

PRODUCT: MYOBLOC® (rimabotulinumtoxinB) Injection
STATISTICAL ANALYSIS PLAN PROTOCOL NUMBER: SN-SIAL-351

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

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Drug Name:	MYOBLOC® (rimabotulinumtoxinB) injection
Indication:	Troublesome Sialorrhea
Sponsor:	Solstice Neurosciences, LLC a Subsidiary of US WorldMeds, LLC 4010 Dupont Circle, Suite L-07 Louisville, KY 40207
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STATISTICAL ANALYSIS PLAN

ABBREVIATIONS AND DEFINITIONS.....	5
1 INTRODUCTION	6
1.1 Trial Objectives	6
1.2 Background Information	6
2 STUDY DESIGN.....	7
2.1 Rationale.....	7
2.2 Description of Trial Design	7
2.3 Schedule of Assessments	8
2.4 Randomization	13
2.4.1 Treatment randomization	13
2.4.2 Random allocation of landmarks-confirmation type	13
2.5 Sample Size Estimation	13
2.6 Efficacy and Safety Measurements	13
2.6.1 Effectiveness measures	13
2.6.2 Safety measures	15
2.6.3 Other measures	17
2.7 Drug Concentration and PK Measurements	17
2.8 Handling of Missing, Incomplete, and Repeat Data	18
2.9 Statistical Methods.....	18
2.9.1 Effectiveness analysis.....	19
2.9.2 Safety analysis.....	19
2.9.3 Other analysis	21
2.10 Interim Analysis.....	22
3 STUDY POPULATION	22
3.1 Definition of Subject Populations.....	22
3.2 Screening and Enrollment.....	22
3.3 Population Demography.....	22
3.4 Disease Diagnosis and Prior Therapy	22
3.5 Medical History	23
3.6 Disposition of Study Participants	23
3.7 Protocol Deviations and Violations	23
4 EFFICACY EVALUATION.....	23
4.1 Datasets Analyzed	23
4.2 Treatment Compliance.....	23
4.3 Baseline Measures	23
4.4 Efficacy Results and Tabulations	23
5 SAFETY EVALUATION	24
5.1 Extent of Drug Exposure	25
5.2 Early Termination.....	25
5.3 Adverse Events.....	25
5.4 Adverse Events of Special Interest (AESI)	25
5.5 Adverse Events Associated with Dental Disease	25
5.6 Adverse Events Associated to Distant Spread of Toxin Effect.....	26
5.7 Vital Signs and Weight.....	26

5.8	Neurologic Exam.....	27
5.9	Lung Functioning Test.....	27
5.10	Physical Examination.....	27
5.11	Clinical Laboratory Evaluation.....	27
5.12	Suicidality Assessment.....	27
5.13	Dental and Oral Examinations.....	27
5.14	Concomitant Medication.....	27
6	REFERENCE	28
7	LIST OF STATISTICAL TABLE SHELLS	29
8	LIST OF LISTING SHELLS	35
9	LIST OF FIGURES	36

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALS	Amyotrophic Lateral Sclerosis
AUC	Area Under the Curve
CGI-C	Clinical Global Impression - Change
CGI-S	Clinical Global Impression - Severity
CI	Confidence Interval
CRF	Case Report Form
C-SSRS	Columbia Suicidal Severity Rating Scale
eCRF	Electronic Case Report Form
DAE	Dental Adverse Event
DFSS-I	Droling Frequency and Severity Scale - Assessor
DFSS-S	Droling Frequency and Severity Scale - Subject
DIS	Droling Impact Scale
FVC	Forced Vital Capacity
ITT	Intent-to-Treat Population
MedDRA	Medical Dictionary for Regulatory Activities
NCE	New Chemical Entity
NDA	New Drug Application
OL	Open-Label Population
OTC	Over the Counter
PD	Parkinson's Disease
PGI-C	Patient Global Impression - Change
PGI-S	Patient Global Impression - Severity
SAE	Serious Adverse Event
SE	Standard Error
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
USFR	Unstimulated Salivary Flow Rate

1 INTRODUCTION

1.1 Trial Objectives

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.

