NLS Study Code: *SPI-1005-251*	Short Title of Study: *SPI-1005-251 (Sound Pharmaceuticals, Inc)*

STATISTICAL ANALYSIS PLAN	
Study Title:s	A Phase 2b, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of SPI-1005 in Meniere's disease
Sponsor Identification:	Sound Pharmaceuticals, Inc.
Phase:	Phase 2b
Sponsor Study Number:	SPI-1005-251
EA Study Number:	SPI-1005-251
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Date of SAP:	30MAY2019
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1 DOCUMENT HISTORY

Version	**Date**	**Change to previous version**
Final 1.0	30MAY2019	Nil

2 ABBREVIATIONS

ABBREVIATIONS	DEFINITION
AE	Adverse Event
AE(DAE)	Discontinuation of the study due to Adverse Events
ATC	Anatomical Therapeutic Chemical Classification
AUC_{0-t}	Area under the curve time 0 to time t
Bid	Twice-daily dosing
BMI	Body Mass Index
CBC	Complete Blood Count
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
dB	decibel, 1/10th of a Bel—measure of ratios on a logscale
dBHL	dB Hearing Level
EXP	Exponential
GCP	Good Clinical Practice
G.Mean	Geometric Mean
Hz	Hertz—unit of measure for frequency
IQR	Inter Quartile Range
ICH	International Conference on Harmonization
LCMS	Liquid Chromatography-Mass Spectrometry
mg	milligram
MD	Meniere's disease
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
Min	Minimum
NA	Not Applicable
PI	Principal Investigator
PK	Pharmacokinetics

Po	By mouth
PTA	Pure-Tone Audiometry
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SIC	Subject Identification Code
SNR	Signal-to-Noise Ratio
SPI	Sound Pharmaceuticals, Inc.
SQRT	Square Root
TFI	Tinnitus Functional Index
TL	Tinnitus Loudness
TTS	Temporary Threshold Shift
VSS	Vertigo Symptoms Scale
WINT	Words-in-Noise Test

3 DOCUMENTS

This statistical analysis plan is based on the study protocol SPI-1005-251, version 1.00 dated 21AUG2017.

4 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the relevant sections of study protocol and includes also the Tables, Listings and Figures (TLF) Specifications. The purpose of the SAP is to describe in more detail how the analyses are to be performed and presented. It quotes the relevant statements directly from the protocol, but it does not give a full description of study design etc.
The TLF Specifications specify the output to support the analysis. The TLF Specifications are considered as a guideline for producing the output.
The SAP will be finalized prior to database lock or any unblinding of study team members.
The objectives of this Phase 2b, randomized, double-blind, Placebo-controlled study are to demonstrate the safety and efficacy of SPI-1005 for the treatment of Meniere's disease.

5 STUDY OBJECTIVES

5.1 Primary Objectives

- To determine the Safety of SPI-1005 treatment in adults with Meniere's disease.
- To determine the Efficacy of SPI-1005 with the following clinically validated methods and measures (responder analysis):
  - Primary pure-tone audiometry assessment (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 1 frequency
  - Secondary pure-tone audiometry assessments (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 2 adjacent frequencies or ≥20 dB at 1 frequency
  - Primary Words-in-Noise Test assessment (0-35): Improvements from baseline of ≥10%
  - Secondary Words-in-Noise Test assessments (0-35): Improvements from baseline of ≥20% or ≥4 words
  - Tinnitus Functional Index (TFI): (0-100) ≥ 10 pt. reduction from baseline
  - Tinnitus Loudness: Q#2 of TFI: (0-10) ≥ 2 pt. reduction from baseline
  - Vertigo Symptom Scale (0-60): ≥ 6 pt. reduction from baseline

The responder analysis from each method and measure will be compared between treatment groups for significance.

• The efficacy of SPI-1005 treatment in adults with Meniere's disease will be based on:

- Improvement in sensorineural hearing loss using pure-tone audiometry at 250, 500, or 1000 Hz; or

- Word recognition score using WINT at 24, 20,16, 12, 8, 4 and 0 SNR; or
- Improvement in the Tinnitus Functional Index (TFI); or
- Improvement in Tinnitus Loudness (TL); or
- Improvement in the Vertigo Symptoms Scale (VSS)

5.2 Secondary Objectives

To determine the pharmacokinetics at each dosing level of SPI-1005.

6 STUDY DESIGN

6.1 Overview

This clinical trial is a phase 2b, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of SPI-1005 in Meniere's disease. The study is planned to be conducted in adult volunteers with Meniere's Disease (probable or definitive diagnosis) with active symptoms in the months preceding study enrollment. Study participants will be randomized into three dosing arms: SPI-1005 200 mg/BID, SPI-1005 400 mg/BID, or placebo (1:1:1). This double-blind study will evaluate both safety and efficacy of the investigational treatment.

