

STATISTICAL ANALYSIS PLAN

SPI-1005-351

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN MENIERE'S DISEASE AND OPEN LABEL EXTENSION STUDY TO EVALUATE THE CHRONIC SAFETY OF SPI-1005

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SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Sounds Pharmaceuticals, Inc. protocol SPI-1005-351.

The SAP should be read in conjunction with the study protocol and Electronic Case Report Form (eCRF). This version of the SAP has been developed using the protocol version 1.1 dated 08 Apr 2021.

1.1 Change from Protocol

The protocol version 1.1 (p. 10, 23) states, "Planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 56 after the start of study treatment (i.e., 28 days after cessation of dosing)."

Section 9 of this Statistical Analysis Plan version 2.0 states, "For the RCT, planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 84 after the start of study treatment. Endpoints will also be assessed at Day 28 and Day 56."

This change from protocol to assess endpoints at Day 84 is more consistent with the End-of-Phase 2 Meeting Minutes, which state, "You should plan to measure the primary endpoint three months after initiation of dosing. Including measurements of these endpoints at 4 and 8 weeks, as you proposed, in addition to the 12-week measurement for the co-primary endpoints, would be informative."

2 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of SPI-1005 capsules, 400 mg BID, administered for 28 days compared to placebo in patients with Meniere's disease. The safety of SPI-1005 capsules, 400 mg BID, administered open-label for up to 180 or up to 360 days, in patients with Meniere's disease will also be evaluated.

The safety of open-label extension of SPI-1005 treatment for up to 180 or up to 360 days will be determined by examining the toxicities and adverse events that are attributable to treatment.

3 STUDY DESIGNS

3.1 Overall Study Design

This study comprises a randomized, double-blind, parallel assignment, placebo-controlled study to evaluate the safety and efficacy of SPI-1005 Randomized Clinical Trial (RCT) and Open Label Extension (OLE) to evaluate the chronic safety of SPI-1005. Eligible subjects enrolled in the RCT to assess safety and efficacy will immediately rollover into the OLE for chronic safety.

Adult males and females, aged 18-75 years, with Meniere's disease will undergo the informed consent process and be enrolled in the study. Following the informed consent and screening procedures, subjects will be evaluated by the Investigator for eligibility. Eligible subjects will be assessed for baseline safety, audiometry, and vestibular function before being randomized to study treatment.

In the RCT, eligible subjects will be randomized by third party CRO to either SPI-1005 400 mg BID or matching placebo (1:1) and treated for 28 days. Subjects will return to clinic at 28, 56, and 84 days after the start of RCT study treatment for safety, audiometry, and vestibular assessments.

In the OLE, subjects will receive open label treatment with SPI-1005 400 mg BID for 180 days. A subset of subjects may continue the open label treatment for up to 360 days. Subjects will undergo monthly safety assessments via telehealth and will return to clinic approximately every 90 days after the start of OLE open label treatment for drug resupply, safety, audiometry, and vestibular assessments.

During the study, participants will be evaluated for safety: adverse events, physical exams, vital signs, clinical laboratory testing (Hematology (CBC), serum chemistry), suicidality. Trough plasma levels of ebselen and its major metabolite will be determined using liquid chromatography-mass spectrometry (LCMS) at specified visits. Additionally, plasma will be analyzed for selenium at the corresponding visits using inductively coupled mass spectrometry (ICPMS). Participants who are women of childbearing potential will receive pregnancy testing at specified visits, and those found to be pregnant will be excluded from the study and/or discontinued from study treatment and monitored for adverse events.

The effect of SPI-1005 on hearing and balance will be evaluated. Hearing loss, tinnitus, vertigo, dizziness, and aural fullness will be evaluated at baseline and at specified follow-up visits. Hearing thresholds (HL) will be determined using pure tone audiometry (air-conduction) 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 minimally in the affected ear (>15 dBHL). The Words-in-Noise Test will be performed at 24, 20, 16, 12, 8, 4, and 0 Signal-to-Noise ratio (SNR), bilaterally, to evaluate word recognition and hearing. Patient-reported outcomes will be used to evaluate vestibular symptoms by the following assessments: Tinnitus Functional Index (TFI) & Tinnitus Loudness (TL), Vertigo Symptoms Scale (VSS), Aural Fullness Scale (AFS), and Dizziness Handicap Inventory (DHI).

