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Investigational Product: SPI-1005

Clinical Protocol: SPI-1005-151

**A PHASE 1b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-
CONTROLLED STUDY TO EVALUATE THE SAFETY,
PHARMACOKINETICS AND PHARMACODYNAMICS OF SPI-1005
IN ADULTS WITH MENIERE'S DISEASE**

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Chemical Name: 2-phenyl-1,2-benzisoselenazol-3 (2H) -one

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Statement of Confidentiality

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure for SPI-1005. I have read the Protocol SPI-1005-151 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

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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
bid	Twice-daily dosing
CBC	Complete Blood Count
Chem-20	Chemistry-20 blood test
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
dB	decibel, $1/10^{\text{th}}$ of a Bel—measure of ratios on a log scale
dBHL	decibels of hearing loss (also decibels of hearing level)
ECochG	Electrocochleography
GCP	Good Clinical Practice
GPx	Glutathione peroxidase
GSH	Glutathione
HPLC-ICP-MS	High Performance Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometry
Hz	Hertz—unit of measure for frequency
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
LCMS	Liquid chromatography-mass spectrometry
ONOO-	Peroxynitrite
PA	Physician Assistant
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
po	By mouth
PTA	Pure-Tone Audiometry
RN	Registered Nurse
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
SD	Speech Discrimination
SIC	Subject Identification Code
SNR	Signal-to-Noise ratio
SPI	Sound Pharmaceuticals, Inc.
TFI	Tinnitus Functional Index
USP	United States Pharmacopoeia
VS	Vital Signs
VSS	Vertigo Symptoms Scale
WINT	Words-in-Noise Test

SPI-1005-151: CLINICAL TRIAL SYNOPSIS	
Sponsor: Sound Pharmaceuticals, Inc.	
Investigational Product: SPI-1005	
A PHASE 1b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SPI-1005 IN ADULTS WITH MENIERE’S DISEASE	
Study Center: Northwest Ear, Inc.	
Lead Principal Investigator: May Huang, MD	
Estimated date first patient enrolled: December 19, 2015 Estimated date last patient enrolled: December 31, 2016	
Phase 1b	
Study Objective(s)	The primary objective of this study is to determine the: • Safety and tolerability of SPI-1005 treatment in adult patients with Meniere’s disease using histories, physical exams, vital signs (VS), adverse events (AEs), hematology (CBC) and chemistry (Chem-20). The secondary objectives of this study are to determine the: • Pharmacokinetics of oral SPI-1005 at 200, 400 and 600 mg twice daily for 21 days. Peak/trough assessments will be determined for ebselen, its major metabolite and selenium. • Severity of sensorineural hearing loss in dBHL using repeated pure-tone audiometry at 0.25, 0.5, 1, 2 ,3 ,4, 6 and 8 kHz and speech discrimination using the Words-in-Noise Test at 24, 20, 16, 12, 8, 4 and 0 Signal-to-Noise Ratio. • Pharmacodynamic response using electrocochleography (ECochG) • Severity of vertigo using the Vertigo Symptoms Scale (short form). • Severity of tinnitus using the Tinnitus Functional Index.
Study Design	Randomized, double-blind, placebo-controlled, dose-escalating, safety, PK, and PD study of oral SPI-1005 in adults with Meniere’s disease. All patients will undergo baseline audiometric testing and have their severity of sensorineural hearing loss, tinnitus and vertigo determined before the start of SPI-1005 treatment. At the end of the 21-day course of SPI-1005, and 28 days following the cessation of SPI-1005, patients will have their hearing loss and vertigo assessed. Tinnitus will be assessed weekly, and 7 and 28 days following treatment. ECochG will be performed at baseline, at the end of the SPI-1005 treatment, and 28 days after SPI-1005 treatment. Six outpatient visits will be performed over a 7-9 week period.

