

CLINICAL RESEARCH PROTOCOL

DRUG: SPI-1005

STUDY NUMBER(S): SPI-1005-351

PROTOCOL(S) TITLE: 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

IND NUMBER: 127540

NCT NUMBER: NCT04677972

ORIGINAL PROTOCOL DATE: 22 Apr 2020

VERSION NUMBER: 1.1

VERSION DATE: 08 Apr 2021

CHEMICAL NAME: 2-phenyl-1,2-benzisoselenazol-3(2H)-one

Lead Investigator: Paul R Lambert, MD
Dept. of Otolaryngology-HNS
135 Rutledge Ave, MSC 550
Medical University of South Carolina
Charleston, SC 29425

Company Contact: Jonathan Kil, MD
Sound Pharmaceuticals, Inc.
4010 Stone Way North
Suite 120
Seattle, WA 98103

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: 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

Study No: SPI-1005-351

Original Protocol Date: 22 Apr 2020

Protocol Version No: 1.1

Protocol Version Date: 08 Apr 2021

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in The Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
Clinical Operations: _____ [Name] [Title]	Yes No (circle one)		
Medical Lead: _____ [Name] [Title]	Yes No (circle one)		
Regulatory Affairs: _____ [Name] [Title]	Yes No (circle one)		

Statement of Confidentiality

The information contained in the Clinical Protocol, including unpublished data, is the property of Sound Pharmaceuticals, Inc., and is provided in strict confidence to investigators, potential investigators, or consultants for review. This information shall not be disclosed to third parties without prior written authorization from Sound Pharmaceuticals, Inc., except as necessary to obtain informed consent from study participants who may receive this

Statement of Compliance

This trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participant(s). All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure's for SPI-1005. I have read the Protocol SPI-1005-351 and agree to conduct the study as outlined. I agree to maintain compliance and confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

Contact Information

Table 1 Contact Information

Role in Study	Name	Address and Telephone number
Lead Investigator	Paul R. Lambert, MD Chair, Dept. of Otolaryngology-HNS	135 Rutledge Ave, MSC 550 Medical University of South Carolina Charleston, SC 29425
Drug Safety Physician	TBD (Drug safety physician and/or medical monitoring to be provided by third party CRO)	TBD
24-Hour Emergency Contact	TBD (Drug safety physician and/or medical monitoring to be provided by third party CRO)	TBD

TABLE OF CONTENTS

CLINICAL RESEARCH PROTOCOL	1
CLINICAL PROTOCOL APPROVAL FORM	2
TABLE OF CONTENTS	5
ABBREVIATIONS	8
1 PROTOCOL SUMMARY.....	10
1.1 Synopsis.....	10
1.2 Schema.....	15
1.2.1 Randomized Controlled Trial (RCT)	15
1.2.2 Open Label Extension (OLE)	16
1.3 Schedule of Assessments.....	18
2 INTRODUCTION	21
3 STUDY OBJECTIVES	23
3.1 Primary Objectives	23
3.2 Secondary Objectives	23
3.3 Additional Objectives	24
4 INVESTIGATIONAL PLAN.....	24
4.1 Overall Study Design.....	24
4.2 Safety Criteria for Stopping Dosing	25
4.3 Criteria for Study Termination	25
5 STUDY POPULATION.....	25
5.1 Inclusion Criteria	25
5.2 Exclusion Criteria	26
6 DESCRIPTION OF STUDY TREATMENT	26
6.1 Compound	26
6.2 Dosing Levels	26
6.3 Dosing Regimen	27
6.3.1 RCT Dosing Regimen.....	27
6.3.2 OLE Dosing Regimen.....	27
6.4 Dosage Form.....	27
6.5 Manufacturer	27
6.6 Route of Administration	27
6.7 Packaging and Labeling.....	27
6.8 Storage	27
6.9 Study Drug Accountability	27
6.10 Study Drug Handling and Disposal	28
7 STUDY CONDUCT	29
7.1 Study Duration.....	29

7.2	RCT Study Procedures by Visit.....	29
7.2.1	RCT-Visit 1 (Day -28 to 1).....	29
7.2.2	RCT-Visit 2 (Day 28)	30
7.2.3	RCT-Visit 3 (Day 56)	31
7.2.4	RCT-Visit 4 (Day 84)	31
7.3	OLE Study Procedures by Visit.....	32
7.3.1	OLE-Visit 1 (Day 1)	32
7.3.2	OLE-Visit 2 (Day 30)	33
7.3.3	OLE-Visit 3 (Day 60)	34
7.3.4	OLE-Visit 4 (Day 90)	34
7.3.5	OLE-Visit 5 (Day 120)	35
7.3.6	OLE-Visit 6 (Day 150)	36
7.3.7	OLE-Visit 7 (Day 180)	36
7.3.8	OLE-Visit 8 (Day 210)	37
7.3.9	OLE-Visit 9 (Day 240)	38
7.3.10	OLE-Visit 10 (Day 270)	38
7.3.11	OLE-Visit 11 (Day 300)	39
7.3.12	OLE-Visit 12 (Day 330)	39
7.3.13	OLE-Visit 13 (Day 360)	40
7.4	Early Termination of Study Participants	41
8	DESCRIPTION OF STUDY PRODECURES	42
8.1	Informed Consent Procedures and Documentation	42
8.2	Randomization and Blinding.....	42
8.3	Medical History	42
8.4	Physical Exam	43
8.5	Vital Signs	43
8.6	Clinical Laboratory Tests	43
8.7	Pharmacokinetics.....	44
8.8	Columbia-Suicide Severity Rating Scale	45
8.9	Patient-Reported Outcomes.....	45
8.9.1	Tinnitus Functional Index & Tinnitus Loudness	45
8.9.2	Vertigo Symptoms Scale.....	45
8.9.3	Aural Fullness Scale	45
8.9.4	Dizziness Handicap Inventory	46
8.10	Audiology	46
8.10.1	Otoscopy	46
8.10.2	Tympanometry.....	46
8.10.3	Pure Tone Audiometry.....	46
8.10.4	Words-in-Noise Test.....	47
8.11	Concomitant Medications.....	47
8.11.1	Prohibited Medications	47
8.12	Study Drug Diary.....	47
9	ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS	48

9.1	Definition of Adverse Event.....	48
9.2	Definition of Serious Adverse Event.....	48
9.3	Classification of an Adverse Event	48
9.3.1	Severity of Event.....	48
9.3.2	Relationship to Study Treatment	48
9.3.3	Unanticipated Adverse Event	49
9.3.4	Time Period and Frequency for Event Assessment and Follow-up.....	49
9.3.5	Adverse Event Reporting.....	50
10	STATISTICAL CONSIDERATIONS	51
11	INVESTIGATIONAL RECORD KEEPING.....	52
11.1	Protocol Deviations and Amendments	52
11.2	Publication Policy.....	52
11.3	Study Monitoring.....	52
11.4	Audits and Inspections.....	53
11.5	Retention of Records	53
11.6	Confidentiality	54
12	INSTITUTIONAL REVIEW BOARD (IRB).....	54
12.1	Ethical Conduct of the Study.....	54
	REFERENCES.....	55
13	APPENDICES	57
13.1	APPENDIX I - Diagnosis of Meniere's Disease	57
13.2	APPENDIX II - Tinnitus Functional Index (TFI)	58
13.3	APPENDIX III - Vertigo Symptom Scale (VSS) – Short Form	62
13.4	APPENDIX IV – Aural Fullness Scale (AFS).....	64
13.5	APPENDIX IV – Dizziness Handicap Inventory (DHI).....	65

LIST OF TABLES

Table 1	Contact Information.....	4
Table 2	A list of abbreviations and specialist terms found in clinical protocol.....	8
Table 3	Approximate number of study participants randomized to each dose.....	42
Table 4	SPI-1005-351 Clinical Laboratory Tests	44

ABBREVIATIONS

Table 2 A list of abbreviations and specialist terms found in clinical protocol

Abbreviation	Meaning
AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
AE	Adverse Event
AFS	Aural Fullness Scale
ASHA	The American Speech-Language-Hearing Association
BID	Twice-daily dosing
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CSC	Controlled Sound Challenge
dB	decibel, 1/10 th of a Bel—measure of ratios on a log scale
dBHL	dB Hearing Level
DHI	Dizziness Handicap Inventory
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPx	Glutathione Peroxidase
GSH	Glutathione
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
Hz	Hertz—unit of measure for frequency
ICH	International Conference on Harmonization
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IEC	Institutional Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
WIRB	Western Institutional Review Board
LCMS/MS	Liquid Chromatography-Tandem Mass Spectrometry
mg	milligram
MD	Meniere's Disease
OLE	Open Label Extension
ONOO-	Peroxynitrite
PI	Principal Investigator
PK	Pharmacokinetics
po	By mouth
PTA	Pure-Tone Audiometry
PRN	As needed
RCT	Randomized Clinical Trial
ROS	Reactive Oxygen Species

SAE	Serious Adverse Event
SNR	Signal-to-Noise ratio
SPI	Sound Pharmaceuticals, Inc.
TFI	Tinnitus Functional Index
TL	Tinnitus Loudness
TTS	Temporary Threshold Shift
VSS	Vertigo Symptoms Scale
WIN	Words-in-Noise Test

1 PROTOCOL SUMMARY

1.1 Synopsis

SPI-1005-351: CLINICAL TRIAL SYNOPSIS	
Title	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
Study Objective(s)	Primary objectives: • Safety of SPI-1005 treatment compared to placebo in adults with definite Meniere’s disease, assessed based on comparison of adverse events in patients treated with SPI-1005 compared to placebo. • Efficacy of SPI-1005 determined by (co-primary endpoints): ○ ≥ 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. • 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). Secondary objectives: • 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.

SPI-1005-351: CLINICAL TRIAL SYNOPSIS	
	• $\geq 20\%$ improvement in Words-in-Noise Test (WIN) in patients treated with SPI-1005 compared to placebo. Additional objectives: • Safety of open-label extension of SPI-1005 treatment in adults with definite Meniere's disease for 6 or 12 months to support chronic, intermittent use.
Study Design	The study is a randomized, double-blind, placebo-controlled, multi-center clinical trial (RCT) with open-label extension study (OLE), of SPI-1005 in adult subjects with definite Meniere's disease with active symptoms within three months preceding study enrollment. All subjects will undergo baseline safety, audiometric, and vestibular assessments before initiating treatment. For the RCT study component, subjects will be randomized to study treatment, 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 start of study treatment for safety, audiometric, and vestibular assessments. Following the final visit of the RCT study component, subjects will begin the OLE study component, with open-label treatment of SPI-1005 400 mg BID for 180 days. A subset of subjects may continue the open-label treatment for up to 360 days. While on open-label treatment, subjects will have monthly safety assessments via telehealth, and will return to clinic every 90 days for safety, audiometric, and vestibular assessments. In summary, 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 and 4 to 8 scheduled telehealth interactions over a 180- or 360-day period. All safety and efficacy assessments will be performed at each scheduled clinic visit. Subjects are allowed to continue with their existing maintenance therapies (e.g., low salt diet, thiazide diuretic, or other PRN medications), except for the use of oral or locally injected steroids. The start of new therapies or treatments should be avoided while on study.
Power Analysis	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. Comparison of PTA and WIN responder rates at 56 days from the start of study drug:

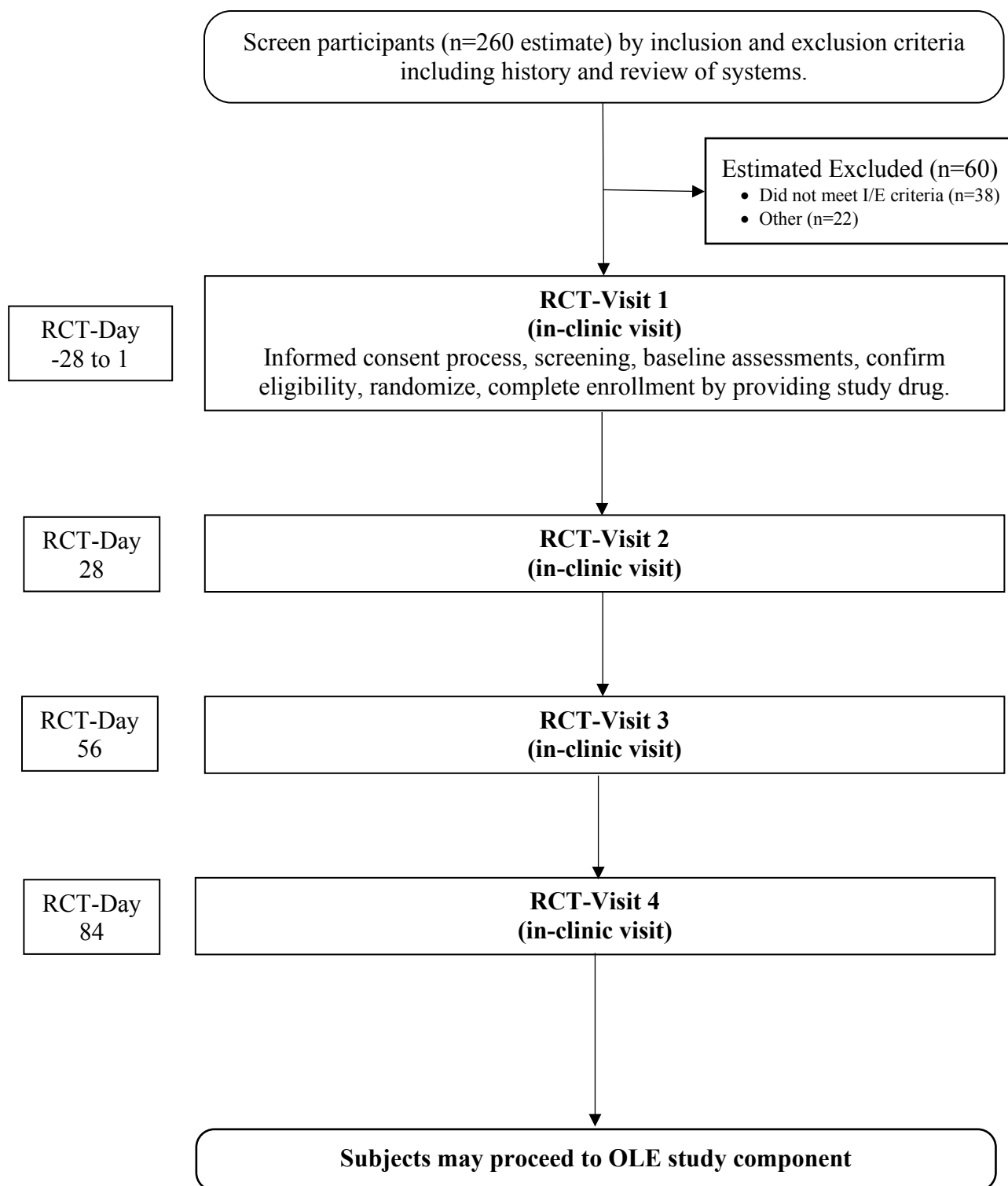
SPI-1005-351: CLINICAL TRIAL SYNOPSIS	
	- Assuming PTA responder rates observed in Phase 2b Study (SPI-1005-251), Active 61% vs Placebo 37%, power is 0.909. - Assuming WIN responder rates observed in Phase 2b Study (SPI-1005-251), Active 60% vs Placebo 34%, power is 0.949.
Study Centers	Approximately 16 to 20 U.S. sites will participate in this study
Subjects	Male and female adults with definite Meniere's disease; up to 260 subjects in order to achieve ≥ 200 evaluable in the RCT.
Inclusion Criteria	- Adult males/females, 18-75 years of age at the time of enrollment. - Diagnosis of definite Meniere's Disease by AAO-HNS Amended 2015 Criteria. - Hearing loss of ≥ 30 dB at 250, 500, or 1000 Hz at study enrollment. - At least two of three active symptoms (tinnitus; aural fullness; vertigo or dizziness) of Meniere's disease by AAO-HNS Amended 2015 Criteria, within 3 months of study enrollment. - Subject is willing and able to provide informed consent. - Males who are sexually inactive (abstinent), have surgical sterilization (vasectomy) at least 6 months prior to study enrollment, or use a barrier method (condom or diaphragm) with spermicide throughout the study period and 90-days following study completion. - Females of childbearing potential who are sexually inactive (abstinent) for 14 days prior to screening and throughout the study; or who use one of the following acceptable birth control methods: - IUD in place for at least 3 months prior to study; or - Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or - Stable hormonal contraceptive for at least 3 months prior to study and through study completion; or - Surgical sterilization (vasectomy) of partner at least 6 months prior to study enrollment. - Females of non-childbearing potential who are surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study enrollment; hysterectomy; or bilateral oophorectomy at least 2 months prior to study), or least 1 year since last menses.
Exclusion Criteria	Current, or within 60 days prior to study enrollment, use of IV or intratympanic ototoxic medications such as chemotherapy including cisplatin, carboplatin, or oxaliplatin; aminoglycoside antibiotics including gentamicin, amikacin, tobramycin,

SPI-1005-351: CLINICAL TRIAL SYNOPSIS	
	kanamycin, or streptomycin; or loop diuretics including furosemide. • History of otosclerosis or vestibular schwannoma. • History of significant middle ear or inner ear surgery in the affected ear. • Conductive hearing loss with air-bone gap ≥ 15 dB, otitis media, or mixed hearing loss. • Significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, neurological, or psychiatric disease. • Current use or within 30 days prior to study enrollment systemic steroids. • Current use or within 7 days prior to study enrollment intratympanic steroids. • Hypersensitivity or idiosyncratic reaction to compounds related to ebselen or excipients. • Female patients who are pregnant or breastfeeding. • Participation in another investigational drug or device study within 30 days prior to study consent.
Study Duration	Estimated duration of 24 months
Participant Duration	Participation for study participants will be approximately 84 days over 4 clinic visits for the RCT study component ($N \geq 200$), and approximately 180 ($N \geq 200$) or 360 days ($N \geq 100$) over 3 to 5 clinic visits and 4 to 8 telehealth interactions for the OLE study component.
Dose & Regimen	For the (RCT) study treatment, subjects will receive either SPI-1005 400 mg or matching placebo (oral BID) for 28 days. Subjects will be dispensed approximately 28 days of clinical supply. For the (OLE) open-label extension treatment, subjects will receive sufficient clinical supply for open-label oral SPI-1005 400 mg BID for up to 180 or 360 days.
Safety & Tolerability Assessments	Physical examinations, vital signs, adverse events, hematology (CBC) and serum chemistries will encompass safety assessments. Adverse events will be coded using MedDRA (Version 18.1 or higher) and summarized by treatment group for the number of adverse events and compared. Vital signs and clinical laboratory results will be summarized for each treatment group and compared.

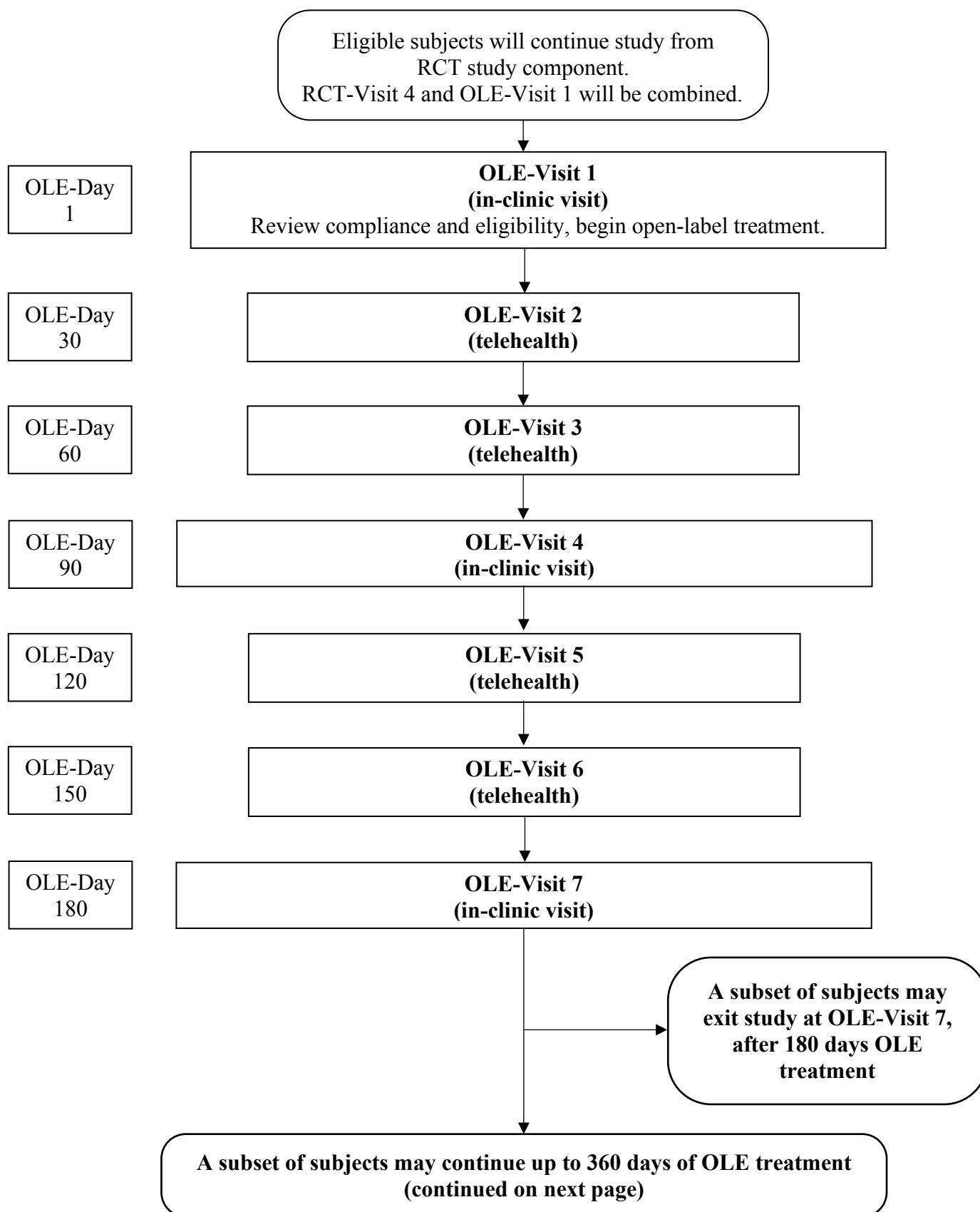
SPI-1005-351: CLINICAL TRIAL SYNOPSIS	
PK Assessments	The trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined using LC-MS/MS. The corresponding plasma levels of selenium will be determined by ICP-MS. PK results will be summarized by treatment group.
Lead Investigator (s)	Paul R. Lambert, MD