3.2 Number of Subjects

Up to 260 subjects will be screened for eligibility to achieve ≥200 completed subjects through the RCT.

3.3 Randomization and Blinding

In the RCT study component, eligible subjects will be randomized to SPI-1005 or placebo (1:1), and receive one of the following accordingly:

- 400 mg po BID for 28 days;
- Placebo po BID for 28 days.

The RCT study component is a randomized, double-blind, parallel assignment, placebo-controlled study design. The physical appearance of active and placebo capsules are identical. The study center and sponsor personnel involved in the conduct and interpretation of the study data will not have access to treatment codes. Laboratory personnel, and contracted designees of Sound Pharmaceuticals, Inc. (SPI) who statistically analyze the data, will be blinded to the study treatment received by each study participant until after database lock. The bioanalytical staff analyzing PK samples will be provided with a copy of the randomization 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.

Study participants who are eligible for enrollment and who take part in the RCT will be randomized according to the procedure established by the designated CRO. The designated CRO labeling the product maintains a confidential list of codes identifying the contents of each study drug bottle.

Table 1 shows the number of SPI-1005 and placebo study participants in each study treatment group.

Table 1 Approximate number of study participants randomized to each dose.

SPI-1005 (400 mg BID)	Placebo (BID)
100	100

If a study participant experiences a serious adverse event that requires unblinding, the Investigator will request decoding of the study participant's group assignment and drug product information through SPI.

In the OLE study component, eligible subjects will receive SPI-1005 open-label:

- 400 mg po BID for up to 180 days or up to 360 days.

3.4 Study treatment Groups and Duration

Enrolled subjects will receive either SPI-1005 or matching placebo during the RCT, and SPI-1005 during the open-label portion of the study.

The RCT study component comprises a minimum of 4 scheduled clinic visits over an 84-day period, whereas the OLE study component comprises a minimum of 3 to 5 scheduled clinic visits over a 180- or 360-day period.

4 ANALYSIS SETS

The analysis sets of the study are defined below:

4.1 Intent-to-Treat (ITT) Set

Subjects who were randomized and received at least one dose of study drug. Subjects in the ITT set will be analysed based on the study treatment they were assigned to. The ITT set will be used for tables of demography, safety, and efficacy, as well as other relevant listings. The ITT will be the primary analysis set for analysis of the co-primary efficacy endpoints.

4.2 Per-Protocol (PP) Set

Subjects who satisfy the ITT criteria and have no major protocol deviations that impact the primary efficacy endpoint. Subjects in the PP set will be analyzed based on the study treatment they were assigned to. The PP set will be used for efficacy tables only.

4.3 Safety Set

Subjects who were randomized and received at least one dose of investigational drug. The safety set will be analyzed based on the actual study treatment received and will be used for safety tables only.

4.4 Pharmacokinetic Set

Subjects who were randomized and has at least one pharmacokinetic sample. The pharmacokinetic set will be used to present the pharmacokinetic data only.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The efficacy of SPI-1005 will be determined by the following clinically significant methods and measures (co-primary):

- ≥ 10 dB improvement in low frequency hearing (250, 500, or 1000 Hz) by Pure Tone Audiometry (PTA) in patients treated with SPI-1005 compared to placebo; and
- ≥ 4 words improvement in Words-in-Noise Test (WIN) in patients treated with SPI-1005 compared to placebo.

5.2 Secondary Endpoints

Secondary efficacy endpoints are:

- Improvement in tinnitus loudness (TL) in patients treated with SPI-1005 compared to placebo.
- Improvement in tinnitus severity by Tinnitus Functional Index (TFI) in patients treated with SPI-1005 compared to placebo.
- Improvement in vertigo severity by Vertigo Symptoms Scale (VSS) in patients treated with SPI-1005 compared to placebo.
- Improvement in aural fullness by Aural Fullness Scale (AFS) in patients treated with SPI-1005 compared to placebo.
- Improvement in dizziness by Dizziness Handicap Inventory (DHI) in patients treated with SPI-1005 compared to placebo.
- ≥ 10 dB improvement in two adjacent low frequencies (250 and 500, or 500 and 1000 Hz) by Pure Tone Audiometry (PTA) in patients treated with SPI-1005 compared to placebo.
- $\geq 20\%$ improvement in Words-in-Noise Test (WIN) in patients treated with SPI-1005 compared to placebo.

