Statistical Analysis Plan

Protocol Title:	A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Single-Treatment Efficacy and Safety Study of MYOBLOC® in the Treatment of Adult Upper Limb Spasticity Followed by an Open-Label Extension, Multiple-Treatment Safety Study of MYOBLOC®
Protocol Number:	SN-SPAS-201
Investigational Drug	MYOBLOC® (rimabotulinumtoxinB)
Protocol Version No./ Date	Amendment 4 / 06Oct2016
Sponsor	Solstice Neurosciences, LLC, a subsidiary of MDD US Operations, LLC 9715 Key West Avenue Rockville, MD 20850
Statistical Analysis Plan	Version 2-Final
Statistical Analysis Plan Date:	09May2023

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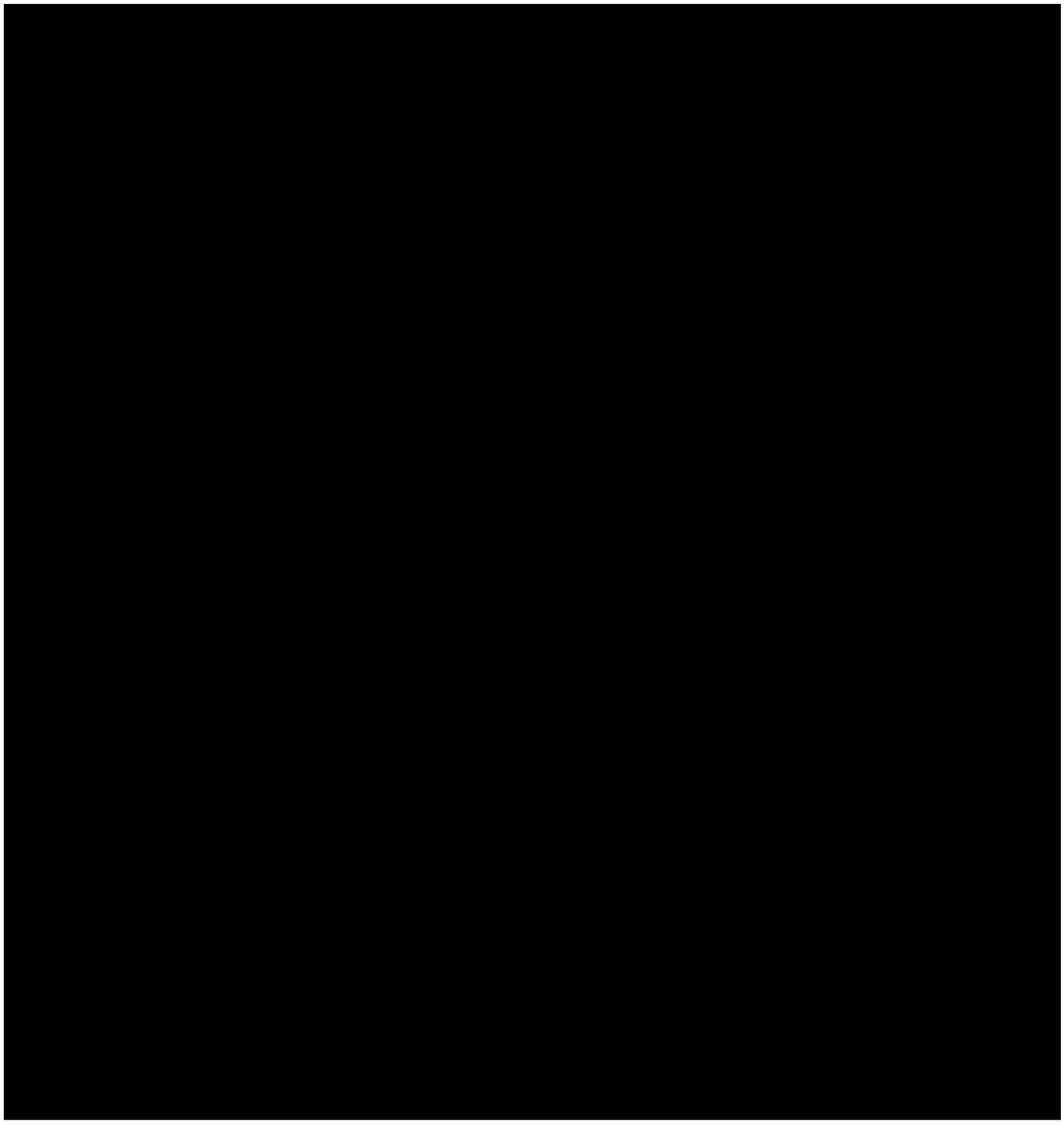

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1 INTRODUCTION

Protocol SN-SPAS-201 is a phase 2/3, multicenter, randomized, double-blind, placebo-controlled, single-treatment efficacy and safety study of MYOBLOC® in the treatment of adult upper limb spasticity followed by an open-label extension, multiple-treatment safety study of MYOBLOC®. [redacted]

This statistical analysis plan (SAP) will describe methods for presenting all data collected during the conduct of the clinical trial. Final Version 1.3 Dated 14DEC2016, cannot be implemented. This SAP will supersede the SAP Version 1.3 Dated 14DEC2016.