1.2 Schema

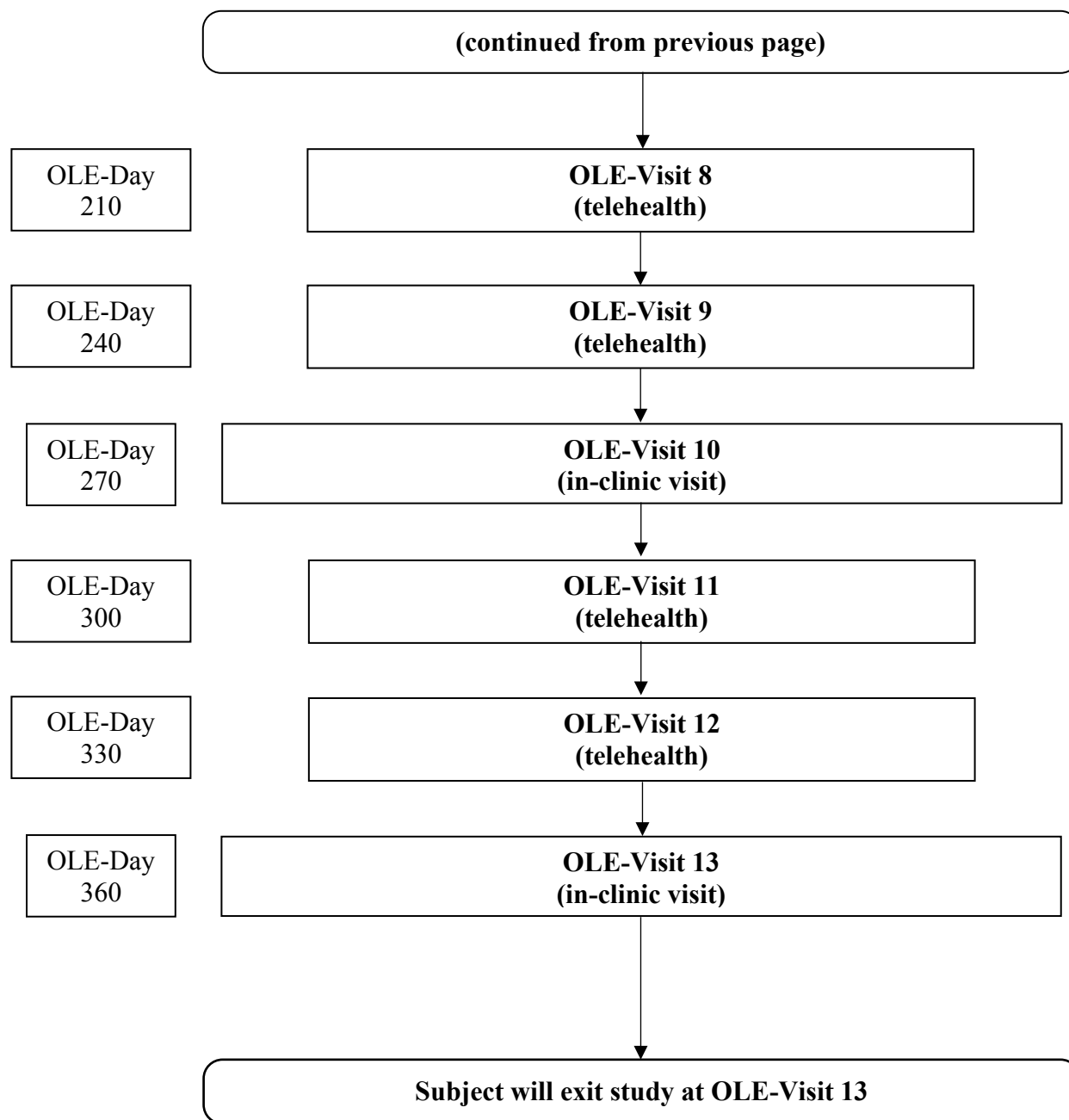
1.2.1 Randomized Controlled Trial (RCT)



1.2.2 Open Label Extension (OLE)



Open Label Extension (OLE) – continued for 360 day treatment



1.3 Schedule of Assessments

Randomized Controlled Trial (RCT)				
Visit	RCT-V1	RCT-V2	RCT-V3	RCT-V4
RCT-Day	-28 to 1	28 (+/- 3)	56 (+/- 3)	84 (+/- 3)
Visit Type	in-clinic	in-clinic	in-clinic	in-clinic
Informed Consent	X			
Demographics	X			
Medical History	X			
Physical Exam	X	X	X	X
Height	X			
Weight	X	X	X	X
Vital Signs	X	X	X	X
CBC	X	X	X	X
Serum Chemistry	X	X	X	X
Urine Pregnancy¹	X			
C-SSRS	X	X	X	X
TFI	X	X	X	X
AFS	X	X	X	X
VSS	X	X	X	X
DHI	X	X	X	X
Otoscopy	X	X	X	X
Tympanometry	X			
PTA	X	X	X	X
WIN	X	X	X	X
Concomitant Medications	X	X	X	X
Randomization	X			X
Study Treatment²	X	X		
Study Drug Diary	X	X		
AE	X	X	X	X
PK	X	X	X	X

⁽¹⁾Urine pregnancy test will be performed in women of childbearing potential.

⁽²⁾Study treatment (SPI-1005 400 mg or matching placebo BID for 28 days) will begin on RCT-Day 1 provided eligibility criteria have been reviewed and met.

Open Label Extension (OLE)							
Visit	OLE-V1 ¹	OLE-V2	OLE-V3	OLE-V4	OLE-V5	OLE-V6	OLE-V7 ⁴
OLE-Day	1	30 (+/- 7)	60 (+/- 7)	90 (+/- 7)	120 (+/- 7)	150 (+/- 7)	180 (+/- 7)
Visit Type	in-clinic	telehealth	telehealth	in-clinic	telehealth	telehealth	in-clinic
Physical Exam	X			X			X
Weight	X			X			X
Vital Signs	X			X			X
CBC	X			X			X
Serum Chemistry	X			X			X
Urine Pregnancy ²	X			X			X
C-SSRS	X	X	X	X	X	X	X
TFI	X			X			X
AFS	X			X			X
VSS	X			X			X
DHI	X			X			X
Otoscopy	X			X			X
PTA	X			X			X
WIN	X			X			X
Concomitant Medications	X	X	X	X	X	X	X
Open Label Treatment ³	X	X	X	X	X	X	X
Study Drug Diary	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X
PK	X			X			X

⁽¹⁾ OLE-V1 will be the baseline visit for the OLE study component. RCT-Visit 4 and OLE-Visit 1 will be combined.

⁽²⁾ Urine pregnancy test will be performed in women of childbearing potential.

⁽³⁾ Open label treatment (SPI-1005 400 mg BID for 180 or 360 days) will begin on OLE-Day 1 provided eligibility criteria have been reviewed and met.

⁽⁴⁾ OLE-V7 will be the study exit visit for subjects receiving 180 days of open label treatment.

Open Label Extension (OLE) – continued for 360 day treatment						
Visit	OLE-V8	OLE-V9	OLE-V10	OLE-V11	OLE-V12	OLE-V13 ⁴
OLE-Day	210 (+/- 7)	240 (+/- 7)	270 (+/- 7)	300 (+/- 7)	330 (+/- 7)	360 (+/- 7)
Visit Type	telehealth	telehealth	in-clinic	telehealth	telehealth	in-clinic
Physical Exam			X			X
Weight			X			X
Vital Signs			X			X
CBC			X			X
Serum Chemistry			X			X
Urine Pregnancy¹			X			X
C-SSRS	X	X	X	X	X	X
TFI			X			X
AFS			X			X
VSS			X			X
DHI			X			X
Otoscopy			X			X
PTA			X			X
WIN			X			X
Concomitant Medications	X	X	X	X	X	X
Open Label Treatment	X	X	X	X	X	X
Study Drug Diary	X	X	X	X	X	X
AE	X	X	X	X	X	X
PK			X			X

⁽¹⁾ Urine pregnancy test will be performed in women of childbearing potential.

⁽²⁾ OLE-V13 will be the study exit visit for subjects receiving 360 days of open label treatment.

2 INTRODUCTION

Meniere's disease (MD) is defined as a triad of episodic vertigo, hearing loss and tinnitus. Aural pressure or fullness is often reported, and most auditory and vestibular symptoms fluctuate in frequency and intensity. While the etiology of MD is unknown, it is thought to be due to endolymphatic hydrops, a swelling of the endolymphatic compartment of the inner ear. Currently, there are no FDA approved treatments that prevent or treat MD. Most MD patients are medically managed using a low-salt diet and/or a thiazide diuretic with limited success. After an acute phase where vertigo or dizziness is the most common feature, the chronic phase emerges, where hearing loss and tinnitus become the most common features, although disequilibrium is often reported.

Several preclinical animal studies conducted by Sound Pharma (SPI) and other independent laboratories have demonstrated the efficacy of SPI-1005 (ebselen) at preventing and treating different acquired forms of sensorineural hearing loss (Kil, Pierce et al., 2007; Lynch, Gu et al., 2005a, 2005b). Ebselen is a novel anti-inflammatory compound with glutathione peroxidase (GPx1) activity. GPx1 is the dominant catalytic antioxidant enzyme in the mammalian inner ear, and its activity is decreased after ototoxic insult. Ebselen treatment has been shown to prevent or reverse the pathologic changes in the cochlea following noise- or ototoxin-induced injury. In an acute animal model, ebselen was shown to reduce the swelling of the endolymphatic compartment and the stria vascularis following an intense noise exposure (Kil, Pierce et al., 2007). While there are no animal models that recreate the phenotype of human MD, this reduction or improvement in noise-induced endolymphatic hydrops suggests that ebselen may be valuable in idiopathic endolymphatic hydrops and human MD.

In the cochlea, glutathione peroxidase (GPx) reacts with glutathione (GSH) to limit free-radical toxicity. In mice treated with cisplatin, an elevation of hydroxyl radicals and nitrotyrosine within the cochlea has been correlated with the degeneration of outer hair cells and consequently a loss of auditory function (Lee, Nakagawa et al., 2004). Augmentation of GPx activity with the enzyme itself is not practical due to its large size, cytosolic location, and relative instability. However, small-molecule mimics of GPx activity have been synthesized and studied by a number of groups.

Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] is a mimic of GPx activity (Müller, Cadenas et al., 1984; Reiter & Wendel, 1984; Wendel, Fausel et al., 1984). It has strong activity against peroxynitrite (ONOO⁻), a reactive oxygen species (ROS) formed by the combination of two free radicals, superoxide anion and nitric oxide (Noguchi, Gotoh et al., 1994; Noguchi, Yoshida et al., 1992). Ebselen reduces cytochrome-C release from mitochondria and nuclear damage during lipid peroxidation (Namura, Nagata et al., 2001). Ebselen acts as a catalyst and is not consumed during detoxification reactions (Müller, Gabriel et al., 1988). SPI-1005, a novel anti-inflammatory, constitutes a new drug class and each capsule contains 200 mg of ebselen. SPI-1005 offers the potential for a safe, well tolerated, oral treatment for Meniere's disease, a disease for which there are no approved treatments.

Sound Pharmaceuticals has completed a Phase 1 study in healthy subjects (SPI-1005-101). In this Phase 1 study, 32 subjects were randomized to receive either a single oral dose of placebo or one of four different doses of SPI-1005, up to 1600 mg. There were no treatment- or dose-related trends in overall AE incidence when compared to placebo (Lynch & Kil, 2009). Pharmacokinetic analysis

of ebselen and its metabolites supported twice daily dosing by oral route of administration. SPI has completed a Phase 2 study in healthy subjects (SPI-1005-202) that were exposed to a Controlled Sound Challenge (CSC). In this Phase 2 study, 83 subjects were randomized to placebo or one of three doses of SPI-1005 capsules and treated for 4 days, twice daily by oral route of administration, up to 600 mg BID. There were no treatment- or dose-related trends in overall AE incidence when compared to placebo. SPI-1005 was found to be safe and effective in reducing the incidence and severity of the temporary threshold shift (TTS) induced by the CSC when compared to placebo (Kil, Lobarinas et al., 2017).

SPI has completed a Phase 1b safety and efficacy study in Meniere's Disease (SPI-1005-151). In this study, 40 adults with probable or definite MD were randomized to placebo or one of three doses (200, 400, or 600 mg, BID) of SPI-1005, and treated for 21 days by oral route of administration. No treatment- or dose related trends in overall AE incidence, nor selenosis, were observed. SPI-1005 was found to be safe and well tolerated during the three week course of treatment. SPI-1005-treated subjects showed clinically relevant improvements (≥ 10 dB from baseline) in low frequency hearing (250, 500, or 1000 Hz), the frequencies of hearing that are most typically affected in MD, at a significantly greater responder rate (52%) vs placebo-treated subjects (10%), that were statistically significant p-value < 0.05 (Kil, Huang et al., 2018).

SPI has now completed a Phase 2b safety and efficacy study in Meniere's disease (SPI-1005-251). In this study, 125 subjects with active probable or definite MD were randomized to placebo or one of two doses (200 or 400 mg, BID) of SPI-1005, and treated for 28 days by oral route of administration. SPI-1005 was found to be safe and well tolerated during the four week course of treatment. SPI-1005-treated subjects showed clinically relevant improvements (≥ 10 dB from baseline) in low frequency hearing (250, 500, or 1000 Hz), at a significantly greater responder rate (61%) vs placebo-treated subjects (37%), that were statistically significant p-value < 0.05 . In addition, clinically relevant improvements in word recognition and tinnitus were also noted.

In addition to these SPI sponsored studies in the US, Daiichi Pharmaceuticals sponsored three safety and efficacy studies testing ebselen in Japan for the indication of acute stroke. See the Investigator's Brochure for summaries of all non-clinical and clinical studies involving SPI-1005.