5.3 Safety Endpoints

The safety parameters will include the physical exam, vital signs, adverse events, and abnormal laboratory findings (CBC, serum chemistry).

6 STATISTICAL CONSIDERATIONS

6.1 Descriptive Statistics

All data analysis will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF and PDF format for tables, listings, and figures using landscape orientation. All study data will be listed by study treatment group, subject and visit (as applicable).

Descriptive statistics will be used to summarize continuous and categorical variables. For continuous variables, sample size (n), mean, standard deviation (SD), median, minimum (min) and maximum (max) will be presented for summarization, while categorical variables will be summarized by the frequency and its percentage.

6.2 Sample Size Determination

The proposed Phase 3 RCT study design (N=200, 1:1 active and placebo) has sufficient power to reject the Type I error of the co-primary efficacy endpoints using a two-tailed test for significance. Comparison of PTA and WIN responder rates at 84 days from the start of study drug using Fisher's Exact Test:

- Assuming PTA responder rates observed in Phase 2b Study (SPI-1005-251), Active 61% vs Placebo 37%, power is 0.909.
- Assuming WIN responder rates observed in Phase 2b Study (SPI-1005-251), Active 60% vs Placebo 34%, power is 0.949.

6.3 Missing Data

Unless otherwise stated, missing data will be handled using the following approach:

- For start date, partial dates will have first day of the month imputed if day is missing, and January of that year will be imputed if month is missing. If both day and month are missing, January 01 will be imputed.

- For end date, partial dates will have last day of the month imputed if day is missing, and December of that year will be imputed if month is missing. If both day and month are missing, December 31 will be imputed.
- Missing dates of prior and concomitant medications will not be imputed.

In the Pure Tone Audiometry (PTA) dataset, hearing thresholds coded as 997 (Not Done, ND) or 999 (No Response, NR) will be treated as missing data.

In the Words-in-Noise Test (WIN) dataset, words correct coded as 9 (Not Done, ND) will be treated as missing data. If words correct at any SNR which would be used to calculate a total score is missing, then that total score will be treated as missing. Additionally, WIN scores corresponding to specific ears and timepoints where No Response values were recorded at all low frequencies (250, 500, and 1000 Hz) during PTA will be treated as No Response, i.e. treated as missing.

6.4 Baseline

For summary purposes, Baseline during the RCT will be defined as any assessment made prior to dosing during RCT-V1. OLE-V1 will be the baseline visit for the OLE study component. Per the Schedule of Assessments, RCT-V4 and OLE-V1 will be combined; therefore, for the OLE study component, RCT-V4 will be used as OLE-V1.

7 DISPOSITION AND EXIT STATUS

7.1 Subject Disposition

The number and percentage of subjects who are assessed for eligibility, excluded (including reasons), randomized, allocated to intervention, received intervention or did not receive intervention (including reasons), discontinue study medication (including reasons), lost to follow-up or withdraw from study (including reasons), and/or complete the study, will be summarized by study treatment group. The summary will include a flow diagram in accordance with Figure 1 of the "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials" (Schulz, Altman, & Moher, 2010). Individual subject disposition data will be listed.

7.2 Extent of Study Drug Exposure

Study drug details will be summarized by study treatment for safety set. A listing will present all study treatment details. These details will include duration and the amount of drug administered. Compliance with study treatment will be measured by the subject-reported study drug diary and final remaining capsule count.

7.3 Protocol Deviations

The number and percentage of subjects with protocol deviations will be summarized by study treatment groups. A subject listing including deviation date, and deviation description.

8 BASELINE CHARACTERISTICS

8.1 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by study treatment group and overall, for the Safety Analysis Set.

Demographics and baseline characteristics will be examined to assess the comparability of the study treatment groups at baseline. Continuous variables such as subject age, weight, height, and body mass

index (BMI) will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as subject sex and race will be summarized using number of observations and percentages for each category.