Number of Patients	Enrollment is planned for up to 40 adult patients with approximately equal numbers of males and females.
Inclusion Criteria	• Adult male and female patients, 19-70 years of age. • Diagnosis of probable or definite Meniere's disease by AAO-HNS 1995. • Active symptoms including vertigo or disequilibrium, fluctuating hearing loss, and tinnitus within 12 months of study enrollment. • Voluntarily consent to participate in the study. • Females of childbearing potential should be using and committed to continue using one of the following acceptable birth control methods: ○ Sexual abstinence (inactivity) for 14 days prior to screening through study completion; or ○ IUD in place for at least 3 months prior to study through study completion; 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 through study completion; or ○ Surgical sterilization (vasectomy) of partner at least 6 months prior to study. • Females of non-childbearing potential should be surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study, hysterectomy, or bilateral oophorectomy at least 2 months prior to study) or be at least 3 years since last menses.
Exclusion Criteria	• Current use or within 90 days prior to study the following excluded ototoxic medications: IV aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin); IV platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or IV loop diuretic (furosemide). • History of idiopathic sensorineural hearing loss, otosclerosis, or vestibular schwannoma. • History of middle ear or inner ear surgery. • Current conductive hearing loss or middle ear effusion. • Significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, or psychiatric disease. • History of hypersensitivity or idiosyncratic reaction to compounds related to ebselen. • Current use or within 30 days prior to study of drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes.

	• Participation in another investigational drug or device study within 90 days prior to study enrollment. • Female patients who are pregnant or breastfeeding.
Dosage Form	Capsule form of SPI-1005 in 200 mg quantities and matching placebo.
Dose and Regimen	Patients will be randomized to SPI-1005 or placebo in three successive dose-escalation cohorts: Cohort 1: 200 mg po BID (n=10) or placebo (n=3) x 21 days; Cohort 2: 400 mg po BID (n=10) or placebo (n=3) x 21 days; Cohort 3: 600 mg po BID (n=10) or placebo (n=4) x 21 days.
Safety Parameters	Repeated history and physical examinations, vital signs, adverse event monitoring, CBC and Chem-20 will be performed. Adverse events will be coded using MedDRA[®] (version 18.1 or greater) and summarized by each dose level (placebo, 200, 400 and 600 mg BID) for the number of adverse events. Comparisons will be made between baseline, while on treatment, and 7-day and 28-day follow-up values. Vital signs and clinical laboratory results will be summarized for each dose level. Comparisons will be made between baseline, on treatment, 7-day and 28-day follow-up values.
PK and PD Assessments	The peak and trough plasma levels of ebselen and its major metabolite will be determined using LCMS. The corresponding peak and trough total plasma selenium levels will be determined by HPLC-ICP-MS. PK and PD results will be summarized for each dose level and compared.
Statistical Methods	Audiometric data will be collected in the form of categorical and continuous variables. Categorical data will be analyzed using the chi-square distribution. Continuous data will be analyzed using mixed-effects multiple-repeated measures methods, 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 .05. Backwards stepwise regression will be used to determine the final model including only variables with significance at a .05 level.
Institutional Review Board	Western Institutional Review Board 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 (360) 252-2500 (office) (800) 562-4789 (toll-free) (360) 252-2498 (fax) help@wirb.com

1 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. No drugs have been FDA approved to 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 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. 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 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). In cells, GPx functions at near maximal levels. Augmentation of GPx activity with the enzyme itself is not practical due to its large size 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 super 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). Because it acts as a catalyst, and is not consumed during detoxification reactions (Müller, Gabriel et al., 1988), low doses are effective at reducing cisplatin-induced hearing loss in preclinical animal models (Lynch, Gu et al., 2005a, 2005b).

SPI-1005, a novel anti-inflammatory, constitutes a new drug class. It offers the potential for a safe, well tolerated, oral treatment for Meniere's disease, a disease for which there are no approved treatments.

The general approach for investigation of the safety and efficacy for Meniere's disease will be to conduct a phase 1b, safety, pharmacokinetic and pharmacodynamic study in 40 adults with Meniere's disease. The planned study will evaluate escalating doses of SPI-1005 at 200, 400 or

600 mg po BID versus placebo for twenty-one days for impact on pure-tone audiometry, speech discrimination, electrocochleography, and patient-reported outcomes using validated questionnaires for assessing vertigo and tinnitus (Hornibrook, Kalin et al., 2012; Meikle, Henry et al., 2012; Yardley, Donovan-Hall et al., 2004). This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

The rationale for using this compound along with information regarding pharmacology, human experience, and toxicology are discussed in the Investigators Brochure.

2 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, PK and PD of three dose levels of SPI-1005 given for 21 days compared to placebo in patients with Meniere's disease.

2.1 Primary Objective

The safety and tolerability of SPI-1005 will be determined by examining the toxicities and adverse events that are attributable to treatment. The safety parameters will include an evaluation of the clinical signs and symptoms from the history and physical exam; vital signs, the incidence of adverse events; and abnormal laboratory findings (CBC, Chem-20).