The objectives for this Phase 3 study (SPI-1005-351) are to demonstrate the safety and efficacy of SPI-1005 for the treatment of Meniere's Disease. This randomized, double-blind, placebo-controlled study (RCT) will evaluate the safety and efficacy of SPI-1005 400 mg BID compared to placebo in 200 adults with MD following 28 days of treatment. Improvements in pure-tone audiometry, word recognition, and patient-reported outcomes using validated questionnaires for tinnitus (Meikle, Henry et al., 2012), vertigo severity (Yardley, Donovan-Hall et al., 2004), dizziness (Jacobson & Newman, 1990), and aural fullness (Patel, Agarwal et al., 2016) will be compared between the SPI-1005 group and the placebo group. This Phase 3 RCT is adequately powered to demonstrate a clinically relevant improvement in MD using the responder analysis detailed below with 100 study participants per treatment group. The RCT will be followed by an open label extension (OLE) for chronic safety data following 180 or 360 days of open label treatment with SPI-1005 400 mg BID.

3 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, efficacy, and 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 180 or 360 days, in patients with Meniere's disease will also be evaluated.

3.1 Primary Objectives

The safety of SPI-1005 compared to placebo will be determined by examining the toxicities and adverse events that are attributable to treatment. The safety parameters will also include the physical exam, vital signs, and abnormal laboratory findings (CBC, serum chemistry). Changes in these laboratory values from baseline values will be averaged and compared between treatment groups by ANOVA.

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.

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

Planned primary analyses for safety and efficacy of SPI-1005 vs placebo will assess endpoints at Day 56 after the start of study treatment.

3.2 Secondary Objectives

The secondary objectives are to determine the efficacy of SPI-1005 by the following clinically significant methods and measures (responder analysis):

- 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.

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

3.3 Additional Objectives

The safety of open-label extension of SPI-1005 treatment for 180 or 360 days will be determined by examining the toxicities and adverse events that are attributable to treatment. The safety parameters will also include the physical exam, vital signs, and abnormal laboratory findings (CBC, serum chemistry). Changes in these laboratory values from baseline values will be averaged and compared between treatment groups by ANOVA.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This study comprises a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of SPI-1005 (RCT) and open label extension to evaluate the chronic safety of SPI-1005 (OLE). Eligible subjects enrolled to the study will participate in the RCT study component followed by the OLE study component.

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

In the RCT study component, 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 start of RCT study treatment for safety, audiometric, and vestibular assessments.

In the OLE study component, 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 start of OLE open label treatment for drug supply, safety, audiometric, and vestibular assessments.

During the study, participants will be evaluated for safety (adverse events, physical exams, vital signs, clinical laboratory testing (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. 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 & Tinnitus Loudness, Vertigo Symptoms Scale, Aural Fullness Scale, and Dizziness Handicap Inventory.

All assessments for the RCT and OLE study components will take place as specified according to the Schedule of Assessments in Section 1.3.

4.2 Safety Criteria for Stopping Dosing

If a study participant has an unanticipated, severe or serious adverse event potentially related to study treatment, the Investigator should contact the Sponsor to determine whether to discontinue study treatment. Regardless of communication with the Sponsor, the Investigator should make a determination about discontinuing the study treatment if it is in the best interest of the safety of the study participant. Study treatment may also be discontinued at the request of the study participant.

4.3 Criteria for Study Termination

Study participants who must discontinue study treatment or open-label treatment for any reason should continue to complete the study through their study exit visit. If a study participant is not able to comply with study safety monitoring or is non-compliant with the study protocol and/or study treatment, the Investigator should contact the Sponsor about early termination of the study participant's study participation. Criteria for early termination are in Section 7.4, Early Termination of Participants.

5 STUDY POPULATION

Study participants will be required to meet all inclusion criteria to enroll in this study. If any exclusion criteria are met, enrollment will be declined.

5.1 Inclusion Criteria

- Adult males/females, 18-75 years of age at the time of enrollment.
- Diagnosis of definite Meniere's Disease by AAO-HNS Amended 2015 Criteria.
- Hearing loss of ≥ 30 dB at 250, 500, or 1000 Hz at study enrollment.
- At least two of three active symptoms (tinnitus; aural fullness; vertigo or dizziness) of Meniere's disease by AAO-HNS Amended 2015 Criteria, within 3 months of study enrollment.
- Subject is willing and able to provide informed consent.
- Males who are sexually inactive (abstinent), have surgical sterilization (vasectomy) at least 6 months prior to study enrollment, or use a barrier method (condom or diaphragm) with spermicide throughout the study period and 90-days following study completion.
- Females of childbearing potential who are sexually inactive (abstinent) for 14 days prior to

screening and throughout the study; or who use one of the following acceptable birth control methods:

- IUD in place for at least 3 months prior to study; or
 - Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or
 - Stable hormonal contraceptive for at least 3 months prior to study and through study completion; or
 - Surgical sterilization (vasectomy) of partner at least 6 months prior to study enrollment.
- Females of non-childbearing potential who are surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study enrollment; hysterectomy; or bilateral oophorectomy at least 2 months prior to study), or least 1 year since last menses.

5.2 Exclusion Criteria

- Current, or within 60 days prior to study enrollment, use of IV or intratympanic ototoxic medications such as chemotherapy including cisplatin, carboplatin, or oxaliplatin; aminoglycoside antibiotics including gentamicin, amikacin, tobramycin, kanamycin, or streptomycin; or loop diuretics including furosemide.
- History of otosclerosis or vestibular schwannoma.
- History of significant middle ear or inner ear surgery in the affected ear.
- Conductive hearing loss with air-bone gap ≥ 15 dB, otitis media, or mixed hearing loss.
- Significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, neurological, or psychiatric disease.
- Current use or within 30 days prior to study enrollment systemic steroids.
- Current use or within 7 days prior to study enrollment intratympanic steroids.
- Hypersensitivity or idiosyncratic reaction to compounds related to ebselen.
- Female patients who are pregnant or breastfeeding.
- Participation in another investigational drug or device study within 30 days prior to study consent.

6 DESCRIPTION OF STUDY TREATMENT

6.1 Compound

SPI-1005 is a formulation of ebselen, consisting of white, opaque hard gelatin capsules, each containing 200 mg of the active pharmaceutical ingredient ebselen and approximately 150 mg of the excipients: microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Placebo capsules contain only the excipients.

6.2 Dosing Levels

There is one dose level: 400 mg of SPI-1005.

6.3 Dosing Regimen

6.3.1 RCT Dosing Regimen

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.

6.3.2 OLE Dosing Regimen

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

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

6.4 Dosage Form

#1 size opaque white capsule will contain either 200 mg of ebselen or matching placebo.

6.5 Manufacturer

SPI-1005 capsules are GMP manufactured by WuXi AppTech for Sound Pharmaceuticals, Inc.

6.6 Route of Administration

SPI-1005 capsules (or matching placebo) is orally administered with approximately 240 ml of water, 1-2 hours prior to food. Each dose will be administered as two capsules in the morning and two capsules in the evening.

6.7 Packaging and Labeling

White size#1 hard gelatin capsules are supplied in white, opaque, high density polyethylene bottles, induction sealed, with a child-resistant white, opaque polypropylene cap.

In the RCT study component, SPI-1005 capsules (or matching placebo) are provided in bottles, each with at least a 28-day supply (with 3 days extra for a total of 124 capsules/bottle).

In the OLE study component, SPI-1005 capsules (open label) are provided in bottles, each with at least a 30 day supply (with 1 day extra for a total of 124 capsules/bottle). The subject will be provided 3 bottles at each dispensation, which will comprise at least a 90-day supply.

For additional information, refer to SPI-1005 Investigator's Brochure V4.1 dated March 12, 2020, or most recent version.

6.8 Storage

SPI-1005 capsules should be stored in a dry place at room temperature (20 to 25°C; 68-77°F). For additional information, refer to SPI-1005 Investigator's Brochure V4.1 dated March 12, 2020, or most recent version.

6.9 Study Drug Accountability

In the RCT study component, one bottle of study drug (SPI-1005 or matching placebo) will be

dispensed at RCT-Visit 1. The bottle and any study drug that the subject has remaining in the bottle must be returned to the study personnel at RCT-Visit 2, along with the study drug diary.

In the OLE study component, three bottles of open-label drug will be dispensed at each in-clinic visit, except for the study exit visit. The bottles and any open-label drug that the subject has remaining in the bottles must be returned to the study personnel at the next scheduled in-clinic visit, along with the study drug diary.

If the subject does not return the bottles and drug as scheduled, the subject should be instructed to refrain from taking any drug from the to-be-returned bottles and to return the bottles and any remaining drug to the study personnel at the earliest possibility or the next scheduled in-clinic visit.

Returned drug should be obtained from the subject at the beginning of the in-clinic visit, and should not be re-dispensed to the subject. Study personnel should examine the returned study or open-label drug in order to count and record the number of capsules dispensed, taken by the study participant, remaining, and lost. The study drug diary should be retrieved from the subject and reviewed with the subject for completion and subject testimony regarding missed doses.

Compliance with study treatment will be measured by the subject-reported study drug diary and final remaining capsule count. Study staff should retain study treatment packaging and remainder of study drug capsules for drug accountability monitoring.

Study drug return and accountability are not required on unscheduled study visits that occur between scheduled study visits, provided the subject is continuing study treatment. Study drug return and accountability must occur immediately if the subject is discontinuing study treatment or experiencing early termination of their study participation.

Study drug accountability (e.g. bottle identifier, date of dispensation, number of capsules dispensed) will also be performed when dispensing any study treatment to the subject.

The subject should refrain from taking their morning dose of study treatment on the day of any study visit (RCT or OLE), until after the blood draw for pharmacokinetic analysis has been collected, in order to obtain trough plasma levels in the blood sample collection.

6.10 Study Drug Handling and Disposal

All study drug will be retained by the study site in an environment that is secure, limited access, and is monitored daily for temperature. All study drug will be retained at the site until otherwise instructed by the Sponsor.

7 STUDY CONDUCT

7.1 Study Duration

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.

7.2 RCT Study Procedures by Visit

7.2.1 RCT-Visit 1 (Day -28 to 1)

Informed consent for study participation must be obtained before study procedures are conducted.

RCT-Visit 1 comprises screening and baseline testing, determination of eligibility, and randomization and dispensation of study treatment for eligible subjects. An approximately 28-day window is allowed for completion of RCT-Visit 1 procedures prior to the initiation of study treatment on RCT- Day 1. Subjects should not be randomized or dispensed study treatment until all screening procedures have taken place, and the investigator confirms the subject is eligible for participation in the study.

If the subject performs a screening audiogram and does not meet the criteria of hearing loss of ≥ 30 dB at 250, 500, or 1000 Hz, then in order to be eligible, they may return for up to 2 additional audiograms within the 28-day screening window. Each screening audiogram will be captured in the eCRF. Patient-reported outcomes should be performed before each screening audiogram. The WIN should not be performed until after an eligible audiogram has been obtained. Baseline will be defined as the day of the eligible audiogram.

The following study procedures will be performed during RCT-Visit 1. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Informed Consent
- Demographics
- Medical History
- Physical Exam
- Height & Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Urine pregnancy test, for women of childbearing potential only
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)

- Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Tympanometry
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Bone conduction testing, if applicable
 - Words-in-Noise Test
- Concomitant medications
- Randomization (if eligibility criteria are met)
- Dispensation of study drug, study drug accountability
- Study drug diary
- Adverse Events

Following the informed consent process and confirmation of eligibility (inclusion/exclusion criteria), randomization will take place. Each study participant will be randomized to either SPI-1005 400 mg or matching placebo, double-blinded. The subject will be dispensed one bottle of study drug containing capsules of SPI-1005 or placebo. The date of first dose of study treatment will be recorded and is by definition RCT-Day 1.

The subject will be instructed to take two (2) capsules from the bottle at each dosing time (morning and evening), and to refrain from taking their morning dose on the day of RCT-Visit 2. The subject will be instructed to return the bottle of study drug and any remaining capsules at their next visit.

7.2.2 RCT-Visit 2 (Day 28)

RCT-Visit 2 will take place in the clinic on RCT-Day 28, which is 28 days after the start of RCT study treatment.

The following study procedures will be performed during RCT-Visit 2. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)

- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Return of study drug, study drug accountability
- Study drug diary
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of RCT-Visit 2. The subject will return the study drug bottle and any remaining capsules to study personnel at the beginning of RCT-Visit 2, and the study drug will not be re-dispensed to the subject. The patient-reported time and date of last dose will be captured and recorded in the CRF.