The secondary objective of this study is:

- 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.

2 STUDY DESIGN

2.2 Description of Trial Design

This is a multi-center study with a single arm to evaluate the long-term safety and effectiveness of repeated doses (MYOBLOC 3,500 Units single-injection treatment) at intervals of every 13 weeks over a maximum possible duration of 1 year in subjects with troublesome sialorrhea. The study population will be comprised of a mixture of patient populations, including subjects with PD-related sialorrhea, subjects with sialorrhea secondary to other non-PD conditions (e.g., cerebral palsy, ALS, stroke, traumatic brain injury) or secondary to oral cancer or medications (e.g., neuroleptics).

After a screening period (up to 21 days), those subjects who satisfy all eligibility criteria will receive single dose injections of 3,500 Units of MYOBLOC at Day 1 and at subsequent intervals of 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 of 11 weeks from the prior injection. After the 1st treatment session for which subjects are injected

with 3,500 Units, the Investigator has the discretion to decrease subsequent injection doses, as a result of poor tolerability, but to no less than a total dose of 2,500 Units.

Subjects will undergo safety and effectiveness assessments at Day 1 (1st injection), and Weeks 4, 8, 13 (2nd injection), 17, 26 (3rd injection), 30, 39 (4th injection), 43, and 52. Telephone follow-up will occur at Weeks 14, 21, 27, 34, 40 and 47 to assess how the subject feels after 1 week (± 1 day) of study drug injection, document adverse events as appropriate, document any new medications the subject may be taking and remind the subject to complete their diary.

At each visit, the following efficacy assessments will be collected, when possible by the same assessor for a given subject:

- Unstimulated salivary flow rate (USFR)
- Clinical Global Impression of Severity (CGI-S)
- Clinical Global Impression of Change (CGI-C), except for Day 1
- Drooling Frequency and Severity Scale (DFSS-I) by Investigator
- Drooling Frequency and Severity Scale (DFSS-S) by subject
- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C), except for Day 1
- Drooling Impact Score (DIS) by Subject

Efficacy and safety assessments will be made throughout the study as detailed in the following section.

2.3 Schedule of Assessments

The complete schedule of assessments for this study is shown in table below.

Table A 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

Table A 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)
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
Review of Common Classes of Anticholinergic & Antihistamine Medications	X								
Study Drug Injection (m)		X (1 st) (n)			X (2 nd)				X (3 rd)
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 B 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		

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)	

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.
- (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.

2.4 Randomization

2.4.1 Treatment randomization

This is an open-label study with a single arm, and all eligible subjects will receive the same dose of 3,500 Units of MYOBLOC. No treatment randomization is necessary.

2.4.2 Injection Technique Assignment

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 using external anatomical landmarks with ultrasound-guided confirmation.

2.5 Sample Size Estimation

No sample size estimation is performed for this open-label study. The study plans to enroll a total of 120 to 200 subjects. The sample size, 187 subjects is based on the requirements of the final safety database for approval.

2.6 Efficacy and Safety Measurements

In this study, efficacy will be assessed, using USFR, CGI (severity and change), DIS, DFSS-I, DFSS-S, PGI (severity and change). DFSS-S will be collected through subject’s diaries.

Safety will be assessed through subject early terminations, adverse events, adverse events of special interest (including aspiration, aspiration pneumonia, and choking, dysphagia), dental and oral examination (dental adverse events), physical examination, neurological examination, vital signs, lung functioning assessment, pregnancy test, clinical laboratory evaluations (hematology, chemistry, urinalysis), and concomitant medications as well as Columbia Suicide Severity Rating Scale (C-SSRS).

2.6.1 Effectiveness measures

Several effectiveness measures are assessed over each of the treatment Sessions 1 through 4 at the injection visit (i.e., Day 1, and 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). Where applicable, the measurement value obtained at pre-injection of each treatment session (i.e., Day 1 and Weeks 13, 26, and 39 for each of the 4 treatment sessions, respectively) is defined as the baseline of the corresponding measures. For the CGI-C and PGI-C, the corresponding severity score observed at pre-injection of each treatment session will be used as the baseline measurement of the corresponding session in analysis.

