted based on predefined safety criteria at Week 43;
- Oral exam by Investigator at Week 43;

- C-SSRS Since Last Visit version;
- Review of concomitant medications;
- Review of subject diary;
- CGI-S and CGI-C (Assessor) before USFR;
- USFR collection;
- DFSS-I;
- PGI-S and PGI-C (Subject);
- DIS (Subject); and
- DFSS-S via entry in the subject's diary, not during study visit, daily for first 2 weeks after injection of MYOBLOC and then weekly for remainder of treatment session.

14.7 Early Discontinuation

If the subject is withdrawn from the study before completion of the study, the reason for withdrawal from the study must be documented in the subject's source document and eCRF. Whenever a subject withdraws, the procedures/assessments listed below should be conducted.

- Evaluation of adverse events;
- Complete physical exam (including vital signs and weight);
- FVC (as clinically warranted);
- Clinical laboratory tests (fasting), including full chemistry panel (including glucose and alkaline phosphatase), hematology, and urinalysis;
- Urine pregnancy test;
- Neurologic exam;
- Dental exam by a licensed dentist (including 4 bite-wing radiographs or panoramic imaging [if edentulous or if bite-wing x-rays are difficult due to limited teeth]);
- C-SSRS Since Last Visit version;
- Review of concomitant medications;
- Review of subject diary;
- CGI-S and CGI-C (Assessor) before USFR;
- USFR collection;
- DFSS-I;
- PGI-S and PGI-C (Subject);
- DIS (Subject); and
- DFSS-S via entry in subject's diary, not during study visit.

14.8 Interim Telephone Follow-ups

Study staff will perform an Interim Telephone Follow-Up 24 hours (±1 day) after the first injection of MYOBLOC, 1 week (±1 day) after each subsequent injection of MYOBLOC, and at Weeks 21, 34, and 47 (±5 days) to assess how the subject feels, document adverse events as appropriate, review concomitant medications, and to remind the subject to complete their diary.

14.9 Post-Study Telephone Contact

If a subject discontinues study participation because of an adverse event, the subject will be evaluated in the office as soon as possible, and also contacted 13 weeks (±3 days) after the last injection of study drug to determine if the adverse event has resolved, continues unabated, or has reached a new baseline.

15 EFFECTIVENESS ASSESSMENTS

Global Measures of Effectiveness

The global measures of effectiveness by the clinician (CGI-S and CGI-C) should be completed before the quantitative measure of saliva.

Assessors

In order to maintain consistency of rating assessments, an assessor will be trained (i.e., Investigator or other clinician named on Form FDA 1572) and this same assessor should perform a given assessment for a subject throughout the study. Another assessor (clinician named on Form FDA 1572) will also undergo training to ensure consistency in scale ratings should a back-up assessor be necessary to perform assessment(s).

Caregiver Assistance

If a subject elects to have a caregiver assist with completing rating scale activities, that same caregiver should then consistently assist with the ratings throughout the study. Note that the caregiver may assist in the physical completion of scales, but all responses recorded on the scales must be provided from the subject either verbally or by gesture.

Study Participants with Parkinson's Disease

Therefore, PD subjects should complete the rating scales at least 1 hour after their first dose of PD medication and at least 1 hour postprandial.

Study Participants with ALS

For ALS subjects on short-acting anticholinergics or antihistamines (duration of action of 8 hours or less), for the treatment of troublesome sialorrhea, these medications must be held at least 8 hours before the screening, baseline, and all subsequent study visits, so that the effectiveness of the study drug can be properly evaluated. All subjects must be converted to a short-acting medication (duration of action of approximately 8 hours or less) at least 2 weeks before the first injection of study drug (i.e., Day 1 of Treatment Session 1).

15.1 Unstimulated Salivary Flow Rate (USFR)

Salivary flow rate, as described by Proulx and colleagues [2005] and Vivino and colleagues [1999] will be determined in an unstimulated state (i.e., at least 1 hour postprandial) at screening, just before the first injection of study drug (Day 1) to establish a baseline salivary flow rate, and at each subsequent study visit according to instructions detailed in Appendix B. Briefly, saliva will be collected over a 5-minute collection period using weighing cups

They will be asked to expectorate, as needed, any saliva that accumulates in their mouth into the pre-weighed cup during the 5-minute collection period.

Although not a rating scale, the same person should conduct this assessment throughout the study to minimize collection technique bias.

15.2 Clinical Global Impression of Severity (CGI-S) and Change (CGI-C)

The CGI-S scale will be used to record the severity of illness (sialorrhea) on Day 1 (i.e., study baseline) before the first injection of study drug, at each subsequent study visit or, if applicable, at discontinuation from the study. CGI-S will be assessed by a trained assessor on a 7-point scale ranging from "normal" to "among the most extremely ill patients" (Appendix C). The CGI-C, used to record change or improvement in illness from baseline (i.e., pre-injection) of each treatment session, will be assessed at each study visit after Day 1 by the assessor on a 7-point scale ranging from "very much improved" to "very much worse" (Appendix C). Both CGI scales will be completed independent of the subject's self-assessment (PGI-S and PGI-C) so neither party knows how the other has rated the scales.

15.3 Patient Global Impression of Severity (PGI-S) and Change (PGI-C)

The PGI-S scale will be used by the subject to rate the severity of his/her illness (sialorrhea) on Day 1 (i.e., study baseline) before the first injection of study drug, at each subsequent study visit, or, if applicable, at discontinuation from the study. PGI-S will be assessed on a 8-point scale ranging from "normal" to "among the most extremely ill" (Appendix D). The PGI-C will be used by the subject to rate his/her impression of change in symptoms (drooling or sialorrhea) from Day 1 (i.e., study baseline) or just before subject's most recent injection of study drug to the time of assessment at each study visit. The PGI-C is assessed on a

7-point scale ranging from "very much improved" to "very much worse" (Appendix D). Both PGI scales need to be completed independent of the assessor who completes the CGI scales so neither party knows how the other has rated the scales.