2.2 Secondary Objectives

The secondary objectives of this study are to determine the pharmacokinetics at each dose level of SPI-1005; severity of sensorineural hearing loss using pure-tone audiometry and speech-discrimination testing using Words-in-Noise Test (WINT) before, during, and after treatment; severity of vertigo using the Vertigo Symptoms Scale (VSS, short form) before, during, and after treatment; severity of tinnitus using the Tinnitus Functional Index (TFI) before, during, and after treatment; and pharmacodynamic response using electrocochleography (ECochG) before, during, and after treatment.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

Study participants will be randomized to SPI-1005 or placebo in this double-blind, dose-escalation study to evaluate its safety and preliminary efficacy. Patients, aged 19-70 years, with probable or definite Meniere's disease will undergo baseline testing to have their severity of sensorineural hearing loss, tinnitus and vertigo determined before the start of study treatment (See [Table 3](#) Schedule of Assessments)

Before, during, and for 28 days after administration of SPI-1005, patients will be evaluated for safety by history, physical examination, vital signs and blood tests (complete blood count [CBC], Chemistry-20 [Chem-20]). Peak and trough plasma levels of ebselen and its major metabolite will be determined using liquid chromatography-mass spectrometry (LCMS) at certain time points. Additionally, plasma will be analyzed by High Performance Liquid Chromatography-Inductively Coupled Plasma-Mass Spectrometry (HPLC-ICP-MS) for total selenium at the corresponding time points. Patients will be monitored for adverse events at each clinic visit. Female patients will receive pregnancy testing, and those found to be pregnant will be excluded or discontinued from the study and monitored for adverse events. Safety monitoring will continue for four weeks after completion of treatment.

The effect of SPI-1005 on hearing and vertigo will be evaluated at baseline, at the end of 21 days of treatment and 28 days after completing treatment. Tinnitus will be evaluated at baseline, weekly during treatment, and 7 and 28 days after treatment. Hearing will be evaluated using pure-tone audiometric testing at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz, and speech discrimination using the WINT at 24, 20, 16, 12, 8, 4, and 0 Signal-to-Noise ratio (SNR). The severity of vertigo will be assessed using the VSS. The severity of tinnitus will be assessed using the TFI. In addition, ECochG will be conducted at baseline, at the end of treatment and 28 days after completing treatment in order to measure the pharmacodynamic response.

3.2 Treatment Assignment

Following receipt of informed consent, completion of baseline assessments at Clinic Visit 1 and meeting study inclusion and exclusion criteria, the patient will be evaluated by the Principal Investigator for enrollment eligibility. Enrolled patients will be assigned the next Subject Identification Code from the list of Subject Identification Codes. The Subject Identification Code must be carefully matched to study drug cards before dispensing study drug at Clinic Visits 1, 2, and 3.

3.3 Safety Criteria for Stopping Dosing

If a patient has an unacceptable, severe (grade 4) or serious adverse event potentially related to treatment, the Principal Investigator should contact the Sponsor to determine whether to discontinue treatment. Regardless of communication with the Sponsor, the Principal Investigator should make a determination about discontinuing the treatment if it is in the best interest of the safety of the patient. Treatment may also be discontinued at the request of the patient.

3.4 Criteria for Study Termination

Patients who must discontinue treatment for any reason should continue to complete the study follow-up visits through Day 28 after the last dose of treatment. If a patient is not able to comply with study safety monitoring or is significantly non-compliant with study protocol and/or treatment, the Principal Investigator should contact the Sponsor about early termination of the patient's study participation. Criteria for early termination are in the Study Procedures – Early Termination of Patients section of this protocol.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

- Adult male and female patients, 19-70 years of age at the time of enrollment.
- Each patient will give informed consent to participate in this study and voluntarily agrees to the treatment protocol.
- Diagnosis of probable or definite Meniere's disease by AAO-HNS 1995 criteria .
- Active symptoms including vertigo or disequilibrium, fluctuating hearing loss, and tinnitus within 12 months of study enrollment
- Females of childbearing potential should either be sexually inactive (abstinent) for 14 days prior to screening and throughout the study or be using 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.
- Females of non-childbearing potential should be surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study, hysterectomy, or bilateral oophorectomy at least 2 months prior to study) or be at least 3 years since last menses.