Unstimulated Salivary Flow Rate (USFR)

The USFR (g/minute) is the salivary flow rate assessed by the independent assessor 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 (Appendix B of the protocol). To determine USFR at each study

visit, saliva will be collected over a 5-minute collection period using weighing cups

hey 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.

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

The CGI-S scale is 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 of the protocol). 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 of the protocol). 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.

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 of the protocol). 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 of the protocol). 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.

Drooling Frequency and Severity Scale (DFSS)

The DFSS is a 2-item scale used to assess the frequency and severity of drooling. The DFSS will have two forms in this study, with one being performed by an independent assessor (DFSS-I) and the other by the subject (DFSS-S). In both forms, drooling severity is assessed on a 5-point scale ranging from 1 (dry, never drools) to 5 (profuse, clothing, hands, tray, objects become wet), whereas drooling frequency is assessed on a 4-point scale ranging from 1 (never drools) to 4 (constantly drools) (Appendix E of the protocol). The total score ranges from 2 to 9 in each DFSS form. The assessor’s initial assessment

of DFSS on Day 1 of Treatment Session 1 should be based on the prior 4 weeks, whereas the subsequent assessments of DFSS should be based on the timeframe since the prior study visit. The independent assessor should not review the subject-rated scales before performing his/her own assessment.

DFSS-S is collected via subject's diary in this study on a daily basis for the first 2 weeks of each treatment session and then weekly for the remainder of the treatment session.

Drooling Impact Score (DIS)

The DIS is a 10-item questionnaire with each item rated by the subject to evaluate the impact of the disorder (sialorrhea) on daily activities (e.g., speech, social activities). 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) (Appendix F of the protocol). The DIS total score ranges from 10 to 40. The initial assessment of DIS on Day 1 of Treatment Session 1 before the first injection of study drug should be based on the prior 4 weeks, whereas the subsequent assessments should be based on the timeframe since the prior study visit.

2.6.2 Safety measures

Adverse events are recorded at each study visit, starting from the first injection of MYOBLOC on Day 1 of Treatment Session 1 and ending at study completion (i.e., 52 ± 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 to assess the adverse event. Serious adverse events, adverse events of special interest, and other immediately reportable adverse events were collected during the study period (or within 13 weeks ±3 days of last study drug injection for subjects discontinuing participation prematurely). Dental and oral health are followed closely throughout the course of the study by monitoring dental adverse events (DAE), as defined in the study protocol.

Vital signs (blood pressure, pulse, respiratory rate, and temperature) are measured after sitting quietly for at least 5 minutes at screening and each study visit, if applicable, at early termination from the study.

Subjects' suicidal ideation and behavior are measured at each study visit (including Day 1 and Weeks 4, 8, 13, 17, 26, 30, 39, 43, and 52) or, if applicable, early termination from the study, using the Columbia Suicidal Severity Rating Scale (C-SSRS). The C-SSRS baseline version (Appendix I of the protocol) will be used for Day 1, whereas the C-SSRS since last visit version (Appendix J of the protocol) will be used for all of the other visits. The C-SSRS has three subscales: suicidal ideation (Categories 1-5), suicidal behavior (Categories 6-10), and intensity of suicidal ideation. Both suicidal ideation subscale and suicidal behavior subscale have 5 yes-no categories each, with a sum score ranging from 0 to 5 and higher score indicating greater severity.

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

- Category 6 – Actual Attempt
- Category 7 – Interrupted Attempt
- Category 8 – Aborted Attempt
- Category 9 – Preparatory Acts or Behavior
- Category 10 – Suicidal Behavior

The intensity of suicidal ideation has 5 items (2 are scored from 1 through 5 and the other three from 0 to 5), with a sum score ranging from 2 to 25 where higher score indicate greater risk.

For the analysis, an intensity of suicidal ideation will be defined as the maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. A score of 0 will be assigned if no ideation is present.