15.4 Drooling Frequency and Severity Scale (DFSS)

The DFSS will be used to assess the frequency and severity of drooling. The DFSS-I will be performed by a trained assessor independent of the DFSS performed by the subject (DFSS-S) (Appendix E). The DFSS-I will be completed at screening, on Day 1 (i.e., study baseline) before the first injection of study drug, at each subsequent study visit, or, if applicable, at discontinuation from the study. Severity is assessed on a 5-point scale ranging from 1 (dry, never drools) to 5 (profuse, clothing, hands, tray, objects become wet). Frequency is assessed on a 4-point scale ranging from 1 (never drools) to 4 (constantly drools). The DFSS total score ranges from 2 to 9. The assessor's initial assessment at screening should be based on the prior 4 weeks, with subsequent assessments based on the timeframe since the prior study visit. The assessor should not review the subject-rated scales before performing his/her own assessment. The subject will complete this assessment in the diary on a daily basis for the first 2 weeks of each treatment session and then weekly for the remainder of the treatment session.

15.5 Drooling Impact Score (DIS)

The DIS is a 10-item questionnaire with each item rated by the subject to evaluate the impact of sialorrhea on daily activities (e.g., speech, social activities) (Appendix F). The DIS will be completed on Day 1 (i.e., study baseline) before the first injection of study drug, at each subsequent study visit, or, if applicable, at discontinuation from the study. For each question the subject is requested to compare their current status to their last study visit using a 4-point scale ranging from 1 (not at all) to 4 (very much). The DIS total score ranges from 10 to 40. On Day 1 before the first injection of study drug, the subject will be asked to reference the prior 4 weeks, with subsequent assessments based on the timeframe since the prior study visit.

16 SAFETY ASSESSMENTS

16.1 Medical/Surgical/Medication History

The medical history (with demographic information, sialorrhea history with date of onset), should also include current co-morbidities, relevant past illnesses, all current medications (including those taken within 30 days before screening), surgical procedures performed within the prior 6 months, and past treatment(s) for sialorrhea.

As part of the screening medical history assessment and exclusion criteria review, subjects will be evaluated for presence or prior history of aspiration, aspiration pneumonia, choking, and/or dysphagia.

To ensure that these events are consistently rated across investigator sites, the definitions for the diagnosis and intensity provided in Section 16.2.4 should be used for

baseline evaluation and all subsequent assessments. The Investigator must determine, based on clinical evaluation, whether subsequent occurrences of aspiration, aspiration pneumonia, choking, and/or dysphagia during the study qualify as adverse events, as defined in Section 16.2.1.

16.2 Adverse Events

All adverse events and details for the events will be recorded on the subject's source document and on the Adverse Event eCRF. An adverse event should be documented in terms of a medical diagnosis. When this is not possible, the adverse event should be documented in terms of signs and/or symptoms observed or reported.

Adverse events can be collected by either the Investigator or the Study Coordinator; however, the Investigator must determine the intensity of the adverse event (Section 16.2.2.1), assess whether or not the study drug caused the adverse event (Section 16.2.2.2), record whether the adverse event led to discontinuation of the subject from the study (Section 16.2.2.3), record the outcome of the adverse event (Section 16.2.2.4), and determine if the adverse event is serious (Sections 16.2.2.5 and 16.2.6).

For this study, adverse events will be collected beginning with the start of dosing on Day 1 and will end at study completion (52 weeks ±1 week). Subjects who discontinue because of an adverse event before study completion will be contacted 13 weeks (±3 days) after their last injection of study drug (see Section 16.2.7). Serious adverse events will be collected after signing informed consent until 30 days after study completion if the study site becomes aware of the event.

16.2.1 Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient administered a medicinal product. An adverse event includes any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with study drug, active comparator, or placebo, and whether or not considered to be drug related.

Examples include an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the disease under investigation that is not recorded elsewhere in the eCRF under specific effectiveness assessments. Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered adverse events.

In clinical studies, an adverse event 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.

Intercurrent illness and/or sequelae from intercurrent illness occurring between study screening/enrollment and dosing with study drug will be captured on the Adverse Event eCRF.

16.2.2 Investigator Assessment of Adverse Events

16.2.2.1 Intensity of Adverse Event

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

- Mild: an awareness of symptoms but easily tolerated
- Moderate: symptoms interfering with daily activities
- Severe: incapacitating, with inability to perform normal daily activities

16.2.2.2 Relationship of Adverse Events to Study Drug

For each adverse event, the Investigator must assess the attribution of the study drug to the adverse event and determine whether the adverse event is or is not related to the study or test drug as defined below. The Investigator must also assess if the adverse event is related to the primary underlying condition/disease (e.g., PD, ALS). When in doubt, the adverse event should be considered at least "possibly related" to the study drug until further evidence becomes available to refute this assessment. Generally, an adverse event would not be considered related to both study drug and the underlying condition/disease.

Definitely Not Related

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

Possibly Related

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

16.2.2.3 Action Taken with Regard to Study Continuation/Discontinuation

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

16.2.2.4 Outcome of Adverse Event

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

16.2.2.5 Indication of Seriousness of Adverse Event

For each adverse event, the Investigator must determine if the adverse event meets the criteria for a Serious Adverse Event (SAE) as defined in Section 16.2.6.