4.2 Exclusion Criteria

- Current use or within 90 days prior to study of the following excluded ototoxic medications: IV aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin); IV platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or IV loop diuretic (furosemide).
- History of idiopathic sensorineural hearing loss, otosclerosis, or vestibular schwannoma.
- History of middle ear or inner ear surgery.
- Current conductive hearing loss or middle ear effusion.
- Significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, or psychiatric disease.
- History of hypersensitivity or idiosyncratic reaction to compounds related to ebselen.
- Current use or within 30 days prior to study of drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes.
- Participation in another investigational drug or device study within 90 days prior to study enrollment.
- Female patients who are pregnant or breastfeeding.

5 DESCRIPTION OF TREATMENT

5.1 Compound

SPI-1005 is a proprietary formulation of the compound ebselen, consisting of gelatin capsules containing 200 mg of the active pharmaceutical ingredient ebselen and 150 mg of the excipients, microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

5.2 Dosing Levels

There are three dose levels: 200 mg, 400 mg, and 600 mg of SPI-1005.

5.3 Dosing Regimen

Patients will be randomized to SPI-1005 or placebo in three successive dose-escalation cohorts:

Cohort 1: 200 mg po BID (n=10) or placebo (n=3) for 21 days;

Cohort 2: 400 mg po BID (n=10) or placebo (n=3) for 21 days;

Cohort 3: 600 mg po BID (n=10) or placebo (n=4) for 21 days.

Each dose will be administered as three capsules in the morning before eating and three capsules in the evening before eating. The three capsules will include a combination of SPI-1005 and/or identical placebo capsules to provide the targeted dose level.

5.4 Dosage Form

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

5.5 Manufacturer

SPI-1005 is manufactured by Catalent Pharma Solutions, Somerset, NJ.

5.6 Route of Administration

SPI-1005 (or matching placebo) is orally delivered.

5.7 Packaging and Labeling

Individual capsules are hermetically sealed in blister packs on a card indicating the dose, the Study Day and the time of day, either AM or PM, when the capsules will be taken. Product labeling states:

CC X LID X Card	CAUTION: NEW DRUG Limited by United States Law to Investigational Use	
	<i>Each capsule contains 200 mg of ebselen or placebo</i>	
	<i>This package contains 42 capsules.</i>	
	Protocol Number: SPI-1005-151	
	Subject Identification Code: XXX	Lot Number: XXXXXXXXX
	Card X of 3	
	Date of Issue: _____	
	Directions for Use:	
	1. Take 3 capsules twice daily for 7 days. Swallow 3 capsules in the morning (AM) and swallow 3 capsules in the evening (PM). You will be taking a total of 6 capsules each day.	
	2. Take capsules ONLY from the row representing that day's number (e.g., day 1, or day 2, etc.) and column AM or PM. You will be taking a total of 42 capsules over 7 days.	
<i>IMPORTANT: Do not mix up capsules from different rows or columns.</i>		
<i>If you forget to take a dose, leave the capsules unopened in the blister card.</i>		
3. Save this blister card and return it to the Study Coordinator at each clinic visit.		
4. Store this investigational drug in a dry place and at room temperature (59-86°F).		
SPI-1005 is for ORAL USE ONLY		
Sound Pharmaceuticals, Inc., Seattle, WA 98103		

5.8 Storage

SPI-1005 should be stored in a dry place at room temperature (59-86 °F).

5.9 Study Drug Accountability

All study cards that the patient has should be returned to the study personnel at each clinic visit. At each clinic visit, study personnel should examine returned cards in order to count and record the tablets dispensed, taken by patient, remaining and lost. The AM dose for that day will be taken in the clinic after obtaining a trough plasma level (along with a new card at Clinic Visits 2 and 3).

5.10 Study Drug Handling and Disposal

All study drug will be retained by the study site in a locked cabinet until otherwise instructed by the Sponsor.

6 STUDY PRODECURES

6.1 Duration of Treatment

Study treatment will be administered over a 21-day period beginning on Study Day 1.

6.2 Duration of Study

Patients will participate in this clinical trial for approximately seven to nine weeks beginning at baseline testing and continuing for four weeks beyond their final dose to allow for drug safety monitoring. A two-week window (Study Day -14 to -1) is allowed to complete baseline testing. Each patient will have six clinical visits during the study (see **Table 3** Schedule of Assessments). The initial screening will occur by telephone to obtain a brief history, review inclusion and exclusion criteria, discuss the informed consent form, explain remuneration for clinic visits and

blood draws, and to schedule the first clinic visit if appropriate and agreeable.