Clinical laboratory tests are conducted at screening, Weeks 13, 26, as needed at the Investigator's discretion throughout the study and at study completion (i.e., Week 52) or, if applicable, at early termination from the study. Laboratory tests are analyzed by a central laboratory and include the following parameters:

Serum Chemistry:
cholesterol, phosphorus, sodium (Na ⁺), potassium (K ⁺), calcium (Ca), urea nitrogen (BUN), creatinine, albumin, total protein, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), uric acid, total bilirubin, glucose, and lactate dehydrogenase (LDH).
Hematology:
hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, MCV, MCH, MCHC, white blood cell (WBC) count, WBC differentials (%), including bands, neutrophils, lymphocytes, monocytes, eosinophils, and basophils
Urinalysis:
specific gravity, pH, glucose, blood, protein, color, nitrites, ketones, bilirubin, urobilinogen, and leukocyte esterase.

A complete physical examination is performed at screening, Weeks 4, 13, 26, 39, and at study completion (i.e., Week 52) or, if applicable, at early termination from the study. The complete examination will involve gross examination of general appearance; head, ears, eyes, nose and throat; skin; extremities; chest; abdomen; and lymph nodes. Cardiac and pulmonary auscultation and measurement of vital signs and weight will also be conducted as part of the complete physical exam. A brief physical examination, consisting of cardiac and pulmonary auscultation is performed on Day 1 prior to injection of study drug and at Weeks 8, 17, 30, and 43. Height will be recorded at screening only. Lung functioning is measured for subjects with ALS, using forced vital capacity (liter) (FVC), 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). If any of the Physical Exam findings were abnormal and clinically

significant prior to treatment, the event was recorded as medical history, while if occurred after treatment they event was recorded as an Adverse Event.

A neurologic exam is performed at screening, on Day 1 prior to injection of study drug, at Week 13, as needed at the Investigator's discretion throughout the study, and at study completion (i.e., Week 52) or if applicable, at early termination from the study. The neurologic exam consists of 9 sections to evaluate: 1) level of consciousness; 2) speech; 3) cranial nerves; 4) motor; 5) sensory; 6) coordination; 7) gait; 8) reflexes; and 9) Romberg test (Appendix G of the protocol).

A dental exam is performed by a licensed dentist (DDS or DMD) at screening, at Weeks 4, 13, 26, as needed at the Investigator's discretion throughout the study and at study completion (i.e., Week 52) or, if applicable, at early termination from the study.

Findings of dental exam that meet the DAE criteria as defined in the protocol will be reported as such. Subjects or their caregiver will also complete a dental questionnaire at screening.

An oral exam (Appendix H of protocol) is performed by the Investigator at each study visit where a dental exam is not planned by protocol.

Findings of the oral exam that meet the DAE criteria as defined in the protocol will be reported as such.

A urine pregnancy test is performed on all females of child-bearing potential at screening, on Day 1 (before the first injection of the study drug), as needed at the Investigator's discretion throughout the study, and at study completion (i.e., Week 52) or, if applicable, at early termination from the study.

2.6.3 Other measures

Prior treatment for sialorrhea and concomitant medications (including those taken within 30 days before screening) taken over the course of the study will be recorded.

The medical history with disease history, co-morbidities, relevant past illness, and surgical procedures performed within the prior 6 months are recorded at screening. Subjects are also evaluated for presence or prior history of aspiration, aspiration pneumonia, choking, and/or dysphagia.

2.7 Drug Concentration and PK Measurements

No drug concentration measures will be taken in this trial.

2.8 Handling of Missing, Incomplete, and Repeat Data

Missing Data of Effectiveness Measures

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.

Missing Data of Safety Parameters

For safety parameters, missing or invalid data will be treated as missing for the corresponding assessment, except that for partial start dates of adverse events, missing day and month will be imputed to the date of first injection. Completely unknown start dates will be imputed to date of first injection. If day is missing and month and year are present then day is either set to the 1st of the month or the day of the month for the first injection.

Handling of Repeated Data Records

All data records with valid data of efficacy and safety measures are identified for initial and repeat within each study visit and/or assessment time point. Should repeated data records exist within a study visit and/or assessment time point, the initial data record will be utilized for any statistical analyses of the corresponding study visit and/or assessment time point. All existing data records including the repeat data records in the study database will be presented in data listings and CRF data tabulations.