16.2.3 Dental Adverse Events

Dental and oral health will be followed closely throughout the course of the study, with exams performed by either a licensed dentist (DDS or DMD) at each site, or oral examination by the Investigator. Dental adverse events (i.e., anything related to oral and dental health) will be reported as such if:

- Any finding from the dental or oral exam is determined to be clinically significant or require treatment/follow-up with a dentist, in the opinion of the Investigator or study dentist.

- An issue related to tooth or mouth discomfort is mentioned by the subject in response to a traditional non-leading question (e.g., "how have you been feeling since the last time I saw you?").

All adverse events meeting the classification of "dental adverse events" will be included in the all adverse events analysis, as well as designated as a dental adverse event in the adverse event eCRF to enable appropriate safety sub-analyses.

16.2.4 Adverse Events of Special Interest

Adverse events indicative of compromised airway protection as manifested by aspiration, aspiration pneumonia, choking, and dysphagia will be closely evaluated as adverse events of special interest (AESI). In order to properly evaluate the events pre-identified for compromised airway protection, a detailed baseline evaluation of the subject's presence or

prior history of aspiration, aspiration pneumonia, choking, and dysphagia must be taken at screening and captured in the subject's source documents and eCRF.

To ensure that these events are consistently rated on the same criterion throughout the study, the definitions for diagnosis and intensity identified below should be used for baseline evaluations. This thorough baseline evaluation will assist the Investigator in determining, based on a clinical evaluation, whether or not occurrences of aspiration, aspiration pneumonia, choking, and dysphagia during the study qualify as adverse events, as defined in Section 16.2.1.

16.2.4.1 Aspiration and Aspiration Pneumonia

Definition

The presence of oral secretions, food substances, fluids, and/or gastric contents in the airways and/or the lungs may be the result of choking and/or dysphagia. Aspiration of small fragments of material can produce airway obstruction as well as lung abscesses. Aspiration of gastric contents with a low pH due to the presence of hydrochloric acid may injure the alveolar epithelium producing diffuse interstitial and alveolar edema. Anaerobic organisms may also be present in the lung and peripheral blood cultures.

ASPIRATION

Diagnosis

The diagnosis of aspiration should include:

- New onset of respiratory symptoms and one of the following without an alternative medical cause:
  - Abnormal chest examination (rales, wheezing)
  - Abnormal gas exchange
  - Abnormal chest x-ray

Supportive information –

- Recent diagnosis of aspiration pneumonia
- Recent diagnosis of dysphagia

Intensity

- Mild
  - Asymptomatic or associated with a cough
- Moderate (any one of the following)
  - Abnormal chest x-ray
  - Productive cough

- Abnormal lung examination (wheezing, rales)
- Hypoxia

- Severe (any one of the following)
  - Respiration compromise
  - Pneumonia
  - Pneumonitis

ASPIRATION PNEUMONIA

Diagnosis

One or more serial chest x-rays with one of the following:

- New or progressive and persistent infiltrate
- Consolidation
- Cavitation

And at least one of the following

- Fever (>38°C) with no other cause
- Leukopenia (<4,000 white blood cells (WBC)/mm^3) or leukocytosis (>12,000 WBC/mm^3)

And at least one of the following

- New onset purulent* sputum or change in character of sputum
- New onset or worsening cough, or dyspnea, or tachypnea
- Rales or bronchial breath sounds
- Worsening gas exchange
- Cultures positive for anaerobes or mixed oral flora

* Purulent sputum includes secretions from the lungs, bronchi, or trachea that contain >25 neutrophils and <10 squamous epithelial cells per low power field (10X).

Supportive Information –

- Documentation of a temporal relationship between the onset of symptoms and the aspiration of fluids (e.g., gastric contents, inert liquids) or particulate matter (e.g., food)
- Positive peripheral blood and/or sputum culture

Intensity

- Mild (all of the following)

- Defervescence on oral antibiotics
- Satisfactory response to outpatient treatment
- No need for supplemental oxygen

- Moderate (any one of the following)
  - Hospitalized
  - Treated with intravenous antibiotics
- Severe (any one of the following)
  - Supplemental oxygen needed
  - Positive blood culture(s)
  - Invasive procedure required (intubation, lung biopsy, chest tube, surgery)
  - Presence of empyema, cavitation

16.2.4.2 Choking

Definition

Obstruction of the larynx, trachea, or esophagus by a partially swallowed foreign body, food, or liquid or laryngospasm may be described as choking.

Diagnosis

The diagnosis of choking should include:

- An observed episode with description of the circumstances and any inciting factor(s)
- Coughing with self clearance of obstruction or penetration of airway

Supportive Information –

- Recent diagnosis of aspiration pneumonia
- Recent diagnosis of dysphagia
- Imaging study such as a barium swallow

Intensity

- Mild
  - Occasional episode while eating or drinking (<once/day)
- Moderate
  - Frequent episodes while eating or drinking (≥once/day)
- Severe
  - Episode that requires intervention with or without loss of consciousness, may be associated with hypoxia

16.2.4.3 Dysphagia

Definition

Dysphagia is defined as difficulty swallowing (dys meaning difficulty/disordered and phagia meaning to eat). Depending on the severity and the neuromuscular component compromised, dysphagia can impair the subject's ability to swallow liquids (including saliva), solids or both. The normal swallow occurs in 3 phases: oral, pharyngeal, and esophageal with each phase lasting approximately one second. The oral phase is under voluntary neuromuscular control, whereas the pharyngeal and esophageal phases are involuntary requiring an intact swallowing reflex. Damage, compression, paralysis, and/or fatigue of the neuromuscular components may lead to dysphagia.