7.2.3 RCT-Visit 3 (Day 56)

RCT-Visit 3 will take place in the clinic on RCT-Day 56, which is 56 days after the start of RCT study treatment.

The following study procedures will be performed during RCT-Visit 3. These procedures should be performed according to the descriptions detailed in Section 8.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Adverse Events

7.2.4 RCT-Visit 4 (Day 84)

RCT-Visit 4 will take place in the clinic on RCT-Day 84, which is 84 days after the start of RCT

study treatment.

The following study procedures will be performed during RCT-Visit 4. These procedures should be performed according to the descriptions detailed in Section 8.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Adverse Events

Subjects who complete RCT-Visit 4 may proceed to the OLE study component – see Section 7.4.1. Eligible subjects who participate in both the RCT and OLE study components will perform one combined study visit for RCT-Visit 4 and OLE-Visit 1.

RCT-Visit 4 will be the study exit visit for subjects who do not participate in the OLE study component, or those who are discontinued from study treatment or terminated from the study (see Section 7.5) during the RCT study component.

7.3 OLE Study Procedures by Visit

7.3.1 OLE-Visit 1 (Day 1)

Eligible subjects who have completed the RCT study component will proceed to the OLE study component. Investigators are encouraged to review the OLE study component (including study procedures, visit schedule, and ongoing responsibilities) with the subject prior to initiating open label treatment. Subjects who no longer meet the requirements of the study may be eligible for early termination of study participation per Section 7.5 and may not continue to the OLE study component. This may include subjects who are unwilling to comply with study requirements (including dosing compliance and reproductive requirements), subjects who demonstrated noncompliance in the RCT study component, or subjects who experienced a serious adverse event attributable to study treatment in the RCT study component.

Eligible subjects who participate in both the RCT and OLE study components will perform one combined study visit for RCT-Visit 4 and OLE-Visit 1.

The following study procedures will be performed during OLE-Visit 1. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Urine pregnancy test, for women of childbearing potential only
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Bone conduction testing, if applicable
 - Words-in-Noise Test
- Concomitant medications
- Dispensation of study drug, study drug accountability
- Study drug diary
- Adverse Events

Each eligible subject will be dispensed three (3) bottles of open label drug containing capsules of SPI-1005. The date of first dose of open label treatment will be recorded and is by definition OLE-Day 1.

The subject will be instructed to take two (2) capsules from the bottle, twice daily (morning and evening), for a total of four (4) capsules per day. The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 4. The subject will be instructed to return the bottles of study drug and any remaining capsules at their next visit.

7.3.2 OLE-Visit 2 (Day 30)

OLE-Visit 2 will take place via telehealth on OLE-Day 30, which is 30 days after the start of OLE study treatment.

The telehealth interactions in this study will take place remotely via a “non-public facing” remote communication. A “non-public facing” remote communication product is one that, as a default, allows only the intended parties to participate in the communication. Non-public facing remote communication products would include, for example, platforms such as Apple FaceTime, Facebook Messenger video chat, Google Hangouts video, Whatsapp video chat, Zoom, or Skype (US Dept of Health & Human Services, 2020). A telephone call is also acceptable. Only the delegated study staff and subject may participate in the telehealth interaction.

The following study procedures will be performed during OLE-Visit 2. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

7.3.3 OLE-Visit 3 (Day 60)

OLE-Visit 3 will take place via telehealth on OLE-Day 60, which is 60 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 3. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 4.

7.3.4 OLE-Visit 4 (Day 90)

OLE-Visit 4 will take place in the clinic on OLE-Day 90, which is 90 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 4. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Return of study drug, study drug accountability
- Dispensation of study drug, study drug accountability
- Study drug diary
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of OLE-Visit 4, as this dose should not be taken until after blood sample collection for pharmacokinetics. The subject will return the study drug bottles and any remaining capsules to study personnel at the beginning of OLE-Visit 4, and this study drug will not be re-dispensed to the subject. The patient-reported time and date of last dose prior to blood sample collection for pharmacokinetics will be captured and recorded in the CRF.

After blood sample collection for pharmacokinetics, the subject will be dispensed three (3) new bottles of open label drug containing capsules of SPI-1005 for the continuation of open label treatment. The subject should be instructed to take their morning dose from the newly dispensed open label drug after the blood sample collection for pharmacokinetics.

The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 7.

7.3.5 OLE-Visit 5 (Day 120)

OLE-Visit 5 will take place via telehealth on OLE-Day 120, which is 120 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 5. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study

Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

7.3.6 OLE-Visit 6 (Day 150)

OLE-Visit 6 will take place via telehealth on OLE-Day 150, which is 150 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 6. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 7.

7.3.7 OLE-Visit 7 (Day 180)

OLE-Visit 7 will take place in the clinic on OLE-Day 180, which is 180 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 7. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)

- Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Return of study drug, study drug accountability
- Study drug diary
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of OLE-Visit 7, as this dose should not be taken until after blood sample collection for pharmacokinetics. The subject will return the study drug bottles and any remaining capsules to study personnel at the beginning of OLE-Visit 7, and this study drug will not be re-dispensed to the subject. The patient-reported time and date of last dose prior to blood sample collection for pharmacokinetics will be captured and recorded in the CRF.

Subjects exiting study

OLE-Visit 7 will be the study exit visit for subjects who receive 180 days of open label treatment. No study drug will be dispensed to these subjects on OLE-Visit 7, and these subjects will not continue the study or complete OLE-Visit 8–13.

Subjects continuing for 360 day open label treatment

A subset of subjects may continue open label treatment for the 360 day dosing regimen. These subjects will also undergo the following procedure during OLE-Visit 7:

- Dispensation of study drug, study drug accountability

After blood sample collection for pharmacokinetics, the subject will be dispensed three (3) new bottles of open label drug containing capsules of SPI-1005 for the continuation of open label treatment. The subject should be instructed to take their morning dose from the newly dispensed open label drug after the blood sample collection for pharmacokinetics.

These subjects will continue the study and complete the scheduled telehealth interactions and clinic visits in the following sections.

7.3.8 OLE-Visit 8 (Day 210)

OLE-Visit 8 will take place via telehealth on OLE-Day 210, which is 210 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 8. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

7.3.9 OLE-Visit 9 (Day 240)

OLE-Visit 9 will take place via telehealth on OLE-Day 240, which is 240 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 9. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 10.

7.3.10 OLE-Visit 10 (Day 270)

OLE-Visit 10 will take place in the clinic on OLE-Day 270, which is 270 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 10. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)

- Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Return of study drug, study drug accountability
- Dispensation of study drug, study drug accountability
- Adverse Events
- Study drug diary

The subject will be instructed to refrain from taking their morning dose on the day of OLE-Visit 10, as this dose should not be taken until after blood sample collection for pharmacokinetics. The subject will return the study drug bottles and any remaining capsules to study personnel at the beginning of OLE-Visit 10, and this study drug will not be re-dispensed to the subject. The patient-reported time and date of last dose prior to blood sample collection for pharmacokinetics will be captured and recorded in the CRF.

After blood sample collection for pharmacokinetics, the subject will be dispensed three (3) new bottles of open label drug containing capsules of SPI-1005 for the continuation of open label treatment. The subject should be instructed to take their morning dose from the newly dispensed open label drug after the blood sample collection for pharmacokinetics.

7.3.11 OLE-Visit 11 (Day 300)

OLE-Visit 11 will take place via telehealth on OLE-Day 300, which is 300 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 11. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

7.3.12 OLE-Visit 12 (Day 330)

OLE-Visit 12 will take place via telehealth on OLE-Day 330, which is 330 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 12. These procedures

should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
- Concomitant medications
- Adverse Events
- Study drug diary

The subject will be instructed to refrain from taking their morning dose on the day of their next in-clinic visit, OLE-Visit 13.

7.3.13 OLE-Visit 13 (Day 360)

OLE-Visit 13 will take place in the clinic on OLE-Day 360, which is 360 days after the start of OLE study treatment.

The following study procedures will be performed during OLE-Visit 13. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Weight
- Vital Signs
- Blood sample collection for:
 - Clinical laboratory tests (CBC, chemistry)
 - Pharmacokinetics
- Patient-reported outcomes:
 - Columbia-Suicide Severity Rating Scale (C-SSRS)
 - Tinnitus Function Index (TFI)
 - Vertigo Symptoms Scale (VSS)
 - Aural Fullness Scale (AFS)
 - Dizziness Handicap Inventory (DHI)
- Audiology:
 - Otoscopy
 - Pure Tone Audiometry (PTA)
 - Air conduction testing
 - Words-in-Noise Test
- Concomitant medications
- Return of study drug, study drug accountability
- Study drug diary
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of OLE-Visit 13, as this dose should not be taken until after blood sample collection for pharmacokinetics. The subject will return the study drug bottles and any remaining capsules to study personnel at the

beginning of OLE-Visit 13, and this study drug will not be re-dispensed to the subject. The patient-reported time and date of last dose will be captured and recorded in the CRF.

OLE-Visit 13 will be the study exit visit for subjects who receive 360 days open label treatment.

7.4 Early Termination of Study Participants

Study participants may be terminated during the study for any of the following reasons:

- Serious or life-threatening adverse event (AE);
- Failure to comply with the dosing, evaluations, or other requirements of the study;
- Request of the study participant (study participants have the right to discontinue study treatment at any time for any reason);
- Pregnancy;
- Any situation or condition which may threaten the study participant's health or well-being by continuing in the study;
- Administrative (e.g., study termination).

It is the right and the duty of the investigator to interrupt study treatment of any study participant if he/she feels that study discontinuation is necessary to protect the study participant, or that there are unmanageable factors that may interfere significantly with the study procedures and/or the interpretation of results.

If a study participant prematurely discontinues or is discontinued from the study, the primary reason for the discontinuation will be obtained and documented. At the time of discontinuation, every effort (e.g., telephone contact, certified letter) should be made and documented, to ensure all procedures and evaluations scheduled for the study exit visit are performed.

At a minimum collect the following information when a study participant discontinues:

- The reason the study participant discontinued;
- The date of the last dose of test products from the trial;
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
- (Serious) Adverse events;
- Compliance with the test product administration as specified in this protocol;
- Final Assessments: all procedures and evaluations scheduled for the study exit visit (Section 1.3: Schedule of Assessments)

All study participants receiving at least one study treatment dose will be included in the safety analysis, whether or not they complete the study. Reasons for dropouts will be reported and evaluated for possible introduction of bias into the analysis. Adverse events reported by study participants or revealed upon examination or lab testing will be included in the analysis.

8 DESCRIPTION OF STUDY PRODECURES

8.1 Informed Consent Procedures and Documentation

The investigator or qualified designee will explain the study and all study requirements to the subject, answer all of his/her questions, and obtain written informed consent using the most current IRB approved ICF before performing any study-related procedure. A copy of the informed consent will be given to the subject.

8.2 Randomization and Blinding

The RCT study component is a randomized, double-blind, placebo-controlled study design. Appearance of active and placebo capsules is identical. 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 until after database lock. 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.

Study participants who are eligible for enrollment and who take part in the RCT study component 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 3 shows the number of SPI-1005 and placebo study participants in each study treatment group.

Table 3 Approximate number of study participants randomized to each dose

SPI-1005 <i>(400 mg BID)</i>	Placebo <i>(BID)</i>
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.

8.3 Medical History

A detailed medical history will be obtained by the investigator or designee. Medical history should include information on clinically significant personal medical history, including history of diseases, adverse medical events (e.g. seizures, arrhythmias), allergies or reactions to medications or food, and previous surgeries.

Medical history will include Meniere's Disease date of diagnosis, patient report of active symptoms, and history of intratympanic injections. History of any of the following relevant conditions should also be obtained: vestibular migraine, benign paroxysmal positional vertigo,

sudden sensorineural hearing loss, autoimmune inner ear disease, and tinnitus.

Medical history will include COVID-19 vaccination, including which vaccine was received and date(s) of administration. This data will also be captured if a COVID-19 vaccine is received by the subject while the subject is participating in this study.

Medical history will also include whether the subject has participated in a prior SPI-1005 trial.

8.4 Physical Exam

The investigator or designee (must be a licensed medical professional) will perform a physical examination of the following organ systems: Eyes, ears, nose, head, oropharynx, respiratory system, cardiovascular system, abdomen, skin, musculoskeletal reflexes, and extremities. For each abnormal finding, the investigator will comment on clinical significance (clinically significant or not clinically significant). Clinically significant changes from the baseline physical examinations will be recorded as adverse events.