8.1.1 Age

The Age for each subject will be calculated by the difference in date between the Date of Birth (BIRTHDAT) and the Date of Informed Consent (RFICDTC). Age will be reported in years.

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
Age	AGE

8.1.2 Ethnicity

For the variable Ethnicity (ETHNIC), the coded value “Not Hispanic of Latino” (code: 2) will be replaced with “Not Hispanic or Latino” (code: 2), to correct a typo in the study database.

8.2 Concomitant Medications

Concomitant medications will be summarized by drug class and generic name, by study treatment groups for the safety set. Subjects will only be counted once at each level of the generic name or class level. Descending sorting order by the frequency of drug classification, and within that descending order by the frequency of generic name will be followed.

8.3 Medical History

Medical history will be presented by study treatment groups for the safety analysis set. Subject listings of medical history will also be generated for the safety set.

9 STATISTICAL ANALYSES

For the RCT, planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 84 after the start of study treatment. Endpoints will also be assessed at Day 28 and Day 56.

For the OLE, planned analyses for safety and efficacy will be presented from OLE-V1 onwards.

Audiometric data will be collected in the form of categorical and continuous variables. In general, categorical data will be analyzed using the chi-square distribution or Fisher's Exact test. Continuous data will be analyzed using mixed-effects multiple-repeated measures (MMRM), and post-hoc analysis, when necessary, will be adjusted using Bonferroni applications. Non-parametric tests include the Mann-Whitney U. Calculated p-values will be considered statistically significant at or below an alpha value of 0.05.

Further, within treatment comparisons will be made for each post-baseline visit against the baseline result. In these cases, backward stepwise regression may be used to determine the final model including only variables with significance at a .05 level, specifically for secondary endpoints when considering improvement from baseline within treatment.

9.1 Efficacy Analyses

The co-primary efficacy endpoints for the RCT part of the study will be analyzed as follows:

- ≥ 10 dB improvement in low frequency hearing (250, 500, or 1000 Hz) by Pure Tone Audiometry (PTA) in patients treated with SPI-1005 compared to placebo;

Responders will be presented as 'No Improvement', 'Unilateral Improvement', 'Bilateral Improvement', and 'Improvement in either ear' and analyzed using Fisher's Exact test. Improvement in hearing thresholds (250-1000 Hz) is defined as one or more of the thresholds at 250, 500, or 1000 Hz has improved from the baseline value by 10 dB or more.

- ≥ 4 words improvement in Words-in-Noise Test (WIN) in patients treated with SPI-1005 compared to placebo.

Responders will be presented as 'No Improvement', 'Unilateral Improvement', 'Bilateral Improvement', and 'Improvement in either ear' and analyzed using Fisher's Exact test. Improvement in WIN total score is defined as the total score has improved from the baseline value by 4 words or more.

The responder analysis from each method and measure will be compared between treatment groups for significance. Additionally, Hearing Thresholds and the WIN test will also be presented as continuous variables and analyzed using MMRM for between treatment analyses and ANOVA for within treatment analyses.

The following secondary efficacy endpoints will be presented as continuous variables and analyzed using MMRM for between treatment comparison and ANOVA for within-treatment analyses:

- Improvement in tinnitus loudness (TL) in patients treated with SPI-1005 compared to placebo.
- Improvement in tinnitus severity by Tinnitus Functional Index (TFI) in patients treated with SPI-1005 compared to placebo.
- Improvement in vertigo severity by Vertigo Symptoms Scale (VSS) in patients treated with SPI-1005 compared to placebo.
- Improvement in aural fullness by Aural Fullness Scale (AFS) in patients treated with SPI-1005 compared to placebo.
- Improvement in dizziness by Dizziness Handicap Inventory (DHI) in patients treated with SPI-1005 compared to placebo.

The following secondary efficacy endpoints (responder analyses) will be analyzed using Fisher's Exact test:

- ≥ 10 dB improvement in two adjacent low frequencies (250 and 500, or 500 and 1000 Hz) by Pure Tone Audiometry (PTA) in patients treated with SPI-1005 compared to placebo.
- $\geq 20\%$ improvement in Words-in-Noise Test (WIN) in patients treated with SPI-1005 compared to placebo.