Diagnosis

The diagnosis of dysphagia should include:

- New onset of difficulty swallowing for solids, liquids or both
- Assessment of symptoms to identify other causes, such as dry mouth
- Clinical or radiographic observation and/or documentation of the subject's ability to swallow solids and liquids

Supportive Information –

- Recent episode of choking requiring intervention and/or treatment
- Repeated episodes of coughing while eating or drinking
- Recent diagnosis of aspiration pneumonia
- Imaging study such as a barium swallow

Intensity

- Mild
  - Occasional difficulty swallowing but no choking
- Moderate
  - Frequent difficulty swallowing with choking but able to eat and drink without assistance
- Severe
  - Inability to swallow liquids, solids or both without choking or medical intervention

16.2.5 Pregnancy

Although pregnancy is not considered an adverse event, 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. All subjects who become pregnant must be withdrawn from the study and must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) and status of mother and child must also be reported to the Sponsor.

16.2.6 Serious Adverse Events

An SAE or serious adverse drug experience is any untoward medical occurrence at any dose that:

- 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 persistent or significant disability or incapacity; and
- 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 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; and
- Development of drug dependency or drug abuse.

All SAEs will be assessed by the Investigator as detailed in Section 16.2.2.

16.2.7 Follow-up of All Adverse Events/Serious Adverse Events

The clinical course of each adverse event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. 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 adverse event before completing the study (Week 52) will be evaluated immediately and contacted 13 weeks (±3 days) after their last injection of study drug to determine if the adverse event has resolved, continues unabated, or has reached a new baseline.

16.2.8 Adverse Event Reporting

16.2.8.1 Adverse Events Requiring Expedited Reporting

The following events should be forwarded to the Sponsor within 24 hours of becoming aware of the event:

- All SAEs, regardless of causality;
- Overdose (with or without an adverse event);
- Inadvertent or accidental exposure;
- All adverse events of special interest (see Section 16.2.4);
- Pregnancy (see Section 16.2.5); and
- Unexpected therapeutic benefit.

16.2.8.2 Timeframe for Collecting and Reporting Serious Adverse Events, Adverse Events of Special Interest, and Other Immediately Reportable Adverse Events

Serious adverse events, adverse events of special interest, and other immediately reportable adverse events occurring during the study period (or within 13 weeks ±3 days of last study drug injection for subjects discontinuing participation prematurely) must be reported via telephone to the Medical Monitor or designee and then followed up using the appropriate Adverse Event Form, ***within 24 hours*** of the time any study staff member is made aware of the event. Additional eCRF and/or paper documentation may need to be supplied to the Sponsor (or designee).

You must also report any SAE of which you become aware that occurred within 13 weeks after the last dose of study drug (regardless of relationship to study drug). Any SAEs (at least possibly related to study drug) that you become aware of after 13 weeks after the last dose of study drug should also be reported to the Sponsor (or designee) These post-study events should be reported to the Sponsor using MedWatch Forms

When reporting adverse events of special interest, study staff should provide copies of supporting documentation described in Section 16.2.4. Please note that the supporting documentation provided must be redacted to remove any subject identifiers other than the study subject identification number and subject's initials.

16.3 Vital Signs

Resting vital signs (blood pressure, pulse, respiratory 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.

16.4 Clinical Laboratory Evaluations

16.4.1 Standard Laboratory Tests

Safety blood and urine specimens (fasting) (see Table 3) will be will be collected from all subjects at screening and Weeks 13, 26, and 52 or, if applicable, at discontinuation from the study. Clinical laboratory testing will also be performed as needed at the Investigator's discretion throughout the study. For this multicenter study, a central laboratory (TBD) 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 provide the Laboratory Normals for their laboratory values to determine the upper limit of normal (ULN).

Table 3. 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
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	

Abbreviations: MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, WBC = white blood cell

16.4.2 Pregnancy Test

A "dip-stick" urine pregnancy test will be performed for all female subjects of childbearing potential at screening, on Day 1 (before the first injection of study drug), as needed at the Investigator's discretion throughout the study, and at Week 52 or, if applicable, at discontinuation from the study. Sites are encouraged to use any FDA-approved urine pregnancy test.

16.5 Neurologic Exam

A neurologic exam will be performed at screening, on Day 1 (before the first injection of study drug), and at Weeks 13 and 52. A neurologic exam will also be performed as needed at the Investigator's discretion throughout the study and, if applicable, at discontinuation from the study. The neurologic exam 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 H).

16.6 Dental Exam

An oral dental exam (Appendix I) will be performed by a licensed dentist (DDS or DMD) at screening and Weeks 4, 13, 26, and 52 or, if applicable, at discontinuation from the study. Four bite-wing radiographs or panoramic imaging will be obtained at screening and Weeks 26 and 52 or at discontinuation from the study. A dental exam will also be performed as clinically warranted based on predefined safety criteria (e.g., persistent dry mouth). See Section 16.2.3 for findings to be reported as dental adverse events. Subjects will be advised to continue their dental care visits with their regular dentist throughout the course of the study.

Subjects or their caregiver will also complete a dental questionnaire at screening (Appendix I).

16.7 Oral Exam

An oral exam (Appendix I) will be performed by the Investigator at each study visit where a dental exam is <u>not</u> required. This will include a visual inspection for detection of any major dental issues and, if clinically warranted, the subject will undergo a dental exam (see Section 16.6). See Section 16.2.3 for findings to be reported as dental adverse events.

16.8 Physical Exam

A complete physical exam will be performed at screening and Weeks 4, 13, 26, 39, and 52, or, if applicable, at discontinuation from the study. The complete exam will involve gross examination of general appearance; head, ears, eyes, nose and throat; skin; extremities; chest; abdomen; and lymph nodes. Cardiac and pulmonary auscultation and measurement of vital signs (see Section 16.3) and weight will also be conducted as part of the complete physical exam.

A brief physical exam, consisting of cardiac and pulmonary auscultation and measurement of vital signs (see Section 16.3) will be performed on Day 1 (before the first injection of study drug) and at Weeks 8, 17, 30, and 43. Height will be recorded at screening only.