Participants aged 18-75 years, with probable or definitive Meniere's disease will undergo baseline testing to assess severity of sensorineural hearing loss, tinnitus and vertigo. This is a multicenter study that includes patients from approximately 12 US sites.

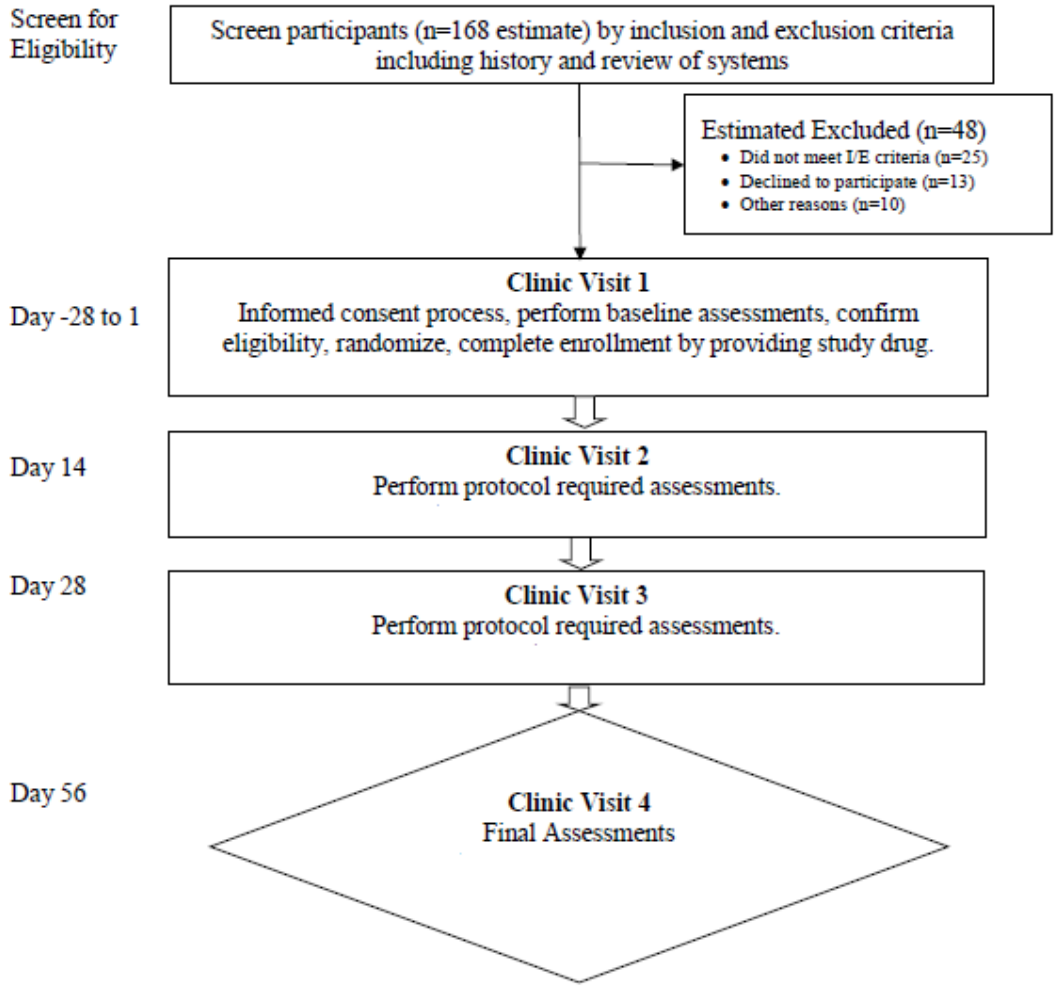
During the study, and 28 days after completion of treatment, participants will be evaluated for safety (adverse events, physical examinations, vital signs and clinical laboratory testing (CBC, serum chemistry). Trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be evaluated using liquid chromatography-mass spectrometry (LCMS) at specified visits. Additionally, plasma will be analyzed for selenium at the corresponding visits. Female participants will receive pregnancy testing at visit 1, and those found to be pregnant will be excluded from the study and monitored for adverse events.