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

9.2 Pure Tone Audiometry

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
Low Frequency Pure Tone Average Right	AULFPTAR
Low Frequency Pure Tone Average Left	AULFPTAL
All Frequency Pure Tone Average Right	AUAFPTAR
All Frequency Pure Tone Average Left	AUAFPTAL

These calculated variables will be removed since they were not pre-specified in the protocol.

9.3 Words-in-Noise

The Words-in-Noise Test (WIN) scores will be calculated as follows: The WIN score for each ear will equal the sum of the words correct at 24, 20, 16, 12, 8, 4, and 0 SNR for that ear. These calculations are further specified below:

- WIN Total Score Right Ear = WNR24 + WNR20 + WNR16 + WNR12 + WNR8 + WNR4 + WNR0
- WIN Total Score Left Ear = WNL24 + WNL20 + WNL16 + WNL12 + WNL8 + WNL4 + WNL0

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
WIN Result Right Total Score	WNRESR
WIN Result Left Total Score	WNRESL

9.4 Tinnitus Functional Index

The Tinnitus Functional Index (TFI) subscale scores and total score (i.e., overall score) will be calculated according to the Clinical Protocol Version 1.1, Section 13.2, Appendix II – Tinnitus Functional Index (TFI).

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
TFI Intrusive Subscale Score	TFII
TFI Sense of Control Subscale Score	TFISC
TFI Cognitive Subscale Score	TFIC
TFI Sleep Subscale Score	TFISL
TFI Auditory Subscale Score	TFIA
TFI Relaxation Subscale Score	TFIR
TFI Quality of Life Subscale Score	TFIQ
TFI Emotional Subscale Score	TFIE
TFI Total Score	TFITOT

9.5 Vertigo Symptom Scale

The Vertigo Symptom Scale (VSS) subscale scores and total scale will be calculated according to the Clinical Protocol Version 1.1, Section 13.3, Appendix III – Vertigo Symptom Scale (VSS) – Short Form.

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
VSS Vertigo/balance sub-scale	VSSVB
VSS Autonomic/anxiety sub-scale	VSSAA
VSS Total Scale	VSSTOT

9.6 Dizziness Handicap Inventory

The Dizziness Handicap Inventory (DHI) impact scores and total score will be calculated according to the Clinical Protocol Version 1.1, Section 13.5, Appendix IV – Dizziness Handicap Inventory (DHI).

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
DHI Functional impact score	DHIF
DHI Physical impact score	DHIP

DHI Emotional impact score	DHIE
DHI Total Score	DHITOT

10 SAFETY ANALYSES

Safety outcomes will be presented by study treatment. The safety parameters will also include the physical exam, vital signs, and abnormal laboratory findings (CBC, serum chemistry).

10.1 Adverse Events

All Adverse Events (AEs) reported during the study will be recorded and coded using MedDRA terminology (version 18.1 or higher). An AE will be considered as treatment-emergent if it has an onset after study treatment or is pre-existing and worsens after the first study medication is administered.

The incidence of all reported TEAEs will be summarized using System Organ Class (SOC) and Preferred Term (PT) by study treatment group and overall, using counts and percentages. All AEs will also be presented by relationship (Not Related, Unlikely to be Related, Possibly Related, Probably Related, and Definitely Related) and severity (mild, moderate, and severe). Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each study treatment group. Commonly occurring TEAEs, i.e., those that occur in 5% or more of the subjects in either study treatment group, will be summarized using descriptive statistics.

Subjects may have more than one AE per SOC and PT. At each level of subject summarization, a subject will be counted once if they reported 1 or more events and will be reported with the highest severity.

A separate listing for TEAEs and SAEs will be generated for safety set showing duration of AEs with onset date, severity, relationship with study medication and change in status of ongoing event. Also, listing for SAEs and AEs leading to discontinuation will be generated for safety set.

10.2 Clinical Laboratory Evaluations

Clinical laboratory test results at each time point and changes from baseline will be provided and compared between treatment groups by ANOVA. Shift tables for the hematology and biochemistry laboratory parameters, comparing values low, normal and high using the standard reference ranges, will be presented for the baseline laboratory measurement versus the endpoint measurement for each subject.