FVC will be measured in all subjects with ALS, and in other subjects if warranted, at the discretion of the Investigator at screening, before the first injection of study drug on Day 1, at Weeks 4, 8 (as clinically warranted), and 13. Thereafter, FVC will be checked if warranted at Investigators' discretion (such as if the subject has ALS).

16.9 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS measures both suicidal ideation and suicidal behavior and will be completed on Day 1 (before the first injection of study drug), at each subsequent study visit, or, if applicable, at discontinuation from the study. The Baseline version of the C-SSRS (Appendix J) will be used to assess lifetime suicidality on Day 1. At all other protocol-specified time points, the C-SSRS – Since Last Visit version (Appendix K) will be used to assess the subject's suicidality since the last assessment.

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.

16.10 Concomitant Medications

In general, concomitant medications that interfere with neuromuscular function or have the potential to confound effectiveness/safety results with regard to sialorrhea will not be allowed during the study, including:

- Aminoglycoside antibiotics (not allowed for entire study);
- Curare-like agents (not allowed for entire study);
- Anticholinergics and Antihistamines
    - Strictly prohibited if used for the treatment of sialorrhea, with the exception of ALS subjects as noted in exclusion criterion #9, which allows for ALS subjects to continue anticholinergic/antihistamine treatment for sialorrhea provided that they continue or convert to a short-acting medication (duration of action approximately 8 hours or less) at a stable dose/regimen for at least 2 weeks before the first injection of study drug (Day 1 of Treatment Session 1). The ALS subject must continue to meet all other eligibility criteria following such conversion/dose stabilization. The ALS subject must hold the medication 8 hours before any clinic visit.
    - Antihistamines and anticholinergic medications taken for a non-sialorrhea condition should be avoided as much as possible, but are not exclusionary.
- Botulinum toxin type A (not allowed for entire study); and
- Botulinum toxin type B, except that provided as study drug.

Additionally, Coumadin (warfarin) and similar anti-coagulant medications will not be allowed during the study.

Other medications not listed above, either specifically or by category, that do not interfere with neuromuscular function or do not have a potential to confound safety/effectiveness results with regard to sialorrhea, may be used by subjects in this study, at the discretion of the Principal Investigator.

17 STATISTICS

Detailed methodology for the summary and statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared and finalized before database lock.

17.1 General Statistical Considerations

Categorical variables will be summarized in general using frequencies and percentages, whereas continuous variables will be summarized in general using descriptive statistics of number of observations (n), mean, standard deviation (SD), minimum (Min), median, and maximum (Max).

17.2 Sample Size

Approximately 120 to 200 subjects will be enrolled in this study. The sample size is based on the requirements of the final safety database for approval.

17.3 Analysis Populations

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

Safety Population

This population is defined as all subjects who are injected with at least 1 dose of study drug. Where applicable, subject grouping will be based on the actual doses the subject received at each session and grouped into 3 groups: low dose (2,500 to 2,999 Units), medium dose (3,000 to 3,499 Units), and high dose (3,500 Units).

Intention-to-Treat (ITT) Population

This population is defined as all subjects who are injected with study drug and have at least 1 post-baseline measurement recorded in the eCRF for both USFR and CGI-C. The ITT population will be used for effectiveness analyses.

17.4 Demographic and Baseline Characteristics

Descriptive summaries of subject demographic and baseline characteristics will be presented for the safety population and ITT population. Subject characteristics will include a summary of demography, baseline disease characteristics, pre-existing medical conditions, prior therapies for the treatment of sialorrhea, as well as baseline effectiveness measures of USFR, CGI-S, PGI-S, DFSS-I, and DFSS-S.

17.5 Subject Disposition

Descriptive summaries of subject disposition will be presented for the safety population and ITT population. A detailed description of individual subject disposition will be provided in a data listing.

17.6 Safety Endpoints

Safety endpoints include adverse events and AESI, vital signs and weight, neurological exam, physical examination, dental exam, C-SSRS, and clinical laboratory tests. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary.

For safety endpoints, records with valid data within each visit or assessment time point will be identified for initial and repeat, where applicable. The initial record will be used in statistical analysis, whereas all records will be presented in data listings. Missing or invalid data will be treated as missing for the corresponding visit or time point.

The baseline of each treatment session consists of the corresponding measurement value obtained at pre-injection of each treatment session (i.e., Day 1, Weeks 13, 26, and 39).

17.7 Statistical Methods for Safety

Frequency of treatment-emergent adverse events (TEAEs) will be calculated for each body system, by preferred term, and by treatment session, for number of subjects and proportion reporting the event and AESI. The incidence of subjects reporting TEAEs will also be reported without those TEAEs categorized as related to the primary underlying disease conditions by the Investigator. The severity of the adverse events and the relationship to study drug will be summarized for each body system and preferred term. Withdrawals due to adverse events will be summarized for each body system and preferred term. Narratives will be presented for all deaths, subjects reporting SAEs, and subjects withdrawn due to adverse events.

Vital signs and weight will be summarized descriptively for continuous variable at each pre-injection visit (i.e., Day 1, Weeks 13, 26, and 39) and at each post-injection time point of 4 weeks post-injection (i.e., Weeks 4, 17, 30, and 43), 8 weeks post-injection (i.e., Week 8, first Treatment Session only), and 13 weeks post-injection (i.e., Weeks 13, 26, 39, and 52). The change scores in weight, vital signs, and neurologic exam average score from pre-injection (i.e., Day 1, Weeks 13, 26, and 39) at 4 weeks post-injection (i.e., Weeks 4, 17, 30, and 43), 8 weeks post-injection (i.e., Week 8, first Treatment Session only), and 13 weeks post-injection (i.e., Weeks 13, 26, 39, and 52) will be analyzed, using a paired t-test where applicable, by treatment dose group defined in Section 17.3 for the safety population (i.e., low dose, medium dose, and high dose).