The effect of SPI-1005 on hearing and balance will be evaluated. Hearing will be evaluated at baseline, at the end of 28 days of study treatment, and 28 days after completing study treatment. Tinnitus and vertigo will be evaluated with the Tinnitus Functional Index (TFI) and the Vertigo Symptoms Scale (VSS), respectively. These tests will be administered at baseline, on days 14 and 28

of treatment, and 28 days after treatment. Hearing thresholds (HL) will be determined using pure-tone audiometric (air conduction) testing at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz, bilaterally. In addition, bone conduction testing with masking will be conducted if the air conduction threshold is >15 dBHL at 250, 500, 1000, 2000, or 4000 Hz. Bone conduction testing will only be performed at screening and in the affected ear (>15 dBHL). A word recognition test using the Words-in-Noise Test (WINT) at 24, 20, 16, 12, 8, 4, and 0 Signal-to-Noise ratio (SNR) will be used to evaluate hearing.

Following completion of informed consent process and baseline assessments, the study participants will be evaluated by the investigator for enrollment eligibility. Participants that meet enrollment criteria will be randomized and assigned a Subject Identification Code from the list of Subject Identification Codes. The Subject Identification Code must be carefully matched to the study drug before the study drug is dispensed at Clinic Visits 1, and 2.

A general diagram of the study design is provided in **Figure 1**.



6.2 Parameters

All parameters through which the study objectives will be carried out, should be listed. Exact computations will be declared in section 7.8 Definitions and Derived Variables.

6.2.1 Primary Parameter

- Efficacy of SPI-1005 will be determined by the following clinically significant methods and measures (responder analysis):
- Pure-tone audiometry assessment (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 1 frequency
- Words-in-Noise Test assessment (0-35): Improvements from baseline of ≥10%
  - Tinnitus Functional Index (TFI) (0-100) ≥ 10 pt. reduction from baseline

- Tinnitus Loudness: Q#2 of TFI (0-10) ≥ 2 pt. reduction from baseline
- Vertigo Symptom Scale (0-60) ≥ 6 pt. reduction from baseline

6.2.2 Secondary Parameters

Pharmacokinetics parameters will be analyzed for the following parameters:

1. AUC_{0-t} (mg_h/L)
2. C_{max} (mg/L)

6.2.3 Safety Parameters

- Safety of SPI-1005 treatment in adults with Meniere's disease will be analysed using:
  - Physical examinations
  - Vital signs
  - Adverse events
  - Hematology (CBC)
  - Serum chemistries.

6.2.4 Exploratory Parameters

- Secondary pure-tone audiometry assessments (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 2 adjacent frequencies or ≥20 dB at 1 frequency
- Secondary Words-in-Noise Test assessments (0-35): Improvements from baseline of ≥20% or ≥4 words

7 GENERAL STATISTICAL CONSIDERATIONS

7.1 Descriptive Statistics

The following descriptive statistics will be calculated for continuously distributed data:

- n
- Mean
- Standard Deviation (also denoted as SD)
- Minimum (also denoted as Min)
- Median
- Maximum (also denoted as Max)
- Inter Quartile Range (IQR)

For categorical variables, counts and percentages will be calculated.

For continuous variables, the decimal places for n, minimum and maximum will be provided as per the reported value. Decimal places for mean, Q1, Q3 and median will be reported one decimal place more than the reported value. The decimal place for standard deviation will be reported two decimal places more than the reported value.

In all statistical tables, p-values will be reported as specified by the statistical program used, at least up to three decimal places. P-values less than 0.001 will be reported as provided by SAS®, Version 9.2 or higher (e.g. '<0.0001'). All tests will be two-sided at the $\alpha = 0.05$ level of significance, if not stated otherwise.

In by-visit summary tables only scheduled visits will be presented. All visits (both scheduled and unscheduled) will be presented in listings.

7.2 Randomization and Blinding Process

This study is a randomized, double-blind, placebo-controlled study design. Patients will be randomized to treatment, either placebo or two different doses of SPI-1005 (1:1:1).
Study center and sponsor personnel involved in the conduct and interpretation of the study will not have access to treatment codes. Laboratory personnel, and contracted designees of SPI who statistically analyze the data, will be blinded to the study treatment received by each study participant. The bioanalytical staff analyzing PK samples will be provided a copy of the random codes but will not report unblinded data until after database lock. The sponsor's medical monitor will receive each treatment code in individual envelopes for use in emergency unblinding.

Apart from this, the data management and biostatistics team will be blinded until the database closure. The lead statistician will receive a copy of the unblinded treatment group after the database lock upon receiving a written authorization from the head of Biometrics/Statistics Lead from Sound Pharma to unblind the study.

7.3 Analysis Population

7.3.1 Randomized Population

The randomized population includes all patients who are randomized for treatments. Patients who have a missing randomization number will be included in this population. This includes patients who answer the question "Is the subject to be randomized?" = 'Yes" and with a non- missing "Subject Identification Code".