6.3 Clinic Visit 1 (Day -14 to -1)

Informed consent for study participation will be obtained before study evaluations are conducted. History and physical examination, vital signs, height/weight, blood tests (Chem-20, CBC) and urine pregnancy test will be conducted up to 14 days prior to initiation of treatment (Study Day 1). Baseline symptoms and concomitant medications should be recorded. Blood for total selenium level will be obtained. Baseline hearing evaluation will consist of otoscopy, tympanometry, pure-tone audiometry at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and speech discrimination using the WINT at 24, 20, 16, 12, 8, 4 and 0 SNR. Baseline vertigo will be assessed using the VSS. Baseline tinnitus evaluation will be conducted using the TFI. Baseline ECoG will be performed.

Following receipt of informed consent, blood testing, history, physical examination, baseline audiometric testing, enrollment in the study, and verbal instructions about the protocol, each patient will receive a drug card containing capsules of SPI-1005 and/or placebo. The dispensing clinician will record the Subject Identification Code, Date of Issue, and Card Number for each card issued. Patient will be counseled to refrain from taking their morning dose on the morning of their next clinic visit prior to returning to clinic.

6.4 Clinic Visit 2 (Day 7, before am dose)

History and physical exam and vital signs will be performed. Adverse events will be recorded. Concomitant medications will be recorded. Compliance with treatment will be measured by patient history and pill count. Blood tests, including but not limited to Chem-20 and CBC, will be conducted. Trough blood samples for total selenium and ebselen and its metabolite levels will be drawn prior to the morning dose of study drug. Tinnitus evaluation will be conducted using the TFI. Patient will be counseled to refrain from taking their morning dose on the morning of their next clinic visit prior to returning to clinic.

6.5 Clinic Visit 3 (Day 14, before am dose)

History and physical exam and vital signs will be performed. Adverse events will be recorded. Concomitant medications will be recorded. Compliance with treatment will be measured by patient history and pill count. Trough blood samples for total selenium and ebselen and its metabolite levels will be drawn prior to the morning dose of study drug. Tinnitus evaluation will be conducted using the TFI. Patient will be counseled to refrain from taking their morning dose on the morning of their next clinic visit prior to returning to clinic.

6.6 Clinic Visit 4 (Day 21, before and after am dose on last day of dosing)

History and physical exam and vital signs will be performed. Adverse events will be recorded. Concomitant medications will be recorded. Compliance with treatment will be measured by patient history and pill count. Blood tests, including but not limited to Chem-20 and CBC, will be conducted. Trough blood samples for total selenium and ebselen and its metabolite levels will be drawn prior to the morning dose of study drug. Peak blood samples for total selenium and ebselen and its metabolite levels will be drawn two hours after study drug administration. Hearing evaluation will consist of pure-tone audiometry at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and speech discrimination using the WINT at 24, 20, 16, 12, 8, 4 and 0 SNR. Vertigo will be assessed using the VSS. Tinnitus evaluation will be conducted using the TFI. End-of-treatment ECoG will be performed.

6.7 Clinic Visit 5 (Day 28, 7 days after last dose of SPI-1005)

History and physical exam and vital signs will be performed. Adverse events will be recorded. Concomitant medications will be recorded. Compliance with treatment will be measured by patient history and final pill count. Blood samples for total selenium and ebselen and its metabolite levels will be drawn. Tinnitus evaluation will be conducted using the TFI.

6.8 Clinic Visit 6 (Day 49, 28 days after last dose of SPI-1005)

History and physical exam and vital signs will be performed. Adverse events will be recorded. Concomitant medications will be recorded. Compliance with treatment will be measured by patient history and final pill count. Blood tests, including but not limited to Chem-20 and CBC, will be conducted. Blood samples for total selenium and ebselen and its metabolite levels will be drawn. Hearing evaluation will consist of pure-tone audiometry at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and speech discrimination using the WINT at 24, 20, 16, 12, 8, 4 and 0 SNR. Vertigo will be assessed using the VSS. Tinnitus evaluation will be conducted using the TFI. Post-treatment ECoG will be performed.