Neurologic exam average score will be summarized descriptively for continuous variable at baseline (Day 1, before first injection of study drug), and post-baseline Weeks 13 and 52. The change scores in neurologic exam average score from baseline at post-baseline time points will be analyzed, using a paired t-test where applicable, by treatment dose group

defined in Section 17.3 for the safety population (i.e., low dose, medium dose, and high dose).

Physical examination will be summarized for abnormal findings at pre-injection of each session and will be reported at post-injection Week 13 (i.e., Weeks 13, 26, 39, and 52), using shift tables.

Each of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation) will be summarized descriptively for continuous variable at each pre-injection visit (i.e., Day 1, Weeks 13, 26, and 39) and at each post-injection time point of 4 weeks post-injection (i.e., Weeks 4, 17, 30, and 43), 8 weeks post-injection (i.e., Week 8, first Treatment Session only), and 13 weeks post-injection (i.e., Weeks 13, 26, 39, and 52).

The change scores in C-SSRS subscales from pre-injection at 4 weeks, 8 weeks (first Treatment Session only), and 13 weeks post-injection will be analyzed, using a paired t-test where applicable, by treatment dose group defined in Section 17.3 for the safety population (i.e., low dose, medium dose, and high dose).

Clinical laboratory tests of hematology, chemistry, and urinalysis (specific gravity and pH) will be summarized descriptively at available visits. Qualitative analysis of laboratory tests in terms of abnormality will be performed, using the shift-table method, for individual post-screening visits. Abnormal findings of clinical laboratory tests for individual subjects will be provided by data listing.

Abnormal findings of dental exam for individual subjects will be provided by data listing.

17.8 Effectiveness Endpoints

Effectiveness endpoints include USFR, CGI-C, CGI-S, DFSS-I, PGI-C, PGI-S, DIS, and DFSS-S.

17.9 Statistical Methods for Effectiveness

As subjects will receive multiple single-dose injections, each single-dose injection plus its follow-up period will be considered as a treatment session. Post-injection effectiveness endpoints over each of the treatment sessions include USFR, CGI-C, CGI-S, DFSS-I, PGI-C, PGI-S, DIS, and DFSS-S at the injection visit (i.e., Day 1, Weeks 13, 26, and 39), 4 weeks post-injection (i.e., Weeks 4, 17, 30, and 43), 8 weeks post-injection (i.e., Week 8, first Treatment Session only), and 13 weeks post-injection (i.e., Weeks 13, 26, 39, and 52). The pre-injection time points are Day 1 and Weeks 13, 26, and 39 for each of the consecutive treatment sessions. Missing post-injection measurements will not be imputed, whereas missing measurements at the pre-injection of each treatment session will be imputed by the site-specific average of those subjects who receive the treatment at the corresponding treatment session.

For each treatment session, effectiveness analysis of the treatment response will be performed on USFR change from pre-injection, CGI-C, CGI-S, PGI-C, PGI-S, and DIS change from pre-injection, DFSS-I change from pre-injection, and DFSS-S change from

pre-injection at each of the post-injection time points for the ITT population, using a paired t-test. The ITT population will be grouped into three groups by the actual doses the subject received at each session as the following: low dose (2,500 to 2,999 Units), medium dose (3,000 to 3,499 Units), and high dose (3,500 Units).

In addition, the proportion of treatment responders will be reported for the CGI-C and PGI-C at both pre-injection and post-injection time points over each treatment session. Before the analysis, the CGI-C and PGI-C variables will be dichotomized into 2 categories, with "very much improved" and "much improved" into 1 category and the remaining levels in the other category.

18 ETHICS

This study will be conducted according to Good Clinical Practice (GCP) guidelines; US Code of Federal Regulations (CFRs) dealing with Protection of Human Subjects (US 21 CFR Part 50) and Institutional Review Boards (US 21 CFR Part 56); the Nuremberg Code; and the Declaration of Helsinki, revised version of Seoul, October 2008 (in compliance with the FDA's guidance).

18.1 Ethics Review

The US FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to regulations and guidance issued by the FDA and are included in the following parts of the US CFR and guideline document:

- 21 CFR Part 11 - Electronic Records; Electronic Signatures;
- 21 CFR Part 50 - Protection of Human Subjects;
- 21 CFR Part 56 - Institutional Review Boards (IRBs);
- 21 CFR Part 312 - Investigational New Drug (IND) Application; and
- ICH E6: Good Clinical Practice.

Copies of these materials can be downloaded from the FDA's website at www.fda/gov.

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.

18.2 Ethical Conduct of the Study

As a Principal Investigator, you agree to conduct this study in accordance with the ethical standards defined within GCP in order to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings; and

- The potential benefits of the research justify the risks.

Solstice Neurosciences is the Sponsor of the IND. The Sponsor is responsible for the following:

- Selecting qualified Investigators;
- Providing Investigators with the information they need to properly conduct an investigation (i.e., protocol training);
- Ensuring proper monitoring of the investigation;
- Ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND;
- Maintaining the IND; and
- Ensuring that FDA and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

18.3 Study Conduct

This study will be conducted in accordance with the Sponsor's standards that meet GCP regulations. These standards reflect the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonization [ICH] Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996);
- US CFR dealing with clinical studies (21 CFR Parts 50, 54, 56, 312, and 314);
- HIPAA of 1996 (45 CFR Part 164); and
- Declaration of Helsinki, revised version of Seoul, October 2008.