7.3.2 Intent-to-Treat (ITT) Analysis Population

The ITT Efficacy Analysis population includes all patients from the randomized population who have received at least one dose of study drug and who have an evaluated post baseline efficacy assessment. The efficacy assessments include the evaluation of:

- Non- missing Pure-tone audiometry at Visit 3 or Visit 4
- Non- missing Words-in-Noise Test at Visit 3 or Visit 4
- Non- missing Tinnitus Functional Index (TFI) at Visit 2 or Visit 3 or Visit 4
- Non- missing Tinnitus Loudness (TL) at Visit 2 or Visit 3 or Visit 4
- Non- missing Vertigo Symptom Scale (VSS) at Visit 2 or Visit 3 or Visit 4

7.3.3 Safety Analysis Population

All study participants receiving at least one study treatment dose will be included in the safety analysis, whether or not they complete the study. The safety population is derived from the patients with evidence of receiving the study treatment in the "Drug Accountability" and eCRF form met with the following criteria:

- "Study Medication dispensed?" as 'Yes' and
- "Date of Dispensing" and
- The value entered for "Number of Capsules Taken" is greater than or equals 1 (missing values are excluded)

The safety population will be the primary population for the safety analysis. Analyses on the safety population will be based on actual treatment received.

7.3.4 Per-Protocol Population

The Per-Protocol Population includes all patients who receive study treatment and have efficacy parameters at Visit 3 and have no major protocol deviations.

The major protocol deviations include:

- Treatment compliance of <80% and >120%
- Did not meet inclusion/exclusion criteria
- Baseline overall WINT score ≥ 2x Standard Deviations above the mean (rounded down to nearest integer)
- Major protocol deviations impacting the primary efficacy outcome measure.

7.3.5 PK Analysis Population

The PK analysis population includes all randomized patients performing PK evaluations, with the study medication compliance, and have a PK profile at all visits. The patients with major protocol deviations impacting PK results will be excluded from the analysis.

7.4 Protocol Violation

Protocol deviations will be summarized by deviation category and treatment group. This analysis will be performed for all randomized patients.

7.5 Data Handling

7.5.1 Imputation of Missing data

Imputation for missing values are not applicable.

7.6 Sample Size Calculation

120 male and female adults with probable or definitive Meniere's disease. This Phase 2b study (SPI-1005-251), is adequately powered to demonstrate a 50% improvement in a symptom of MD using the responder analysis detailed in below with 40 study participants per treatment group.

7.7 Interim Analysis

There is no interim analysis planned for this study.

7.8 Definitions and Derived Variables

For the statistical analysis, two different doses and placebo will be denoted according to the following table.

Treatment	**Label**
SPI-1005 po BID 200mg	SPI-1005 200 mg
SPI-1005 po BID 400mg	SPI-1005 400 mg
Placebo po BID	Placebo

In the following table, the definitions and calculation of derived variables are summarised.

Variable / Term	**Definition / Way of calculation**
Baseline	The last assessment on or before to the treatment start date. The most recent measurement prior to treatment start regardless of whether the measurement is collected at a scheduled or unscheduled visit will be considered for the baseline.
End of study	The date on which the last patient completes the last visit (includes follow-up visit).
BMI	Weight in kg / Height in m^2
Treatment Start	The earliest date of 'date of drug dispense' (Date of dispensing) from Study Drug Dispensing and Drug Accountability eCRF form, where the patient has: • Answered 'Yes' to question, Study medication dispensed? And, • Recorded at least one capsule used for the question, 'Number of capsules taken' If the drug administration date is unavailable and only the last dose date of the patient is available, then the Randomization date will be considered as the treatment start date.

Variable / Term	Definition / Way of calculation
Treatment End	The treatment end date is taken from the field: 'Date of last study medication taken' from 'Study Completion or Early Termination' page. If the 'Date of last study medication taken' is missing and there is evidence that the patient has taken the study medication, the last visit date will be considered as 'Treatment end date'.
Treatment Emergent AE (TEAE)	An adverse event (AE) will be considered as treatment-emergent if the time of onset is on or after the time of the first randomized study drug administration (treatment start date).
Duration of exposure	Treatment end date - treatment start date + 1, refer to section 8.2.1 in SAP for details
Treatment compliance	(Total number of capsules used/Total number of capsules to be taken) *100, refer to section 8.2.2 in SAP for details
Geo CV%	sqrt(exp(log SD)-1)*100

7.9 Statistical Software

All statistical analyses will be performed with SAS®, Version 9.2 or higher on a MS-Windows platform.

8 STATISTICAL ANALYSES

8.1.1 Subject Disposition

The number of patients who have completed the study or early termination from the study and reasons for discontinuations will be grouped by treatment. The summary of patient disposition will be tabulated for all randomized, safety, ITT and PK analysis populations.