Any resultant incomplete or missing data of either efficacy or safety parameters will be treated as missing in the statistical analyses involving these parameters.

2.9 Statistical Methods

Unless specified otherwise, SAS® Version 9.4 or higher will be utilized to perform the statistical analyses of efficacy and safety measures.

Per the protocol, subjects who met all eligibility criteria were to receive single dose injections of 3,500 Units of MYOBLOC every 13 weeks (± 2 weeks) over a maximum possible duration of 1 year, for up to a total of 4 treatments via injections into the submandibular and parotid glands. Repeat injections at each treatment session were to be done when subjects returned 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 developed intolerable side effects, but still wished to remain in the study, the Investigator had the discretion to decrease subsequent doses, but to no less than a total dose of 2,500 Units. Since the majority of subjects received 3500 Units, all statistical tables will present results under one treatment group labeled "Any Dose". Additionally, listings will be categorized as L = low dose (1500-2000 U); M = medium dose (2500-3000 U); H = high dose (3500 U).

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).

In both data listings and CRF domain data tabulations, subject ID will consist of site number plus the assigned subject number.

Hypothesis testing, unless otherwise indicated, will be performed at the 5% significance level. All p-values will be rounded to four decimal places; p-values less than 0.001 will be presented as '<0.001' in all tables. All confidence intervals will be two-sided with 95% coverage.

2.9.1 Effectiveness analysis

As subjects receive multiple single-dose injections, each single-dose injection plus its follow-up period will be considered as a treatment session.

Effectiveness measures obtained over each of the treatment sessions include USFR, CGI-S, CGI-C, DFSS-I, DFSS-S, PGI-S, PGI-C, and DIS at the injection visit (i.e., Day 1, except for CGI-C and PGI-C, and 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 injection visit of Day 1 and Weeks 13, 26, and 39 is considered the baseline (or pre-injection), respectively, for each of the consecutive treatment sessions 1 through 4.

For each treatment session, effectiveness analysis of the treatment response will be performed on USFR change from pre-injection, DFSS-I change from pre-injection, and DFSS-S change from pre-injection, CGI-S, CGI-C, PGI-S, PGI-C, and DIS change from pre-injection, at each of the post-injection time points using a t-test.

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 will be dichotomized into 2 categories, with "very much improved" and "much improved" into 1 category and the remaining levels in the other category.

2.9.2 Safety analysis

Safety measures include adverse events, adverse events of special interest (AESI), dental adverse events (DAE), adverse events associated with distant spread of toxin effect, vital signs and weight, physical exam, neurological exam, dental exam, oral exam, and clinical laboratory tests, as well as lung functioning test for ALS subjects. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary.

Like for effectiveness analyses, the baseline for safety analysis includes the pre-injection visits of Day 1, and Weeks 13, 26, and 39, respectively, for each of the treatment sessions 1 through 4.

Drug Exposure

Frequency of drug exposure will be calculated based on the number of injections of study drug administered. Duration of drug exposure will be calculated for each subject for the average duration of individual treatment sessions and total duration of treatment sessions, with the former being the average of the durations of individual treatment sessions the subject has received and the latter being the sum of the durations of individual treatment sessions the subject has received. Duration of drug exposure will be summarized for the safety population as defined in Section 3.1.

Early Termination

Subjects' study disposition will be summarized. A listing will be provided for all early terminations. This listing will include a subject's demographic variables, primary diagnosis, number of injections administered, and the primary reason for early termination.

Adverse Events, AESI, and DAE

All of adverse events will be coded for preferred terminologies using MedDRA. An AE that occurs on the 1st injection date or later will be defined as a TEAE. An AE with start date missing and no valid stop date or stop date being after the first injection date will be considered as a TEAE. TEAEs will be further separated by treatment session.

TEAEs, AESIs, DAEs, and adverse events associated with distant spread of toxin effect will be analyzed by session. Frequency of these types of adverse events will be calculated for each body system (or system organ class, SOC), by preferred term, for number of subjects and proportion reporting the event. The severity of adverse events and the relationship to study medication 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. Serious adverse events (SAEs) (including deaths) will be listed for individual events.