18.4 Institutional Review Board Approval

Before initiating the study, the Principal Investigator will obtain written approval from a central IRB or the Principal Investigator's IRB (if such site is not eligible to use a central IRB) that complies with the requirements specified in GCP Title 21 Part 56 of the US CFR relating to IRBs and the ICH Guideline for GCP (E6). Study drug will not be shipped until IRB approval is obtained. Should changes to the study protocol become necessary, protocol amendments (provided by the Sponsor) will be submitted in writing to the central IRB (and the Principal Investigator's IRB) for IRB approval before implementation. In addition, the Principal Investigator's IRB must approve all site-specific advertising used to recruit subjects for the study. If the duration of the study is greater than 1 year, re-approval by the IRB must be obtained annually (or at more frequent intervals if required by the IRB).

Progress reports will be submitted to the central IRB annually or at a frequency requested by the IRB. You must also provide progress reports to your IRB, as well as any SAE reports from your study site. You are also responsible for providing the IRB with reports of any SAEs from any other study conducted with the study drug. The latter will be provided by the

Sponsor. If you are using the central IRB selected by the Sponsor, safety updates (except SAEs occurring at your site) will be reported directly to the central IRB on your behalf.

18.5 Informed Consent and HIPAA Authorization

Properly executed written informed consent, in compliance with 21 CFR 50 and ICH guidelines, shall be obtained from each subject before entering the subject into the study. 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. For this study, a standard Informed Consent Form (ICF) will be approved by a central IRB. Any study site that requires a site-specific ICF must have the document approved by the Sponsor before submission to the site's IRB. The final IRB-approved ICF must be provided to the Sponsor for regulatory purposes.

Informed consent is a process of interaction between the Investigator and a potential subject/Legally Authorized Representative (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[2] 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.

Each subject/LAR must also sign a HIPAA authorization form before his/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.

[2] Potential subject/LAR is to be consented using an ICF that is written in a language they understand. It is not acceptable to verbally translate an ICF from the language in which it is written and have the subject/LAR sign the written ICF. Additionally, if the person obtaining consent is not fluent in the language in which the consent is written (able to explain the consent/answer questions to the subject/LAR), the subject/LAR's consent must be witnessed by someone who is fluent in the language in which the consent is written, and will be able translate any questions/explanations during the consent process.

19 INVESTIGATOR OBLIGATIONS

19.1 Protocol Adherence and Subject Welfare

As a Principal Investigator, you are responsible for ensuring that the study is conducted according to the protocol as written, and for protecting the rights, safety, and welfare of subjects under your care.

19.2 Protocol Modification

Only the Sponsor may modify the protocol. You will be immediately notified of protocol changes and provided with a copy of the protocol amendment. A protocol amendment that has an impact on subject risk or has changes to the study objectives, study design, subject population, study procedures, or study drug must be submitted to the IRB for review and approval, in writing, before implementation. If the protocol amendment requires a change to the ICF, then the revised ICF must be IRB-approved in advance of use.

19.3 Compliance with Law, Audit, and Debarment

19.3.1 Statement of Investigator (Form FDA 1572)

As a Principal Investigator, you must sign a Statement of Investigator (Form FDA 1572) before initiating the study. The names of all Sub-investigators and other clinical experts (e.g., study dentist) directly involved in the treatment or evaluation of study subjects must appear on this form.

19.3.2 Financial Disclosure

You as a Principal Investigator, Sub-investigators, and other clinical experts (e.g., study dentist) directly involved in the treatment or evaluation of study subjects must sign financial disclosure forms before initiating this study. Financial disclosure also pertains to the spouse and dependent children of the Investigator(s) and other clinical experts. In general, the FDA is concerned with certain types of financial interests including:

- Compensation affected by the outcome of the study;
- Significant equity interests in the Sponsor exceeding $50,000 including ownership, stick or stock options;
- A proprietary interest in the tested product such as trademark, patent, copyright, or licensing agreement; and
- Significant payments of other types made to the Investigator or institution to support investigator activities (i.e., honoraria, consulting fees) that exceed $25,000 cumulatively. *These payments exclude the costs of this clinical trial.*

Investigators are required to promptly update the information if any relevant changes occur during the course of the study or for 1 year following completion of the study (defined as 1 year after the last study visit by the last study subject at the Investigator's study site).

19.3.3 Inspections and Audits

As a Principal Investigator, you are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by either the Sponsor, its representatives, or any appropriate regulatory agencies.

Additionally, you should inform subjects, in writing, about the possibility of audits by authorized representatives of the Sponsor and/or regulatory authorities and that confidentiality of their data will be maintained in accordance with local laws. See Section 20.2 for further details regarding study audits.

19.3.4 Debarment

Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Solstice Neurosciences, LLC. You are required to immediately disclose to the Sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of your knowledge) threatened.

19.4 Adverse Event Reporting

In accordance with FDA reporting requirements, you are required to collect, document, and report all adverse events/SAEs as outlined in Section 16.2.8 of this protocol. You must also report any SAE of which you become aware that occurred within 13 weeks after the last dose of study drug (regardless of relationship to study drug) and any SAEs (at least possibly related to study drug) that you become aware of after 13 weeks after the last dose.

19.5 Drug Accountability

All investigational agents required for completion of this study will be provided by the Sponsor. The investigational agents are to be used only as described by this study protocol by an appropriately licensed Investigator named in Form FDA 1572. Please refer to Section 13.5 for specific requirements for recording all investigational agents received, dispensed, administered, and returned.

19.6 Data Handling and Recordkeeping

19.6.1 Case Report Forms

You will be provided with secure access to 21 CFR Part 11 compliant eCRFs for collecting subject data. All information recorded in the eCRFs must be supported by source

documentation in the subject's file. The subject's file must include (but is not limited to) the following:

- An entry stating that the subject signed an ICF and HIPAA authorization form before entry into the study and is participating in the study;
- Subject identification number and protocol number;
- Diagnosis;
- Entries for all therapy/medications;
- Entries summarizing all clinic visits, including those for study purposes; and
- Entries for all adverse events.