8.1.2 Inclusion/Exclusion Criteria

The number and percentage of patients violating each inclusion/exclusion criterion will be presented by criterion. Violation of inclusion/exclusion criteria will be listed.

8.1.3 Demographic Data and Baseline Characteristics

Demographic characteristics include age, gender, ethnicity. Baseline characteristics include height, weight, BMI, TFI, VSS, PTA and WINT.

Frequency and percentage will be presented for gender, ethnicity. Descriptive statistics will be presented for age (years), height (cm), weight (Kg), BMI (kg/m^2). These analyses will be performed for the Randomized, Safety, ITT and Per-Protocol populations.

Demographic and baseline characteristics will be presented in the by-patient listings. A data listing will be produced for the randomization details.

8.1.4 Medical History

Medical history terms will be coded using MedDRA dictionary version 19.1.

Medical history will be summarized by MedDRA system organ class and preferred term for safety population. All medical history will be listed by patient and treatment group.

8.1.5 Prior and Concomitant Medication

Prior and concomitant medications will be assessed at screening and at each subsequent study visit. Medications will be coded using WHO Drug Dictionary version MAR2017.

Medication will be classified as prior, if the end date is known and is before the first use of the study medication. Medications that are ongoing or ended after the first use of the study medication will be classified as concomitant. If the end date of the medication is unknown, it will also be considered concomitant. If the end date is partially known, the medication will be considered concomitant, unless the known part of the end date rules out the possibility that the medication could have ended before the start of the study drug.

Prior and concomitant medications will be separately summarized by ATC class (the highest available level) and preferred name for the safety population. The prior and concomitant medications will be listed in a by-patient listing.

8.2 Extent of Exposure and Compliance

8.2.1 Treatment Exposure

Treatments will be dispensed at baseline to patients based on the randomized group assignments and the patients will receive the treatment for a duration of 28 days.

The earliest date of 'date of drug dispense' (Date of dispensing) from Study Drug Dispensing and Drug Accountability eCRF form, where the patient has:

- Answered 'Yes' to question, 'Study medication dispensed?' and,
- Recorded at least one capsule used for the question, 'Number of capsules taken'

If the drug administration date is unavailable and the last dose date of the patient is only available, then the Randomization date will be considered as treatment start date.

The treatment end date is taken from the field:

- 'Date of last study medication taken' from 'Study Completion or Early Termination' page. If the date of last study drug administration is missing and there is evidence that the patient has taken study medication, last visit date will be considered as 'Treatment end date'.

- Duration of treatment exposure is derived as treatment end date - treatment start date + 1

The duration of treatment exposure will be summarized descriptively by treatment group for safety population. Data listing will be presented for study drug administration.

8.2.2 Treatment Compliance

Treatment compliance is defined as intake of 80% to 120% of the dispensed capsules by an individual patient during the treatment period. Hence the compliance is computed as:

- (Total number of capsules used/Total number of capsules to be taken) *100

Where the total number of capsules used is derived as the sum of results recorded for the question 'Number of capsules taken' in the drug accountability form.

Data listing also will be presented for treatment compliance.

8.3 Efficacy Analysis

8.3.1 Analysis of Primary Endpoint

Primary analyses will use the Per-Protocol analysis population and Intent-To-Treat analysis population.

8.3.1.1 Pure-Tone Audiometry

Pure-tone audiometry (PTA) will be measured at visit 1, visit 3 and visit 4.

Both the actual ear value and calculated change from baseline PTA data will be summarized by visits and treatment groups.

PTA data will be analyzed with a mixed-effects model for repeated measures, and a post-hoc Bonferroni correction analysis with significance set to 0.05. The calculated change of PTA data will be calculated by the difference of the actual ear value at baseline and the actual ear value at each visit post baseline. The primary assessment of PTA data will consider a ≥10 dBHL improvement from baseline as a clinically relevant response (only low frequency: 250, 500, 1000 Hz). The secondary assessments of PTA data will consider an improvement from baseline of ≥10 dBHL at two adjacent frequencies or ≥20 dBHL at one frequency as clinically relevant responses (only low frequency: 250, 500, 1000 Hz). The final processed data will be analyzed using a chi-square test or Fisher's Exact test to assess the improvement between treatment groups.

8.3.1.2 Words-in-Noise Test

The Words-in-Noise Test (WINT) will be measured at visit 1, visit 3 and visit 4.

Both the actual ear value and calculated change from baseline WINT data will be summarized by visits and treatment groups.