8.5 Vital Signs

Vital signs will be obtained by the principal investigator or designee. Subjects will be in a seated or semi-recumbent position for at least 5 minutes. If the scheduled time for vital sign measurements coincides with a blood collection, the vital signs should be performed prior to the blood collection, or at least 5 minutes afterwards. This same timing for obtaining the vital signs (before or after the blood collection) should be used for all vital sign measurements.

Systolic and diastolic blood pressure (mmHg), pulse rate (bpm), body temperature (Celsius), and the actual clock time (24:00) will be recorded in source and captured on the CRF.

Vital signs will be reviewed by the investigator for clinical significance (clinically significant or not clinically significant). Any clinically significant change from baseline for vital sign measurement (not associated with another adverse event) will be recorded in source as an adverse event and captured on the CRF.

8.6 Clinical Laboratory Tests

The clinical laboratory tests – hematology (CBC) and serum chemistry, as described in Table 4 – will be performed according to standard laboratory procedures. A central laboratory (CRO) will be used for the study, and a lab manual with detailed instructions for blood collection, processing, and shipping will be provided to study centers. All laboratory tests will be collected according to the schedule of assessments in Section 1.3. Results of laboratory tests will be provided to investigators and captured in the study database with reference ranges.

Table 4 SPI-1005-351 Clinical Laboratory Tests

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

Clinical laboratory samples should be collected in the fasted state (after an overnight fast for morning sample collections and at least 4 hours without food for other samples) when feasible, or date and time of last meal recorded. Clinical laboratory test will be obtained prior to study drug administration.

The clinical laboratory test results will be reviewed by the investigator to determine clinical significance (clinically significant or not clinically significant). Any clinically significant change from baseline in a laboratory test will be recorded as an Adverse Event. The test should be repeated at appropriate time intervals until it returns to baseline or becomes a clinically insignificant finding. If the laboratory result does not return to clinically insignificant levels within a reasonable time, in the opinion of the Investigator, the subject may be discontinued from the study after discussion with the Medical Monitor.

8.7 Pharmacokinetics

Three (3) mL of blood will be collected for pharmacokinetics at the specified time points indicated in schedule of assessments in Section 1.3. The lab manual contains detailed instructions on collection, processing, and shipping of these blood samples. Sample collection times (actual clock time using 24:00) are to be recorded and will be captured in the CRF.

The subject should refrain from taking their morning dose of study treatment on the day of any study visit (RCT or OLE), until after the blood draw for pharmacokinetic analysis has been collected, in order to obtain trough plasma levels in the blood sample collection.

Trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined by LCMS/MS at specified visits. The corresponding plasma levels of selenium will be determined by ICP-MS. In prior ADME studies involving SPI-1005, the plasma half-life of ebselen is approximately 8-12 hours, 2-glucuronyl selenobenzanilide accounts for >90% of the metabolites, and it is cleared through the urine.

8.8 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a validated suicide risk assessment tool (Posner et al., 2011). A licensed version of the C-SSRS for clinical research is obtained from The Research Foundation for Mental Hygiene Inc., the parent organization of The Columbia Lighthouse Project. The C-SSRS is administered by trained research staff and assesses suicidal ideation and behavior across four domains – severity of ideation, intensity of ideation, behavior, and lethality. The C-SSRS will be administered at baseline (lifetime suicidal ideation and behavior assessment) and at each study visit according to the schedule of assessments in Section 1.3. A positive finding in the C-SSRS for suicidal ideation with method and intent and/or suicidal behavior prompts immediate referral to appropriate psychiatric care, and will be reported as a Serious Adverse Event (SAE). Data from the C-SSRS will be captured from participants completing the assessment, and the values captured in the CRF.

8.9 Patient-Reported Outcomes

8.9.1 Tinnitus Functional Index & Tinnitus Loudness

The Tinnitus Functional Index (TFI) is a validated patient-reported questionnaire that scales tinnitus severity and negative impact at baseline and post treatment change across multiple domains (Meikle, Henry et al., 2012). It is a 25-question instrument assessing tinnitus degree of intrusiveness, patient's sense of control, impact to cognition, effect on patient's sleep, impact to hearing, interference with relaxation, overall quality of life, and patient's emotional response to tinnitus. The TFI assesses symptomology within a "past week" window of time. The TFI will be administered according to the schedule of assessments in Section 1.3. Participants should complete the TFI prior to audiologic and clinical laboratory tests. Data from the TFI will be captured from participants completing the assessment, and the values captured in the CRF. Tinnitus Loudness (TL) will be assessed by Question #2 of the TFI, a visual analog scale (0-10) that asks the patient to rate "How strong or loud was your tinnitus?" TL will be a specific secondary efficacy endpoint for this study. See APPENDIX II - Tinnitus Functional Index (TFI) for the TFI questionnaire and instructions.

8.9.2 Vertigo Symptoms Scale

The Vertigo Symptom Scale (VSS) short form is a validated patient-reported instrument consisting of 15 questions or items addressing the frequency and severity of dizziness symptoms within the prior month (Yardley, Donovan-Hall et al., 2004). The VSS has 2 core dimensions: vertigo-balance and autonomic-anxiety symptoms totaling 60 points. The VSS will be administered according to the schedule of assessments in Section 1.3. Study participants will complete the VSS prior to audiological and clinical laboratory tests. Data from the VSS will be captured from study participants completing the assessment, and the values will be captured in the CRF. See APPENDIX III - Vertigo Symptom Scale (VSS) – Short Form questionnaire and instructions.

8.9.3 Aural Fullness Scale

Aural fullness or pressure will be assessed by patient-reported scoring of aural fullness or pressure (Aural Fullness Scale, AFS). Participants will be provided with a Visual Analog Scale from 0-10 and instructed to rate their current symptoms of aural fullness or pressure. The AFS

has been previously validated in a Meniere's Disease population (Patel et al., 2016). The AFS will be administered according to the schedule of assessments in Section 1.3. Study participants will complete the AFS prior to audiological and clinical laboratory tests. Data from the AFS will be captured from study participants completing the assessment, and the values will be captured in the CRF.

8.9.4 Dizziness Handicap Inventory

The Dizziness Handicap Inventory (DHI) is a validated patient-reported questionnaire which evaluates the patient impact of vestibular dizziness and unsteadiness across three domains: functional, emotional, and physical (Jacobson & Newman, 1990). The DHI will be administered according to the schedule of assessments in Section 1.3. Study participants will complete the DHI prior to audiological and clinical laboratory tests. Data from the DHI will be captured from study participants completing the assessment, and the values will be captured in the CRF. See APPENDIX IV - Dizziness Handicap Inventory (DHI) for the DHI questionnaire and instructions.

8.10 Audiology

Audiological evaluations will be performed at specified intervals to evaluate the efficacy of SPI-1005. Tests include otoscopy, tympanometry, pure tone audiometry, and word recognition performed by a physician or audiologist.

8.10.1 Otoscopy

The examination of the ear canal and tympanic membrane via an otoscope will be performed according to the schedule of assessments in Section 1.3. The otoscopic exam is to ensure that the ear canals are clear of wax, fluid or lesions prior to performing tympanometry and audiometry. Results will be documented in the study participant's medical record and abnormalities will be captured in the Physical Examination and/or Adverse Event portions of the CRF.

8.10.2 Tympanometry

Tympanometry is an assessment of middle ear function or tympanic membrane compliance and will be performed according to the schedule of assessments in Section 1.3. Tympanometry will be performed with equipment approved by SPI. Measurements will not be captured in the CRF. Results will be assessed by the investigator as normal or abnormal and documented in the study participant's medical record.

8.10.3 Pure Tone Audiometry

Pure tone audiometry (PTA) will be performed using a modified Hughson-Westlake procedure to evaluate the effects of SPI-1005 on hearing sensitivity. Hearing thresholds levels (HL) will be determined 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). Results will be documented in the study participant's medical record. Sound level and frequency will be captured in the CRF.

To maximize test validity and reliability, ASHA Guidelines for Manual Pure Tone Threshold

Audiometry (ASHA, 2005) will be followed. Audiological evaluations will take place in a sound-treated testing facility having ambient noise levels conforming to ANSI S3.1-1999 standards. Pure tone audiometric testing will be performed using a calibrated audiometer, capable of producing tonal stimuli, with insert earphones calibrated to meet ANSI 3.6-2004 specifications for clinical audiometers (provided or approved by SPI). Study participants may see different audiologists across the four test intervals; however, the same group of audiologists will perform baseline and post-treatment testing in this study. Insert or circumaural earphones placed by the audiologists will be used to eliminate the risk of false positive hearing loss due to poor earphone placement.

8.10.4 Words-in-Noise Test

The Words-in-Noise Test (WIN) is a word recognition test which involves the presentation of 35 monosyllabic words to each ear at 7 different background noise levels. The background noise consists of multi-talker babble and is adjusted based on the individual participant's baseline hearing sensitivity. The WIN is conducted at 7 different signal-to-noise ratios (SNRs): 24, 20, 16, 12, 8, 4 and 0. Five unique words are presented at each SNR to each ear for a total of 70 words bilaterally. For this protocol, the WIN will be performed in alignment with US Department of Defense standard criteria (Wilson & Burks, 2005). Results will be documented in the study participant's medical record and captured in the CRF.

8.11 Concomitant Medications

Each subject will be interviewed about concomitant medications, including over-the-counter medications and non-medicinal treatments or supplements, at screening and at each clinic visit. At the screening visit, prior medications used within 60 days of study enrollment should also be elicited to facilitate screening for ototoxic medications and steroids. Any reported non-study medication will be recorded in the CRF and evaluated by the investigators.

8.11.1 Prohibited Medications

Non-study medications are permitted during the course of this study except for those having known ototoxic side effects such as:

- IV or otic aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin);
- IV platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or
- IV loop diuretics (furosemide);

Or, the use of systemic or otic steroids.

Use of potentially ototoxic medications or steroids may meet criteria for exclusion (see Exclusion Criteria) or merit discontinuation of a study subject.

8.12 Study Drug Diary

The subject will be provided a study drug diary each time study treatment (RCT or OLE) is administered. The subject will be instructed to complete a corresponding entry in the diary each time they take their study treatment. The subject will record the date and time of each dose, whether any doses were missed, and any issues or concerns with the study drug.

9 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1 Definition of Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a study participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this study treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

9.2 Definition of Serious Adverse Event

An adverse event (AE) or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a study participant who received SPI-1005
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse

9.3 Classification of an Adverse Event

9.3.1 Severity of Event

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning
- **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious.”

9.3.2 Relationship to Study Treatment

All adverse events must have their relationship to study intervention assessed by the Investigator

who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.3.3 *Unanticipated Adverse Event*

The Investigator will be responsible for determining whether an adverse event is unanticipated. An AE will be considered unanticipated if the nature, severity, or frequency of the event is not consistent with the risk information previously described protocol and in the Investigator's Brochure.

9.3.4 *Time Period and Frequency for Event Assessment and Follow-up*

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes the event description, time of onset, clinician's assessment of severity, relationship to study product

(assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.3.5 Adverse Event Reporting

The investigator, along with delegated study staff, will record all adverse events with start dates occurring any time after informed consent is obtained until the end of study participation. At each study visit, the investigator will inquire about occurrence of AE/SAEs since the previous visit. Events will be followed for outcome until resolution or stabilization. The AE term should be reported in standard medical terminology when possible.

All SAEs must be reported to the Medical Monitor within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a scanned copy by email to [TBD, Medical Monitor to be provided by CRO].

Additional follow-up information, if required or available, should all be scanned and emailed within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Should a pregnancy occur, it must be reported and recorded in the study participant's medical record and recorded in the Medical History form in the CRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the study participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be dealt with as AEs.

Any serious or unanticipated adverse events must be reported to SPI, including death or life-threatening events, disabling or incapacitating conditions, or any event that requires hospitalization. Serious adverse events occurring during the duration of the study or within 28 days of the study participant's last dose must be reported within 24 hours to [TBD, Medical Monitor to be provided by CRO], even if the event appears unrelated to the study treatment.

Safety Reporting contact information:

[TBD, Medical Monitor to be provided by CRO].