All data entered into the eCRF must be source documented in the subject's medical record. In some instances the source may serve as the eCRF.

19.6.2 Subject Identification

You must maintain a log sheet that lists each subject who is screened for possible participation in this study.

The following information must be entered onto the log sheet:

- Subject identification number and protocol number;
- Subject initials;
- Date (and time, where applicable) subject/caregiver signed the ICF and HIPAA authorization form;
- Date of screening visit;
- Whether or not the subject was treated with study drug; and
- For subjects who do not receive treatment, the reason for exclusion.

19.6.3 Administrative Documentation

You must provide the Sponsor's Study Monitor with the following documents before study initiation and retain a copy in your study files:

- A current and complete curriculum vitae for the Principal Investigator and each Sub-investigator;
- An original completed Form FDA 1572 signed and dated by the Principal Investigator;
- Completed Financial Disclosure Form (copy is acceptable) for Principal Investigator, any Sub-investigators, and other clinical experts directly involved in the treatment or evaluation of study subjects;

- Approved Sponsor protocol (and any protocol amendments) signed and dated by the Principal Investigator (copy is acceptable);
- IRB membership list or assurance number (copy is acceptable);
- ICF and HIPAA authorization form approved by the IRB and accepted by the Sponsor (copy is acceptable);
- Written IRB approval of the protocol (copy is acceptable);
- Certifications and laboratory reference ranges for laboratories, where applicable (copy is acceptable). (Documentation for approved central laboratories will be provided by the Sponsor. The Investigator must provide certifications and current laboratory reference ranges for all local laboratories used for this study.); and
- Acknowledgement of Clinical Investigator Brochure (CIB) receipt (copy is acceptable).

In addition to the documents listed above, you should also retain the following items:

- All original ICFs/HIPAA authorizations with required signatures;
- All IRB approvals and correspondence (e.g., informed consent [including any approved revisions], protocol, adverse events, advertisements, newsletters);
- Site copy of the Study Monitoring Log Sheet;
- Clinical and nonclinical supply shipment forms;
- Copies of all correspondence (emails, faxes, mail) pertaining to the study (except budget issues) between the Sponsor (or Clinical Research Organization [CRO]) and the site;
- Copies of all SAE reports submitted to the Sponsor;
- Copies of the CIB and/or approved package labeling;
- Study personnel signature & delegation of authority log; and
- Copies of all IND safety reports.

The Clinical Study Agreement should be kept in a file separate from any study documents because this is a confidential agreement between you and the Sponsor.

19.6.4 Retention of Records

Essential documents must be retained at least 2 years after the last approval of a marketing application in an ICH region (with no pending marketing application) OR at least 2 years after formal discontinuation of clinical development of the product.

The Investigator/study site must retain copies of all pertinent study information and records (e.g., eCRFs, original data, subject identification lists, ICFs, IRB approvals/approved documents) until notified, in writing, by the Sponsor that these copies are no longer required.

The Investigator is responsible to notify the Sponsor if the site or records are relocated and must provide the address of the new location.

20 STUDY MONITORING AND QUALITY CONTROL/ASSURANCE

20.1 Study Monitoring

A Sponsor or CRO Clinical Research Associate (CRA) will be the Study Monitor for your study. The Study Monitor is your primary contact for all study-related issues.

The Study Monitor will visit your site at periodic intervals throughout the trial as defined in the monitoring plan, after which a report on all monitoring activities will be submitted to the Sponsor. The first visit ("initiation" visit) is before subjects are enrolled into the clinical trial. During this visit, the Study Monitor will review the study protocol with you and your staff, confirm receipt of study supplies, and verify that you are ready to enroll subjects. Subsequent visits will be scheduled at periodic intervals 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. For this study, the Sponsor will be the Data Coordinating Center and 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.

After the close-out visit, you may be asked to provide additional information to support the clarification and/or correction of clinical data entries.

20.2 Inspections and Audits

The Sponsor will secure agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

20.2.1 Inspection of Records

The Sponsor, its agents, the IRB, and any applicable regulatory agency will be provided with direct access to all information in original source documents and/or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

20.2.2 Audits

It may be necessary for the Sponsor, its agents, and/or a regulatory agency to audit your site. The purpose of an audit is to assess the accuracy, adequacy, and consistency of the study records and subject data, as well as to assess your adherence to the procedures described in this protocol. Direct access must be provided to all information in original source documents and/or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

21 CONFIDENTIAL INFORMATION

21.1.1 Confidentiality of Data

Confidential information refers to any information provided to you by the Sponsor or its agents that has not been previously published. This includes, but is not limited to, the clinical protocol (and protocol amendments, if any), eCRFs, assay methods, CIB, and basic scientific data. Any data that you collect during the study are also considered confidential. All confidential information remains the sole property of the Sponsor, may not be disclosed

to others without prior written consent from the Sponsor, and may not be used except in the performance of this study. You are required to provide the Sponsor with complete test results and all data obtained during this study. At the discretion of the Sponsor, the information from this study may be made available to any applicable regulatory agency and/or other physicians who are conducting similar studies.

21.1.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports, and other records will be coded using subject identification numbers and/or subject initials. Only research staff and Sponsor officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the Sponsor or a regulatory agency.

By participating in this protocol, you agree that within local regulatory restrictions and ethical considerations, the Sponsor or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

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

22 STUDY DISCONTINUATION CRITERIA

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

23 DISSEMINATION AND PUBLICATION OF STUDY RESULTS

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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