WINT data will be analyzed with a mixed-effects model for repeated measures, and a post-hoc Bonferroni correction analysis with significance set to 0.05. The calculated change of WINT data will be calculated by the difference of the actual ear value at baseline and the actual ear result at each visit post baseline. The primary assessment of WINT data will consider a ≥10% improvement from baseline as a clinically relevant response. The secondary assessments of WINT data will consider an improvement from baseline of ≥20% or ≥4 words as clinically relevant responses. The final processed data will be analyzed using a chi-square test or Fisher's Exact test to assess the improvement between treatment groups.

8.3.1.3 Tinnitus Functional Index (TFI)

The Tinnitus Functional Index (TFI) will be measured at visit 1, visit 2, visit 3 and visit 4.

The actual patient reported outcome (PRO) value and change from baseline TFI will be summarized by visits and treatment groups.

TFI will be analyzed as a composite score and for the following individual subscales: Intrusiveness, Sense of control, Cognition, Sleep, Auditory, Relaxation, Quality of life, and Emotional.

The overall total score will be calculated by the sum of all valid answers from both TFI pages and will be divided by the number of questions for which that respondent provided valid answers and then multiplied by 10.

SUBSCALE NAME	**ITEMS IN SUBSCALE**
INTRUSIVE	#1, #2, #3
SENSE OF CONTROL	#4, #5, #6
COGNITIVE	#7, #8, #9
SLEEP	#10, #11, #12
AUDITORY	#13, #14, #15
RELAXATION	#16, #17, #18
QUALITY OF LIFE (QOL)	#19, #20, #28, #22
EMOTIONAL	#23, #24, #25

Each of the 8 subscales consists of 3 items (except for the Quality of life subscale, which consists of 4 items). For subscale scores to be valid no more than 1 item should be omitted. Computation of subscale scores is calculated as:

1) Sum all respondent's valid answers for a given subscale.

2) Divide that number by the number of valid answers that were provided by that respondent for that subscale.

3) Multiply by 10. For the respondent in question, this procedure generates a subscale score in the range 0-100 for each valid subscale.

Overall TFI score is not valid if the respondent omits seven or more items. To be considered a valid measure of tinnitus severity, the respondent must answer at least 19 items.

The TFI data will be analyzed with a mixed-effects model for repeated measures, and a post-hoc Bonferroni correction analysis with significance set to 0.05. The calculated change of TFI data will be calculated as the difference of the PRO value at baseline and the PRO value at each post baseline timepoint. The improvement will be considered only if the difference between post baseline and baseline value is ≥10 pts. The final processed data will be analyzed using a chi-square test or Fisher's Exact test to assess the improvement between treatment groups.

8.3.1.4 Tinnitus Loudness

Tinnitus loudness (TL) will be measured at visit 1, visit 2, visit 3 and visit 4. TL is assessed from question number two of the TFI.

The actual patient reported outcome (PRO) value and change from baseline for TL will be summarized by visits and treatment groups. TL data will be analyzed with a mixed-effects model for repeated measures, and a post-hoc Bonferroni correction analysis with significance set to 0.05. The calculated change of TL data will be calculated as the difference of the PRO value at baseline and the PRO value at each post baseline timepoint. The improvement will be considered only if the difference between post baseline and baseline value is ≥2 pts. The final processed data will be analyzed using a chi-square test or Fisher's Exact test to assess the improvement between treatment groups.

8.3.1.5 Vertigo Symptom Scale

Vertigo Symptom Scale (VSS) will be measured at visit 1, visit 2, visit 3 and visit 4.

The actual patient reported outcome (PRO) value and change from baseline for VSS will be summarized by visits and treatment groups.

VSS will be analyzed for Total Scale, Vertigo/balance sub-scale and Autonomic/anxiety sub-scale. The Vertigo/balance sub-scale will be calculated as the sum of questions 1, 3, 4, 6, 8, 10, 13 and 15. The Autonomic/anxiety sub-scale will be calculated as the sum of questions 2, 5, 7, 9, 11, 12 and 14. The range for the Vertigo/balance sub-scale will be 0 – 32 and the range for Autonomic/anxiety sub-scale will be 0 – 28.

VSS data will be analyzed with a mixed-effects model for repeated measures, and a post-hoc Bonferroni correction analysis with significance set to 0.05.

The calculated change of VSS data will be calculated as the difference of the PRO value at baseline and the PRO value at each post baseline timepoint. The improvement will be considered only if the difference between post baseline and baseline value is ≥6 pts. The final processed data will be analyzed using a chi-square test or Fisher's Exact test to assess the improvement between treatment groups.

8.4 Safety Analysis

8.4.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 19.1), the coded terms will be used for summarizing the AE(s).

An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first randomized study drug administration. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the study drug start date. If the start date is partially missing, AE will be considered treatment-emergent unless the known part of the start date or the end date rules out that it occurred after the start of the study drug.