Narratives will be provided for all deaths, non-fatal serious adverse events, and subjects withdrawn due to adverse events.

Vital Signs and Weight

Vital signs and weight will be summarized descriptively by treatment session at pre-injection (i.e., Day 1 and 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 vital signs and weight from baseline at 4 weeks, 8 weeks (first treatment session only), and 13 weeks post-injection will be summarized descriptively.

Neurologic Exam

Abnormal findings of neurological exam data will be listed, respectively, for individual subjects.

Lung Functioning Test

Findings of forced vital capacity (FVC) data will be listed, respectively, for individual subjects.

Physical Examination

A complete Physical Examination was performed at Screening, Week 4, Week 13, Week 26, Week 39, Week 52, and Early Discontinuation. A brief Physical Examination was performed at Day 1, Week 8, Week 17, Week 30, and Week 43 when body weight, height and body mass index (BMI) were recorded. If any of the Physical Examination findings were abnormal and clinically significant prior to treatment, the event was recorded as medical history, while if occurred after treatment the event was recorded as a TEAE.

Suicidality Assessment

For each treatment session, 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 and 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 summarized descriptively.

Dental Examination and Oral Examination

Abnormal findings of dental exam and oral exam will be listed, respectively, for individual subjects. Dental adverse events will be included in the analysis of adverse events.

Laboratory Assessments

For each treatment session, 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.

Pregnancy Test

Any positive findings of the pregnancy test will be listed for individual subjects.

2.9.3 Other analysis

Concomitant medications were grouped into those taken pre-enrollment and those taken post-enrollment, based upon the starting date of both the concomitant medication and the enrollment date. Number and percent of subjects who take concomitant medications were reported for each Treatment Session. Concomitant medications will be listed, respectively, for individual subjects.

2.10 Interim Analysis

No interim analysis is planned.

3 STUDY POPULATION

3.1 Definition of Subject Populations

All subjects who return to the clinic on Day 1 (i.e., study baseline) and have all required baseline (before injection of study medication) assessments/procedures completed will be considered study participants. Study populations are defined in the following sections to assess the safety and effectiveness of MYOBLOC.

Safety Population

The safety population is defined as all subjects who are injected with at least one dose of study medication. The safety population will be utilized for safety analyses. The safety population will be identified and finalized before database is locked.

Intention-to-treat Population

The intention-to-treat (ITT) population is defined as all subjects who are injected with study medication and have at least 1 post-baseline measurement recorded in the eCRF for both USFR and CGI-C. The ITT population will be used as the primary population for effectiveness analyses. The treatment group identification of a subject in the ITT population will follow those of the safety population.

3.2 Screening and Enrollment

An enrollment summary including the number of subjects enrolled (i.e., study participants), treated (i.e., safety population), efficacy evaluable (i.e., ITT population), and completed the study will be presented by site. Study participants include all individuals who have all required baseline (before injection of study medication) assessments/procedures completed at Day 1 visit. The number of subjects who received treatment doses will be summarized by session for safety population and for ITT population.

3.3 Population Demography

For the safety and ITT populations, descriptive summaries of demography will be presented.

Demography includes age in years (continuous and categorical 18 to 49, 50 to 64, 65 to 74, and 75+), sex, race, ethnicity, weight, and height. Demography will also be listed for all subjects enrolled.

3.4 Disease Diagnosis and Prior Therapy

For the safety population, descriptive summaries will be presented for disease diagnosis and use of prior therapy and for severity of troublesome sialorrhea at baseline. The protocol indicated summarizing severity of troublesome sialorrhea at baseline. These were summarized using disease severity at baseline as measured by USFR, DFSS-I, DFSS-S, CGI-C, PGI-S and DIS.

Disease diagnosis, USFR, DFSS-I, DFSS-S, CGI-S, PGI-S, and DIS score at baseline (i.e., Day 1), and use of prior therapy will be listed for all subjects enrolled.

The protocol indicated summarizing Disease Diagnosis and Prior Therapy, Medical History and Disposition for the safety and ITT populations, however since the difference between these two populations was only one subject, these were only summarized for the safety population.