Sound Pharmaceuticals is responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potentially serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Both SPI and investigators have the right to terminate this study at any time, and to arrange an appropriately agreed upon schedule for termination, if necessary. This information will be provided to each study participant during the informed consent process.

10 STATISTICAL CONSIDERATIONS

Adverse events will be coded using MedDRA (Version 18.1 or higher) and summarized by each treatment group (placebo or SPI-1005 400 mg BID) for the number of adverse events. Comparisons will be made between baseline, while on study treatment, while on open-label treatment, and all follow-up values.

Vital signs and clinical laboratory results will be summarized by each treatment group (placebo or SPI-1005 400 mg BID). Comparisons will be made between baseline, while on study treatment, while on open-label treatment, and all follow-up values. Abnormal values will be identified and categorized by severity.

Audiometric data will be collected in the form of categorical and continuous variables. 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, 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. Backward stepwise regression will be used to determine the final model including only variables with significance at a .05 level.

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 analysis will be detailed in the Statistical Analysis Plan. The RCT sample size of 100 study participants per treatment group is sufficient to reject the type I error using two-tailed test for significance with >90% power for the co-primary endpoint involving a ≥ 10 dB improvement in low frequency hearing, and >94% power for the primary endpoint involving ≥ 4 words improvement in word recognition.

All study participants will be included in the analyses and include: all randomized study participants; all dosed study participants; and all evaluable study participants. The intent to treat and per protocol populations used for a given analysis will be detailed in the Statistical Analysis Plan.

11 INVESTIGATIONAL RECORD KEEPING

All study records including the disposition of the drug (i.e., dates, quantity, use by study participants, and unused supplies) and study participant Case Report Forms (CRFs), source documents, consent forms, and chart notes will be maintained and retained in accordance with federal regulations set forth by 28 CFR, Part 312.62. Each study participant case history will contain documentation confirming that informed consent was obtained from the study participant prior to participation in the study. All personnel associated with this study will make their best effort to ensure anonymity and confidentiality of study participant records.

Case histories and study records will be made promptly available upon request to SPI or FDA personnel. SPI will furnish study progress reports annually to the FDA. Any alarming safety reports will be made available immediately to SPI and the FDA in accordance with regulatory requirements.

11.1 Protocol Deviations and Amendments

Any deviation from protocol deemed appropriate to prevent potential harm to an individual study participant does not require pre-approval from the clinical site IRB or authorities at SPI; however, such deviations must be reported to the IRB and SPI within five days of the occurrence.

If a deviation to the protocol is deemed appropriate for all study participants, a formal amendment must be entered for the study to reflect the change. If the deviation applies to only one study participant, the details and reasons for the change must be thoroughly documented in the study file.

Both SPI and clinical investigators must be in concurrence with any formal amendment to the protocol, and such an amendment must be approved by the IRB if it has the potential to impact a study participant's safety.

11.2 Publication Policy

The results of this clinical trial may be presented at scientific meetings or published. All published data, manuscripts, materials, and presentations are the joint property of Sound Pharmaceuticals, Inc. (SPI) and the appropriate clinical investigator(s). Authorship is determined by mutual agreement. Any data, manuscript, or abstract submitted for publication must be copied to all designated personnel at SPI and the appropriate clinical investigator(s) at least 30 days prior to submission so that proprietary information can be protected and all concerned parties will be able to make informed comments.

11.3 Study Monitoring

Before an investigational site can enter a study participant into the study, a representative of SPI will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of SPI or its representatives. This will be documented in a Clinical Trial Agreement between SPI and the investigator.

During the study, a monitor from SPI or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the study participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each study participant (e.g., clinic charts).
- Data are entered into the CRFs in a timely manner.
- Record and report any protocol deviations not previously sent to SPI.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to SPI, and those SAEs that met criteria for reporting have been reported to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

The Investigator assumes ultimate responsibility for the conduct of the study and remains readily accessible throughout the duration of the study.

11.4 Audits and Inspections

Authorized representatives of SPI, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an SPI audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact SPI immediately if contacted by a regulatory agency about an inspection.

The Investigator agrees to allow the monitor to inspect the drug storage area, study drug inventory, drug accountability records, study participant charts and study source documents, and other records relative to study conduct.

11.5 Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for SPI or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records

to ensure compliance with Good Clinical Practices and all applicable regulatory requirements, SPI may conduct a quality assurance audit.

11.6 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Sponsor. However, authorized regulatory officials, IRB/IEC personnel, Sound Pharmaceuticals, Inc. and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and/or treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

12 INSTITUTIONAL REVIEW BOARD (IRB)

The final clinical protocol, the final version of the Informed Consent Form, and recruitment materials must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The central IRB for this study will be Western Institutional Review Board (WIRB). The Investigator must verify that IRB approval of the protocol, consent form and recruitment materials for the investigation is obtained prior to conducting study evaluations. The Investigator must maintain all IRB approvals and all materials approved by the IRB for this study including Informed Consent Form and recruitment materials and made available for inspection.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and biannually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. SPI will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.1 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

REFERENCES

- American Academy of Otolaryngology-Head and Neck Foundation. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg.* 1995; 113:181-5.
- Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease. *Otolaryngol Head Neck Surg.* 2016 Mar;154(3):403-4. doi: 10.1177/0194599816628524. Epub 2016 Feb 16.
- Jacobson GP, Newman CW. The Development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg.* 1990;116(4):424-427. doi:10.1001/archotol.1990.01870040046011
- Kil J, Huang M, Nguyen S, Chandrasekhar S, Lambert P. SPI-1005 a novel investigational drug for the treatment of Meniere's disease. 2018 ARO Abstract PS 824.
- Kil, J., Lobarinas, E., Spankovich, C., Griffiths, S. K., Antonelli, P. J., Lynch, E. D., & Le Prell, C. G. (2017). Safety and efficacy of ebselen for the prevention of noise-induced hearing loss: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet.* doi:10.1016/s0140-6736(17)31791-9
- Kil, J., Pierce, C., Tran, H., Gu, R., & Lynch, E. D. (2007). Ebselen treatment reduces noise induced hearing loss via the mimicry and induction of glutathione peroxidase. *Hear Res,* 226(1-2), 44-51. doi:10.1016/j.heares.2006.08.006
- Lee, J. E., Nakagawa, T., Kim, T. S., Endo, T., Shiga, A., Iguchi, F., Lee, S. H., & Ito, J. (2004). Role of reactive radicals in degeneration of the auditory system of mice following cisplatin treatment. *Acta Otolaryngol,* 124(10), 1131-1135.
- Lynch, E. D., Gu, R., Pierce, C., & Kil, J. (2005a). Combined oral delivery of ebselen and allopurinol reduces multiple cisplatin toxicities in rat breast and ovarian cancer models while enhancing anti-tumor activity. *Anti-Cancer Drugs,* 16(5), 569-579.
- Lynch, E. D., Gu, R., Pierce, C., & Kil, J. (2005b). Reduction of acute cisplatin ototoxicity and nephrotoxicity in rats by oral administration of allopurinol and ebselen. *Hear Res,* 201(1-2), 81-89. doi:10.1016/j.heares.2004.08.002
- Lynch, E. D., & Kil, J. (2009). Development of ebselen, a glutathione peroxidase mimic, for the prevention and treatment of noise-induced hearing loss. *Seminars in Hearing,* 30(01), 047-055. doi:10.1055/s-0028-1111106
- Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. W., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W., Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., Sweetow, R., & Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear Hear,* 33(2), 153-176. doi:10.1097/AUD.0b013e31822f67c0
- Müller, A., Cadenas, E., Graf, P., & Sies, H. (1984). A novel biologically active seleno-organic compound--I. Glutathione peroxidase-like activity in vitro and antioxidant capacity of PZ 51 (Ebselen). *Biochem Pharmacol,* 33(20), 3235-3239.
- Müller, A., Gabriel, H., Sies, H., Terlinden, R., Fischer, H., & Romer, A. (1988). A novel biologically active selenoorganic compound--VII. Biotransformation of ebselen in perfused rat liver. *Biochem Pharmacol,* 37(6), 1103-1109.
- Namura, S., Nagata, I., Takami, S., Masayasu, H., & Kikuchi, H. (2001). Ebselen reduces cytochrome c release from mitochondria and subsequent DNA fragmentation after transient focal cerebral ischemia in mice. *Stroke,* 32(8), 1906-1911.

- Noguchi, N., Gotoh, N., & Niki, E. (1994). Effects of ebselen and probucol on oxidative modifications of lipid and protein of low density lipoprotein induced by free radicals. *Biochim Biophys Acta*, 1213(2), 176-182.
- Noguchi, N., Yoshida, Y., Kaneda, H., Yamamoto, Y., & Niki, E. (1992). Action of ebselen as an antioxidant against lipid peroxidation. *Biochem Pharmacol*, 44(1), 39-44.
- Patel, M., Agarwal, K., Arshad, Q., Hariri, M., Rea, P., Seemungal, B., et al. (2016). Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: a randomised, double-blind, comparative effectiveness trial. *Lancet*, 38(10061), 2753-2762. doi: 10.1016/S0140-6736(16)31461-1
- Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ (2011). The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. *American Journal of Psychiatry* 168(12): 1266-77.
- Reiter, R., & Wendel, A. (1984). Selenium and drug metabolism--II. Independence of glutathione peroxidase and reversibility of hepatic enzyme modulations in deficient mice. *Biochem Pharmacol*, 33(12), 1923-1928.
- U.S. Department of Health and Human Services. FAQs on Telehealth and HIPAA during the COVID-19 nationwide public health emergency. HHS-0945--F-4530. Published October 02, 2020. Accessed March 16, 2021. <https://www.hhs.gov/guidance/document/faqs-telehealth-and-hipaa-during-covid-19-nationwide-public-health-emergency>
- Wendel, A., Fausel, M., Safayhi, H., Tiegs, G., & Otter, R. (1984). A novel biologically active seleno-organic compound--II. Activity of PZ 51 in relation to glutathione peroxidase. *Biochem Pharmacol*, 33(20), 3241-3245.
- Yardley, L., Donovan-Hall, M., Smith, H. E., Walsh, B. M., Mullee, M., & Bronstein, A. M. (2004). Effectiveness of primary care-based vestibular rehabilitation for chronic dizziness. *Ann Intern Med*, 141(8), 598-605.

13 APPENDICES

13.1 APPENDIX I - Diagnosis of Meniere's Disease

Definite Meniere's Disease

Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h
Audiometrically documented low- to midfrequency sensorineural hearing loss in 1 ear, defining the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo
Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis

Probable Meniere's Disease

Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h
Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
Not better accounted for by another vestibular diagnosis

Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease. Otolaryngol Head Neck Surg. 2016 Mar;154(3):403-4. doi: 10.1177/0194599816628524. Epub 2016 Feb 16.

13.2 APPENDIX II - Tinnitus Functional Index (TFI)

TINNITUS FUNCTIONAL INDEX

Today's Date _____ Your Name _____
 Month / Day / Year Please Print

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: 10% or ①.

I	Over the PAST WEEK...
1. What percentage of your time awake were you consciously AWARE OF your tinnitus? <i>Never aware</i> ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◀ <i>Always aware</i>	
2. How STRONG or LOUD was your tinnitus? <i>Not at all strong or loud</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Extremely strong or loud</i>	
3. What percentage of your time awake were you ANNOYED by your tinnitus? <i>None of the time</i> ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◀ <i>All of the time</i>	
SC	Over the PAST WEEK...
4. Did you feel IN CONTROL in regard to your tinnitus? <i>Very much in control</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Never in control</i>	
5. How easy was it for you to COPE with your tinnitus? <i>Very easy to cope</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Impossible to cope</i>	
6. How easy was it for you to IGNORE your tinnitus? <i>Very easy to ignore</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Impossible to ignore</i>	
C	Over the PAST WEEK...
7. Your ability to CONCENTRATE ? <i>Did not interfere</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Completely interfered</i>	
8. Your ability to THINK CLEARLY ? <i>Did not interfere</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Completely interfered</i>	
9. Your ability to FOCUS ATTENTION on other things besides your tinnitus? <i>Did not interfere</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Completely interfered</i>	
SL	Over the PAST WEEK...
10. How often did your tinnitus make it difficult to FALL ASLEEP or STAY ASLEEP ? <i>Never had difficulty</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Always had difficulty</i>	
11. How often did your tinnitus cause you difficulty in getting AS MUCH SLEEP as you needed? <i>Never had difficulty</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Always had difficulty</i>	
12. How much of the time did your tinnitus keep you from SLEEPING as DEEPLY or as PEACEFULLY as you would have liked? <i>None of the time</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>All of the time</i>	

Copyright Oregon Health & Science University 2008 08.15.08

TINNITUS FUNCTIONAL INDEX

PAGE 2

Please read each question below carefully. To answer a question, select **ONE** of the numbers that is listed for that question, and draw a **CIRCLE** around it like this: **10%** or **1**.