An overall summary table which summarizes, the number and percentages of patients with adverse events, treatment emergent adverse events, serious adverse events, adverse events leading to death and adverse events related to study drug will be provided by treatment groups.

Patients experiencing any adverse events will be summarized by Preferred Term (PT), SOC and treatment. Furthermore, listings of SAEs and AEs that lead to withdrawal will be provided. The number and percentage of patients with at least one TEAE, SAE and discontinuation of study treatment due to AE (DAE) will be summarized by system organ class, preferred term and treatment group.

Adverse Events will be summarized by System Organ Class, Preferred Term and Treatment for Any Adverse Events, Serious Adverse Events, Adverse Events leading to medication discontinuation, Adverse leading to death, Adverse Events by severity, Adverse Events by outcome and Adverse Events by relationship.

A patient experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a patient experiences multiple AEs within the same system organ class that patient will be counted only once in that system organ class. In summaries by severity or by relationship, if a patient has the same AE on multiple occasions, the highest severity, and the closest relationship to study drug, respectively, will be used for summary.

All information pertaining to adverse events noted during the study regardless of treatment emergent or not will be listed by patient, detailing verbatim, preferred term, system organ class, start date, stop date, TEAE status, severity, outcome, action taken and causal relationship to the study drug.

8.4.2 Clinical Laboratory Evaluations

Blood samples for clinical safety laboratory assessments will be collected at the following time Visit 1, Visit 2, Visit 3 and Visit 4. The following parameters will be analyzed under these categories:

Hematology	Chemistry	
RBC	Sodium	Albumin
Hematocrit	Potassium	AST (SGOT)
Hemoglobin	Chloride	ALT (SGPT)
Platelets	Bicarbonate	GGT
WBC	Glucose	Total bilirubin
Neutrophils	Blood urea nitrogen (BUN) or Urea	Alkaline phosphatase
Lymphocytes	Creatinine	Uric acid
Monocytes	Calcium	LDH
Basophils	Magnesium	Cholesterol
Eosinophils	Inorganic phosphorus	Triglycerides
	Total protein	

Laboratory results will be summarized descriptively for actual and change from baseline values by visits and treatment for each category of clinical chemistry and hematology. In addition, baseline shift tables will be presented for the lab parameters by visits and treatmnts for laboratory categories, the results falling out of normal ranges will be classified as Normal, Abnormal High and Abnormal Low and will be used for the shift tables. The 'Normal', 'Abnormal Low' and 'Abnormal High' values are determined based on the laboratory normal ranges. The number and percentage of patients reaching 'Normal', 'Abnormal CS' and 'Abnormal NCS' results for laboratory parameters will be summarized All laboratory results will be listed in data listings, the abnormal values will be flagged in the listings.

8.4.3 Vital Signs

Vital signs will be measured at Visit 1, Visit 2, Visit 3 and Visit 4.

The vital signs parameters include:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (Beats/min)
- Oral Temperature (°C)

The actual and change from baseline vital signs parameters will be summarized descriptively by visits and treatment groups.

In addition, number and percentage of patients reaching 'Normal', 'Abnormal CS' and 'Abnormal NCS' results for vital signs parameters will be summarized by visits and treatment groups. Data listings will be presented for vital signs parameters.

Shift tables for the overall interpretation of vital signs parameters will be summarized by visits and treatment groups.

8.4.4 Physical examination

Physical examination will be performed at Visit 1, Visit 2, Visit 3 and Visit 4. Physical examination will include an examination of skin, HEENT (Otoscopic exam) Head/ Eyes/ Ears/Nose/Throat/Thyroid, Respiratory, Cardiovascular, Abdomen, Musculoskeletal, Neurological (and reflexes), Gastrointestinal, Endocrine, Lymph nodes and others.

A summary of these findings , number and percentages of patients achieving 'Normal', 'Abnormal CS', 'Abnormal NCS' will be presented by visit, body system and treatment group. Results will also be listed.

8.5 Pharmacokinetic Analysis

The PK analysis will be performed based on PK analysis population.

Three (3) mL of blood will be collected at visit 1, visit 2, visit 3 and visit 4. Study participants should be instructed to refrain from taking their morning dose until after their blood is drawn at Clinic Visit 2 and Clinic Visit 3. Sample collection times (actual clock time using 24:00) are to be recorded and will be captured in the CRF.

The patient listings as well as Patient's PK profile plots in actual and semi-logarithmic views will be prepared for the PK concentrations. Descriptive summary statistics table including geometric mean & CV% geometric mean will be presented by timepoints and treatment groups. In addition, mean ± SD graphs will be prepared for the concentration by timepoints and treatment groups.