2 DATA FOR ANALYSES

2.1 Efficacy

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

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2.2 Safety

- Adverse events (AE)
- Clinical laboratory test results
- Vital signs
- 12-Lead Electrocardiogram (ECG) results
- Weights
- Physical examination
- Neurologic examination
- Pulmonary function tests (PFTs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

3 STATISTICAL ANALYSES

All statistical analysis will be performed using SAS version 9.2 or higher.

Continuous variables will be summarized descriptively by presenting number of subjects (n), mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum.

Categorical variables will be summarized with counts and percentages. When the denominator for the percentage is different from the number of subjects in the treatment column header, the denominator will be clearly specified in a footnote for the table.

Individual subject data listings will be provided by double-blind treatment group and subject ID. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis in summary tables but will be included in data listings.

3.1 Baseline Definition

For the double-blind period (DBP), baseline is defined as the last non-missing assessment recorded before or at the initiation of the study medication (SM). For the open-label extension (OLE), baseline is defined as the last non-missing value collected prior to the first dose of the SM in the OLE phase.

3.2 Analysis Population

3.1.1 Randomized Population (DB only)

The Randomized Population is defined as all subjects who are randomized to an active treatment or placebo.

3.1.2 Safety Population

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

3.1.3 Modified Intent-to-Treat (MITT) Population

For the DBP, the Double-Blind MITT is defined as all subjects who are injected with study drug, have baseline and have at least one valid post-baseline measurement recorded for either co-primary endpoint (MAS or CGI-C) in the eCRF in the DBP of the study.

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

3.3 Study Subjects and Demographics

3.3.1 Subject Disposition

Subject disposition will be summarized descriptively and separated for the DBP and OLE. Randomized and MITT population will be summarized by planned treatment group. Safety

population will be summarized by actually treatment received. Disposition will include tabulations of the number and percentage of subjects in each of the following analysis populations.

- Randomized Population
- DBP Safety Population
- DBP MITT Population
- OLE Safety Population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study and primary reason for early discontinuation will be summarized. A summary of subject disposition will be presented. A summary of screen failed subjects with reasons for screen failure will be provided. All disposition data will be listed.

3.3.2 Demographics and Baseline Characteristics

Subject demographic data (age, sex, race, and ethnicity) and baseline characteristics (body weight, height, Body Mass Index [BMI], other baseline characteristics) will be summarized by treatment group and overall using descriptive statistics for continuous variables and by the number and percent of subjects for categorical variables. All demographic data and baseline characteristics will be listed.

3.3.3 Drug Exposure

For DBP portion, the study drug injection amount (units) and number of injection sites will be summarized by treatment group, injection location (muscle group) and muscle. For the OLE portion, the study drug injection amount (units) and number of injection sites will be summarized by Visit, injection location (muscle) and limb (if applicable). All data collected for drug administration will be listed.

3.3.4 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. All medical and psychiatric history will be listed for the safety population.

3.3.5 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Global version March 2021and will be summarized and listed for the safety Population.

3.4 Efficacy

All efficacy data will be listed by double-blind treatment group and subject ID

3.4.1 Modified Ashworth Scale (MAS)

The observed MAS score and change from Baseline in MAS for each muscle group will be summarized by treatment group and visit separated for the DBP and OLE.

3.4.2 Clinical Global Impression of Change (CGI-C)

The observed CGI-C score will be summarized and listed by treatment group and visit separated for the DBP and OLE.

3.5 Safety Analyses

All safety analyses will be based on safety population.

3.5.1 Adverse Events

All adverse events (AEs) will be coded using the MedDRA Version 24.0. A treatment-emergent adverse event (TEAE) is defined as an AE with a start date on or after the first treatment injection, or that worsened following first administration of study drug. TEAE relatedness to study medication (SM) assessed by the investigators will be summarized for binary groups as "Related" if the relationship to SM is definitely, possibly, or probably related, or "Not Related" if the relationship to SM is definitely not related.

Overall TEAEs will be summarized. All TEAEs including those that may be indicative of Distant Spread of Toxin (DSOT), serious adverse events (SAEs), TEAEs Leading to Study Drug Discontinuation and will be summarized by system organ class (SOC) and preferred term (PT).

TEAEs will be further summarized by SOC, PT and maximum severity as well as by SOC, PT and relationship to SM. All AE tables will be presented by double-blind treatment group for the DBP and overall, for the OLE. All AE data will be listed.

3.5.2 Clinical Laboratory Tests

Clinical laboratory tests include those for hematology, biochemistry, and urinalysis.

Change from baseline values for hematology, serum chemistry, and urinalysis variables will be calculated for each post-dose visit. Clinical laboratory test results will be summarized descriptively by treatment and time point as both observed values and change from baseline values. Continuous variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum, and maximum by treatment group and visit. Urinalysis qualitative parameters will be reported with the number and percentage of subjects in each category.