A	Over the PAST WEEK, how much has your tinnitus interfered with...	Did not interfere	Completely interfered
		0 1 2 3 4 5 6 7 8 9 10	
	13. Your ability to HEAR CLEARLY ?	0 1 2 3 4 5 6 7 8 9 10	
	14. Your ability to UNDERSTAND PEOPLE who are talking?	0 1 2 3 4 5 6 7 8 9 10	
	15. Your ability to FOLLOW CONVERSATIONS in a group or at meetings?	0 1 2 3 4 5 6 7 8 9 10	
R	Over the PAST WEEK, how much has your tinnitus interfered with...	Did not interfere	Completely interfered
		0 1 2 3 4 5 6 7 8 9 10	
	16. Your QUIET RESTING ACTIVITIES ?	0 1 2 3 4 5 6 7 8 9 10	
	17. Your ability to RELAX ?	0 1 2 3 4 5 6 7 8 9 10	
	18. Your ability to enjoy "PEACE AND QUIET" ?	0 1 2 3 4 5 6 7 8 9 10	
Q	Over the PAST WEEK, how much has your tinnitus interfered with...	Did not interfere	Completely interfered
		0 1 2 3 4 5 6 7 8 9 10	
	19. Your enjoyment of SOCIAL ACTIVITIES ?	0 1 2 3 4 5 6 7 8 9 10	
	20. Your ENJOYMENT OF LIFE ?	0 1 2 3 4 5 6 7 8 9 10	
	21. Your RELATIONSHIPS with family, friends and other people?	0 1 2 3 4 5 6 7 8 9 10	
	22. How often did your tinnitus cause you to have difficulty performing your WORK OR OTHER TASKS , such as home maintenance, school work, or caring for children or others? <i>Never had difficulty</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◄ <i>Always had difficulty</i>		
E	Over the PAST WEEK...		
	23. How ANXIOUS or WORRIED has your tinnitus made you feel? <i>Not at all anxious or worried</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◄ <i>Extremely anxious or worried</i>		
	24. How BOTHERED or UPSET have you been because of your tinnitus? <i>Not at all bothered or upset</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◄ <i>Extremely bothered or upset</i>		
	25. How DEPRESSED were you because of your tinnitus? <i>Not at all depressed</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◄ <i>Extremely depressed</i>		

INSTRUCTIONS FOR SCORING THE TINNITUS FUNCTIONAL INDEX (TFI)

1. PREPARATION FOR SCORING:

- A. **Two items to be transformed:** Items #1 and #3 require a simple transformation from a percentage scale to a 0-10 scale, achieved by dividing the values circled by the respondent by 10. The examiner should write the transformed value in the margin beside the relevant item, preferably using ink of a different color than that used by the respondent.
- B. **Ambiguous items:** Because respondents differ in regard to how clearly, they circle or mark their answers on the 0-10 scale for each item, the examiner should review every item to resolve any ambiguities. It is helpful if examiners note their decision about each answer in the margin beside the given item, using the differently-colored ink. Some commonly-occurring ambiguities and how to handle them are as follows:

(1) More than one value marked on the 0-10 scale for a given item

Typically done by respondents whose tinnitus undergoes large variations over time. The clinic or the examiner should settle on a consistent procedure for all such responses, such as (a) averaging the multiple values indicated for a given item, or (b) marking the item "cannot code", thus removing that item from consideration in the overall TFI score. (The latter choice reduces the information available for calculating the respondent's overall score, and may be desirable only in extremely variable cases where the respondent's reliability is questionable.)

(2) Respondent marks a value between the 0-10 values on the item scale

Again, the clinic or the examiner should settle on a consistent procedure for handling all such ambiguous responses in the same way, such as (a) noting a value of 3.5 in the margin, for a respondent who marked the scale between 3 and 4, or (b) collapsing the intermediate value either to the right (to 4) or to the left (to 3).

(3) Respondent does not make any response to a given item

The clinic or examiner should decide beforehand how they will indicate missing values, and that notation (e.g. "NA" for "No Answer") should be entered in the margin. If the data will be entered into a computer database, a standard missing value such as "99" can be entered in the margin beside the relevant item. Of course, care must be taken to exclude "99" values if the examiner performs a manual calculation of the overall TFI score.

- C. **Unambiguous items:** To facilitate rapid scanning and summing of all valid answers to obtain the respondent's overall TFI score, all of the unambiguous values indicated by the respondent should also be noted in the margin, each such value beside its corresponding item. The examiner can then quickly generate a valid score for the overall TFI.

2. CALCULATION OF OVERALL TFI SCORE:

- (1) Sum all valid answers from both TFI pages (maximum possible score = 250 if the respondent were to rate all 25 TFI items at the maximum value of 10).
- (2) Divide by the number of questions for which that respondent provided valid answers (yields the respondent's mean item score for all items having valid answers).
- (3) Multiply by 10 (provides that respondent's overall TFI score within 0-100 range).

CAUTION

Overall TFI score is **not valid** if respondent **omits 7 or more** items. To be valid as a measure of tinnitus severity, the respondent must answer **at least 19 items** (76% of items).

3. CALCULATION OF SUBSCALE SCORES

The 8 subscales address 8 important domains of negative tinnitus impact as indicated below. Each subscale has a brief title (in capital letters) and a 1- or 2-letter abbreviation (e.g., I for Intrusive, Sc for Sense of Control):

SUBSCALE NAME (and conceptual content)	<u>ITEMS IN SUBSCALE</u>
I: INTRUSIVE (unpleasantness, intrusiveness, persistence)	#1, #2, #3
Sc: SENSE OF CONTROL (reduced sense of control)	#4, #5, #6
C: COGNITIVE (cognitive interference)	#7, #8, #9
SL: SLEEP (sleep disturbance)	#10, #11, #12
A: AUDITORY (auditory difficulties attributed to tinnitus)	#13, #14, #15
R: RELAXATION (interference with relaxation)	#16, #17, #18
Q: QUALITY OF LIFE (QOL) (quality of life reduced)	#19, #20, #28, #22
E: EMOTIONAL (emotional distress)	#23, #24, #25

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

- 1) Sum all of that respondent's valid answers for a given subscale.
- 2) Divide 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.

CAUTION

Do not attempt to compute a respondent's overall TFI score by combining that respondent's valid subscale scores, as the valid subscales may encompass a total number of items that is different from the number of items accepted as valid for the overall TFI score.

13.3 APPENDIX III - Vertigo Symptom Scale (VSS) – Short Form

We would like to know what dizziness-related symptoms you have had just recently. Please circle the appropriate number to indicate about how many times you have experienced each of the symptoms listed below during the **past month**.

How often have you had the following symptoms during the last month :	Never	A few times	Several times	Quite often (every week)	Very often (most days)
1. A feeling that either you, or things around you, are spinning or moving, lasting less than 20 minutes	0	1	2	3	4
2. Hot or cold spells	0	1	2	3	4
3. Nausea (feeling sick), vomiting	0	1	2	3	4
4. A feeling that either you, or things around you, are spinning or moving, lasting more than 20 minutes	0	1	2	3	4
5. Heart pounding or fluttering	0	1	2	3	4
6. A feeling of being dizzy, disoriented or “swimmy”, lasting all day	0	1	2	3	4
7. Headache, or feeling of pressure in the head	0	1	2	3	4
8. Unable to stand or walk properly without support, veering or staggering to one side	0	1	2	3	4
9. Difficulty breathing, been short of breath	0	1	2	3	4
10. Feeling unsteady, about to lose balance, lasting more than 20 minutes	0	1	2	3	4
11. Excessive sweating	0	1	2	3	4
12. Feeling faint, about to black out	0	1	2	3	4
13. Feeling unsteady, about to lose balance, lasting less than 20 minutes	0	1	2	3	4
14. Pains in the heart or chest region	0	1	2	3	4
15. A feeling of being dizzy, disoriented or “swimmy”, lasting less than 20 minutes	0	1	2	3	4

Sum-scores

To obtain a measure of symptom severity, sum marked responses of the total and/or the respective sub-scales. Mean score: divide sum-score by respective number of scale items.	
TOTAL SCALE Range: 0-60	
Vertigo/balance sub-scale Sub-scale score range: 0-32 Sum items: 1,3,4,6,8,10,13,15	
Autonomic/anxiety sub-scale Sub-scale score range: 0-28 Sum items: 2,5,7,9,11,12,14	

13.4 APPENDIX IV – Aural Fullness Scale (AFS)

Please circle one number to answer the following question.

In the past month, how **strong** or **loud** was your aural fullness or pressure?

Not at all strong or loud ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ Extremely strong or loud

13.5 APPENDIX IV – Dizziness Handicap Inventory (DHI)

The Dizziness Handicap Inventory (DHI)

P1. Does looking up increase your problem?	☐ Yes ☐ Sometimes ☐ No
E2. Because of your problem, do you feel frustrated?	☐ Yes ☐ Sometimes ☐ No
F3. Because of your problem, do you restrict your travel for business or recreation?	☐ Yes ☐ Sometimes ☐ No
P4. Does walking down the aisle of a supermarket increase your problems?	☐ Yes ☐ Sometimes ☐ No
F5. Because of your problem, do you have difficulty getting into or out of bed?	☐ Yes ☐ Sometimes ☐ No
F6. Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	☐ Yes ☐ Sometimes ☐ No
F7. Because of your problem, do you have difficulty reading?	☐ Yes ☐ Sometimes ☐ No
P8. Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	☐ Yes ☐ Sometimes ☐ No
E9. Because of your problem, are you afraid to leave your home without having without having someone accompany you?	☐ Yes ☐ Sometimes ☐ No
E10. Because of your problem have you been embarrassed in front of others?	☐ Yes ☐ Sometimes ☐ No
P11. Do quick movements of your head increase your problem?	☐ Yes ☐ Sometimes ☐ No
F12. Because of your problem, do you avoid heights?	☐ Yes ☐ Sometimes ☐ No
P13. Does turning over in bed increase your problem?	☐ Yes ☐ Sometimes ☐ No
F14. Because of your problem, is it difficult for you to do strenuous homework or yard work?	☐ Yes ☐ Sometimes ☐ No
E15. Because of your problem, are you afraid people may think you are intoxicated?	☐ Yes ☐ Sometimes ☐ No
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	☐ Yes ☐ Sometimes ☐ No
P17. Does walking down a sidewalk increase your problem?	☐ Yes ☐ Sometimes ☐ No
E18. Because of your problem, is it difficult for you to concentrate	☐ Yes ☐ Sometimes ☐ No

F19. Because of your problem, is it difficult for you to walk around your house in the dark?	☐ Yes ☐ Sometimes ☐ No
E20. Because of your problem, are you afraid to stay home alone?	☐ Yes ☐ Sometimes ☐ No
E21. Because of your problem, do you feel handicapped?	☐ Yes ☐ Sometimes ☐ No
E22. Has the problem placed stress on your relationships with members of your family or friends?	☐ Yes ☐ Sometimes ☐ No
E23. Because of your problem, are you depressed?	☐ Yes ☐ Sometimes ☐ No
F24. Does your problem interfere with your job or household responsibilities?	☐ Yes ☐ Sometimes ☐ No
P25. Does bending over increase your problem?	☐ Yes ☐ Sometimes ☐ No

Used with permission from GP Jacobson.

Jacobson GP, Newman CW: The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1990;116: 424-427

DHI Scoring Instructions

The patient is asked to answer each question as it pertains to dizziness or unsteadiness problems, specifically considering their condition during the last month. Questions are designed to incorporate functional (F), physical (P), and emotional (E) impacts on disability.

To each item, the following scores can be assigned:

No=0 Sometimes=2 Yes=4

Scores:

Scores greater than 10 points should be referred to balance specialists for further evaluation.

16-34 Points (mild handicap)

36-52 Points (moderate handicap)

54+ Points (severe handicap)