Descriptive statistics including geometric mean & CV% geometric mean will be presented for the PK parameters, AUC_{0-t} (mg. h/L) and C_{max} (mg/L).

8.6 Multicentre Studies

Patients from thirteen sites in U.S. participated in the study and all the data across the sites will be presented.

8.7 Subgroup Analyses

Not Applicable

9 DEVIATION FROM THE STUDY PROTOCOL

The differences between study protocol and statistical analysis plan are summarised in the following table:

Change	Study Protocol	Statistical Analysis Plan
6.2 Study Objectives	The primary objective of this Phase 2 study is to determine the: • Safety of SPI-1005 treatment in adults with Meniere's disease. • Efficacy of SPI-1005 will be determined by the following clinically significant methods and measures (responder analysis): ▪ Pure tone audiometry (>30 dBHL at 250, 500 or 1000 Hz) >10 dB improvement from baseline ▪ Words in Noise Test (0-35) >10 % increase from baseline ▪ Tinnitus Functional Index (TFI) (0-100)	➢ To determine the Safety of SPI-1005 treatment in adults with Meniere's disease. ➢ To determine the Efficacy of SPI-1005 with the following clinically validated methods and measures (responder analysis): ▪ Primary pure-tone audiometry assessment: (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB Secondary pure-tone audiometry assessments (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 2 frequencies or ≥20 dB at 1 frequency ▪ Primary Words-in-Noise Test assessment (0-35): Improvements from baseline of ≥10% ▪ Secondary Words-in-Noise Test assessments (0-35): Improvements from baseline of ≥20% or ≥4 words ▪ Tinnitus Functional Index (TFI): (0-100) ≥ 10 pt. reduction from baseline

	>10 pt. reduction from baseline ▪ Tinnitus Loudness: Q#2 of TFI (0-10) >2 pt. reduction from baseline ▪ Vertigo Symptom Scale (0-60) >6 pt. reduction from baseline The responder analysis from each method and measure will be compared between treatment groups for significance. o Efficacy of SPI-1005 treatment in adults with Meniere's disease based on ▪ Improvement in sensorineural hearing loss using pure tone audiometry at 250, 500, or 1000 Hz; or ▪ Word recognition score using WIN testing at 24, 20,16, 12, 8, 4 and 0 SNR; or	▪ Tinnitus Loudness: Q#2 of TFI: (0-10) ≥ 2 pt. reduction from baseline ▪ Vertigo Symptom Scale (0-60): ≥ 6 pt. reduction from baseline The responder analysis from each method and measure will be compared between treatment groups for significance. • The efficacy of SPI-1005 treatment in adults with Meniere's disease will be based on: ➢ Improvement in sensorineural hearing loss using pure tone audiometry at 250, 500, or 1000 Hz; or ➢ Word recognition score using WINT at 24, 20,16, 12, 8, 4 and 0 SNR; or ➢ Improvement in the Tinnitus Functional Index (TFI); or ➢ Improvement in Tinnitus Loudness (TL); or ➢ Improvement in the Vertigo Symptoms Scale (VSS) **9.1.1 Exploratory Analysis** ▪ Primary pure-tone audiometry assessment: (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB

	▪ Improvement in the Tinnitus Functional Index (TFI); or ▪ Improvement in Tinnitus Loudness (TL); or ▪ Improvement in the Vertigo Symptoms Scale (VSS). ▪ The secondary objectives of this study are to determine the: • Pharmacokinetics of SPI-1005.	▪ Secondary pure-tone audiometry assessments (250, 500 or 1000 Hz): Improvements from baseline of ≥10 dB at 2 frequencies or ≥20 dB at 1 frequency ▪ Primary Words-in-Noise Test assessment (0-35): Improvements from baseline of ≥10% ▪ Secondary Words-in-Noise Test assessments (0-35): Improvements from baseline of ≥20% or ≥4 words

10 SOPS FOR ANALYSIS AND REPORTING

Ecron Acunova's standard operating procedures as well as the ICH guideline E9 will be applied to this analysis. The structure of post-text-tables and the appendices will be in accordance with the ICH guideline E3.

11 DATABASE LOCK AND UNBLINDING

After the data cleaning process is finalised according to the data management manual and the assignment of patients to the analysis population is agreed and signed by the sponsor, the data base will be locked. SAS datasets will be extracted from the data.

After the data base closure, unblinding of randomization will be initiated and the randomisation dataset will be prepared, and it will be validated by a second person.

NLS Study Code: *SPI-1005-251*	Short Title of Study: *SPI-1005-251 (Sound Pharmaceuticals, Inc)*

12 REFERENCES

Further references are given in the study protocol.

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