For visit-based summary tables, in the event of repeat assessments within visit window, the first non-missing value will be used in the tabulations. Results from unscheduled visits will not be included in this summary but will be included in the data listing.

All laboratory data will be listed.

3.5.3 Vital Signs

The analyses will be the same as described in Section 3.5.2 for each vital sign parameter. All vital signs data will be listed.

3.5.4 ECG

The analyses will be the same as described in Section 3.5.2 for each ECG parameter.

In addition, the number and percentage of subjects whose QT interval or QT interval corrected for RR interval using Fridericia's correction formula (QTcF) are within the following ranges at any post baseline visit will be presented by treatment group separated by DBP and OLE.

Actual (observed) values:

- ≤450 msec
- >450 msec to ≤480 msec
- >480 to ≤500 msec
- >500 msec

Changes from baseline values:

- ≤30 msec
- >30 msec to ≤60 msec
- >60 msec

All ECG data will be listed.

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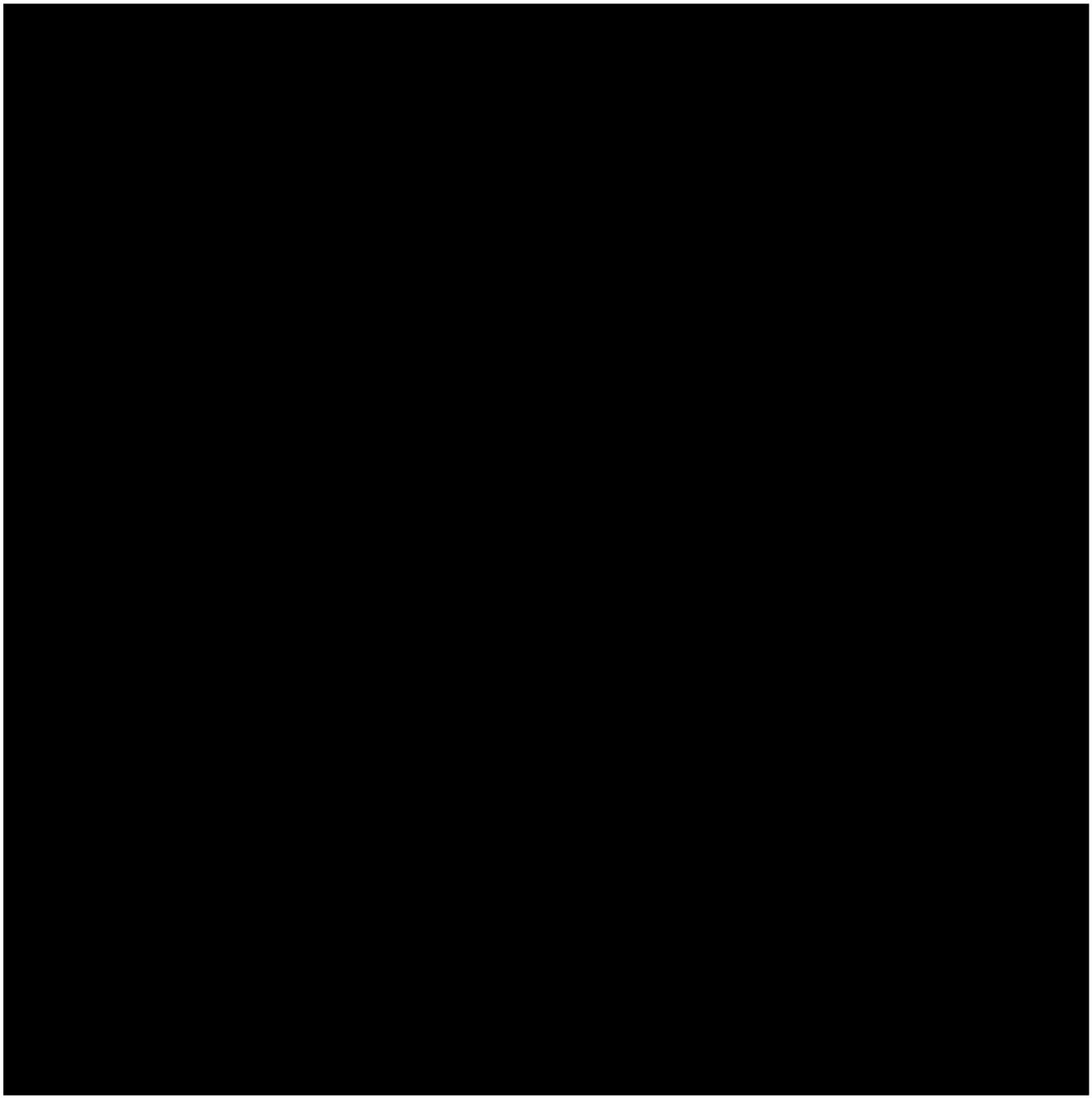
3.5.5 Columbia Suicide Severity Rating Scales (C-SSRS)

Columbia Suicide Severity Rating Scale (C-SSRS) will be listed for the Safety Population.

3.5.6 Other Safety Endpoints

Physical examination, Neurologic Examination Tests and Pulmonary Function Tests will be listed.



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