3.5 Medical History

Medical history will be listed for the safety population.

3.6 Disposition of Study Participants

Subject disposition including completion and discontinuation along with CRF-based termination reason will be summarized for all enrolled subjects.) Subjects' early termination details will be listed for all subjects enrolled.

Subjects' treatment sequence and dose, and treatment date and time will be listed for all subjects treated.

3.7 Protocol Deviations and Violations

A summary of protocol deviation and violations will be provided. Subjects who are treated in the study, but not included in the ITT population will be listed.

4 EFFICACY EVALUATION

4.1 Datasets Analyzed

The ITT population is defined as the population for effectiveness analysis.

4.2 Treatment Compliance

For this study, the overall compliance rate will be summarized by demographic parameters for the safety population. For a treatment session, the compliance rate, expressed as percent, is calculated by dividing the number of drug injections into the 4 locations of the submandibular and parotid glands by the total number of 4 injections that should have been given during a treatment session multiplied by 100. For a subject, the overall compliance rate is defined as the average of compliance rates for all treatment sessions.

4.3 Baseline Measures

Descriptive statistics of the USFR, DFSS-I, DFSS-S, CGI-S, PGI-S, and DIS at baseline (or pre-injection) will be summarized within their corresponding tables indicated in the sections below.

4.4 Efficacy Results and Tabulations

Descriptive and inferential statistics of USFR (g/minute) and changes from pre-injection at Day 1 to Weeks 4, 8 and 13, for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it respectively, will be presented for the ITT population.

Descriptive and inferential statistics of DFSS-I and changes from pre-injection at Day 1 to Weeks 4, 8, and 13, for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of DFSS-S and changes from pre-injection at Day 1 to Weeks 4, 8, and 13, for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of CGI-S and changes from pre-injection at Day 1 to Weeks 4, 8, and 13, for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of CGI-C at pre-injection (except for Day 1), and at Weeks 4, 8, and 13 for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of the proportion of the CGI-C treatment responders with much improved or better at pre-injection (except for Day 1) and at Week 4, 8, 13 weeks post injection for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of PGI-S and changes from pre-injection at Day 1 to Weeks 4, 8, and 13, for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of PGI-C at pre-injection (except for Day 1), and at Weeks 4, 8, and 13 for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of the proportion of the PGI-C treatment responders with much improved or better at pre-injection (except for Day 1) and at Week 4, 8, 13 weeks post injection for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

Descriptive and inferential statistics of DIS and changes from pre-injection at Day 1 to Weeks 4, 8, and 13 for Treatment Session 1 and from each subsequent pre-injection at Weeks 13, 26 and 39 (Treatment Session 2, 3 and 4) to 4 and 13 weeks following it, respectively, will be presented for the ITT population.

5 SAFETY EVALUATION

For safety evaluation, the safety population as defined in Section 3.1 will be utilized to conduct safety analyses.

5.1 Extent of Drug Exposure

Number of MYOBLOC dose injections will be tabulated as continuous variable as well as categorical variable, using the categories of 1 injection, 2 injections, 3 injections, and 4 injections.

Average duration and total duration of treatment sessions, following dose injection, will be also tabulated.

Individual subjects' number of treatment sessions and duration of treatment session will be listed for the safety population .

5.2 Early Termination

Early termination from study will be categorically summarized by subject population. Subjects' study termination details will be listed.

5.3 Adverse Events

An overall summary of AEs reported in this study will be provided for each treatment session.

Incidences of subjects reporting treatment-emergent AEs will be reported for each treatment session.

The severity of the treatment-emergent AEs will be summarized for each treatment session.

The relationship to study drug of the treatment-emergent AEs will be summarized for each treatment session.

Treatment-emergent AEs associated with early terminations will be summarized for each treatment session.

Serious AEs (including death) will be summarized for each treatment session.

Narratives will be presented for all deaths, non-fatal serious adverse events and subjects withdrawn due to adverse events.

Details of all TEAEs will be listed for each subject of the safety population in listings. Details of AEs associated with early terminations will be listed for individual subject. SAEs including deaths will be listed for each event.