Frequency distributions and individual listings of laboratory marked abnormalities will be generated and summarized according to study treatment group.

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
Lab Collection Date/Time	LBDATTIM

This calculated variable will be removed since it is redundant with the Lab Collection Date and Lab Collection Time variables.

10.3 Vital Signs

Vital sign parameters will be summarized by study treatment group and overall, for safety set and compared between treatment groups by ANOVA. A listing of all the vital sign parameters will be presented.

10.3.1 BMI

The BMI will be calculated by the following formula:

$$\frac{\text{Weight at Same Visit}}{(\text{Height at RCT Visit 1 (Baseline)} * 100)^2}$$

BMI will be reported in kg/m².

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
Body Mass Index	BMI

10.4 Physical Examinations

A listing will be presented for physical examination for the safety set.

10.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to determine any reporting of suicidal behavior, suicidal ideation and suicidality. Tabulations will be presented by the study treatment group for safety set. A listing will also be presented for the safety set.

10.6 Pharmacokinetics

The trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined using LCMS/MS. The plasma levels of selenium will be determined by ICP-MS. PK results will be summarized by treatment group.

The following variables calculated in EDC will not be included in the dataset:

Variable Name	Variable Export Name
PK Sample Collection Date/Time	PKDATTIM

This calculated variable will be removed since it is redundant with the PK Sample Collection Date and PK Sample Collection Time variables.

11 INTERIM ANALYSIS

An interim analysis will be performed on the data obtained in the RCT study component, after all subjects participating in the RCT have completed all RCT study visits. This interim will include all safety and efficacy endpoints described above.

12 VALIDATION

Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the two programmers must match 100%. Tables will be independently reprogrammed by a second programmer for numeric results. Statisticians will be involved in the process of programming and validating tables that include inferential statistical results. Any figures presented will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

13 REFERENCES

Schulz, K.F., Altman, D.G., Moher, D. et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8, 18 (2010). <https://doi.org/10.1186/1741-7015-8-18>

14 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AFS	Aural Fullness Scale
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
DHI	Dizziness Handicap Inventory
eCRF	Electronic Case Report Form
ICPMS	Inductively Coupled Mass Spectrometry
ITT	Intent-to-treat
LCMS	Liquid Chromatography Mass Spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Modeling Repeated Measures
OLE	Open-Label Extension
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
PTA	Pure Tone Audiometry
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFI	Tinnitus Functional Index
TL	Tinnitus Loudness
VSS	Vertigo Symptoms Scale
WIN	Words-in-Noise test

15 SUMMARY OF CHANGES

Version	Date	Section	Change
2.0	20 Sep 2024	1 Introduction	Corrected typo in the protocol date.
2.0	20 Sep 2024	1.1 Change from Protocol	Change from protocol added to assess endpoints at Day 84.
2.0	20 Sep 2024	6.2 Sample Size Determination	Comparison timepoint changed to 84 days instead of 56 days.
2.0	20 Sep 2024	8.1.1 Age	Added Section
2.0	20 Sep 2024	8.1.2 Ethnicity	Added Section
2.0	20 Sep 2024	9 Statistical Analyses	Version 2.0 text: "For the RCT, planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 84 after the start of study treatment. Endpoints will also be assessed at Day 28 and Day 56." Version 1.0 text: "For the RCT, planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 56 after the start of study treatment. Endpoints will also be assessed at Day 28 and Day 84."
2.0	20 Sep 2024	9.2 Pure Tone Audiometry	Added Section
2.0	20 Sep 2024	9.3 Words-in-Noise	Added Section
2.0	20 Sep 2024	9.4 Tinnitus Functional Index	Added Section
2.0	20 Sep 2024	9.5 Vertigo Symptom Scale	Added Section
2.0	20 Sep 2024	9.6 Dizziness Handicap Inventory	Added Section
2.0	20 Sep 2024	10.2 Clinical Laboratory Evaluations	Lab Collection Date/Time variable will be removed due to redundancy.
2.0	20 Sep 2024	10.3.1 BMI	Added Section
2.0	20 Sep 2024	10.6 Pharmacokinetics	PK Sample Collection Date/Time variable will be removed due to redundancy.
1.0	29 Sep 2023	All	Original document