5.4 Adverse Events of Special Interest (AESI)

Analyses of AESI will include aspiration, aspiration pneumonia, choking, and dysphagia. Incidences of subjects reporting AESI will be reported for each treatment session. Details of AESIs will be listed for individual subjects will be listed.

5.5 Adverse Events Associated with Dental Disease

Incidences of subjects reporting adverse events associated with dental disease, per sponsor-provided list, will be reported for each treatment session.

Table B – Listing of Dental Disease Terms used for Analysis

Term		
Angular cheilitis	Breath odour	Bruxism
Candida infection	Chapped lips	Dental caries
Dental leakage	Dental necrosis	Device failure
Gingival bleeding	Gingivitis	Glossitis
Glossodynia	Haemoptysis	Lip swelling
Mouth cyst	Mouth swelling	Mucosal inflammation
Mucosal ulceration	Oral candidiasis	Oral discomfort
Oral pain	Periodontitis	Pulpitis dental
Sensitivity of teeth	Stomatitis	Swollen tongue
Tongue coated	Tongue discolouration	Tongue dry
Tooth abscess	Tooth fracture	Tooth infection
Tooth injury	Tooth loss	Toothache

Details of AEs associated with dental disease will be listed for each subject.

5.6 Adverse Events Associated to Distant Spread of Toxin Effect

Incidences of subjects reporting adverse events associated with distant spread of toxin effect per the Agency-provided list will be reported for each treatment session.

Table C – Listing of Distant Spread of Toxin Effect Terms used for Analysis

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

Details of adverse events associated with distant spread of toxin effect will be listed for each subject.

5.7 Vital Signs and Weight

For the safety population, descriptive statistics of vital signs and weight will be presented at pre-injection and post-injection time points for pulse, systolic BP, diastolic BP,

temperature, and respiratory rate as well as body weight for Treatment Session 1, Treatment Session 2, Treatment Session 3 and for Treatment Session 4.

5.8 Neurologic Exam

For the safety population, abnormal findings of neurological exam data will be listed, respectively, for individual subjects.

5.9 Lung Functioning Test

For the safety population, findings of forced vital capacity (FVC) data will be listed, respectively, for individual subjects.

5.10 Physical Examination

Clinically abnormal findings from the physical examinations are either reported with the medical history if they occurred prior to 1st injection or as adverse events if findings are after first injection.

5.11 Clinical Laboratory Evaluation

For the safety population, descriptive statistics of clinical laboratory tests will be presented at screening and end of treatment session respectively, for hematology, chemistry, and urinalysis (specific gravity and pH) for Treatment Session 1, Treatment Session 2, Treatment Session 4 as well as End of Study. Qualitative findings in terms of abnormal low, normal, and abnormal high at screening and end of treatment session will be tabulated for hematology, chemistry, and urinalysis, respectively, for Treatment Session 1, Treatment Session 2, Treatment Session 4 as well as End of Study.

Any clinically significant abnormalities (based upon laboratory ranges) observed during the study will be listed for hematology, chemistry, and urinalysis, as well as pregnancy test.

5.12 Suicidality Assessment

For the safety population, descriptive and inferential statistics of C-SSRS will be presented at pre-injection and post-injection time points, for each of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation) for Treatment Session 1, Treatment Session 2, Treatment Session 3, and for Treatment Session 4. The change scores in C-SSRS subscales from pre-injection at 4 weeks, 8 weeks (first Treatment Session only), and 13 weeks post-injection were summarized descriptively.

5.13 Dental and Oral Examinations

Abnormal findings of dental and oral examination will be listed, respectively, for individual subjects.

5.14 Concomitant Medication

Concomitant medications were grouped into those taken pre-enrollment and those taken post-enrollment, based upon the starting date of both the concomitant medication and the enrollment date. Number and percent of subjects who take concomitant medications are reported for each Treatment Session. Concomitant medications will be listed, respectively, for individual subjects.

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SAP SN-SIAL-351

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22Jul2018
Page 28 of 36

6 REFERENCE

Study Protocol No. SN-SIAL-351