Table 3 Schedule of assessments for Protocol SPI-1005-151

Clinic Visit	Study Day	Briefing/ Consent	Blood/Urine Testing	History/ Physical /VS	Hearing Evaluation (PTA, SD) ⁵	ECochG	Vertigo Evaluation (VSS) ⁶	Tinnitus Functional Index	Treatment (po BID)
CV1 (screening/baseline)	-14 to -1	X	X ^{1,2}	X	X	X	X	X	
	1								X
	2								X
	3								X
	4								X
	5								X
	6								X
CV2	7		X ^{1,3}	X				X	X
	8								X
	9								X
	10								X
	11								X
	12								X
	13								X
CV3	14		X ³	X				X	X
	15								X
	16								X
	17								X
	18								X
	19								X
	20								X
CV4	21		X ^{1,4}	X	X	X	X	X	X
CV5 (7 days post treatment)	28		X ²	X				X	
CV6 (28 days post treatment)	49		X ^{1,2}	X	X	X	X	X	

¹ Chem-20 and CBC. Urine pregnancy test on CV1 screening visit only.

² Blood collection for total plasma selenium levels and plasma ebselen and its metabolite levels (random sample at baseline and Clinic Visits 5 and 6). Only plasma selenium will be tested on the baseline sample.

³ Blood collection for total plasma selenium levels and plasma ebselen and its metabolite levels (trough prior to morning dose of SPI-1005 on Clinic Visit 2 and 3).

⁴ Blood collection for total plasma selenium levels and plasma ebselen and its metabolite levels (trough prior to morning dose of SPI-1005 on study day 21; followed by study drug administration; followed by peak measurement 2 hours following study drug administration).

⁵ Hearing evaluation using pure-tone audiometry (PTA) at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and WINT at 24, 20, 16, 12, 8, 4 and 0 SNR. Tympanometry will be performed at CV1.

⁶ Vertigo assessment using the VSS.

6.9 Non-Study Medications

Non-study medications are permitted during the course of this study except for those having known ototoxic side effects such as aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin); platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or loop diuretics (furosemide). Each patient will be interviewed about potentially ototoxic medications during baseline testing and at each clinic visit. Any reported non-study medication will be recorded and evaluated by the investigators. Use of potentially ototoxic medications may meet criteria for exclusion or discontinuation of a patient (see Exclusion Criteria).

6.10 Selection and Timing of Doses

All patients will take 3 capsules in the morning (AM) and 3 capsules in the evening (PM). Each patient must be instructed to separate AM and PM doses by approximately 12 hours and attempt to maintain consistent timing throughout the 21-day treatment duration. Doses should be taken before meals. Three blister cards of study drug will be assigned to patients, one for each week of treatment. Blister cards are designed with a total of 42 capsules per card divided into AM and PM sections that contain three blisters in each row and seven columns of blisters for seven treatment days. Patients who do not consume capsules (intentionally or unintentionally) for a particular dose period are instructed to leave the capsules intact in the blister card and resume taking capsules at the next dose time. Blister cards must be returned to clinic at each clinic visit. Unconsumed capsules left in the card assist investigators with compliance monitoring.

6.11 Randomization and Blinding

This protocol is a randomized, double-blind, placebo-controlled, dose-escalation study design. The Principal Investigator(s), all sub-investigators including Medical Doctor (MD), Physician's Assistant (PA), Registered Nurse (RN), Audiologist, Study Coordinator (SC), Contract Research Associate (CRA), Clinical Research Coordinator (CRC), laboratory personnel, and contracted designees of SPI who statistically analyze the data, will be blinded to the treatment received by each patient.

The patient will be blinded to treatment assignment and to which pills are active and placebo. The blister cards of drug product, containing drug product, or drug product and placebo are indistinguishable, having been matched for card appearance and capsule size, quantity, color, and opacity. Each card (hermetically sealed blister packs containing 42 capsules) of drug product or drug product and placebo has a numeric code imprinted that uniquely identifies the specific card, the dose strength and the batch number.

Patients who are eligible for enrollment will be assigned the next Subject Identification Code (SIC) from a list of SICs obtained from SPI and maintained by Principal Investigator(s). SIC will determine study drug assignment. When all SICs have been assigned for Cohort 1, the Principal Investigator (s) will review ongoing safety assessment results with SPI before proceeding to enrollment of Cohort 2. When all SICs have been assigned for Cohort 2, the Principal Investigator (s) will review ongoing safety assessment results with SPI before proceeding to enrollment of Cohort 3.

The designated Contract Research Organization labelling the product maintains a confidential list of codes identifying the contents of each product card. The Principal Investigator is responsible

for maintaining the list of SICs and the name of the patient assigned to that code. The list of SICs will be used to track study drug dispensing at Clinic Visits 1, 2 and 3. At Clinic Visit 1, the patient should receive the drug card labelled with their SIC and marked card 1 of 3. At Clinic Visit 2, the patient should receive the drug card labelled with their SIC and marked card 2 of 3. At Clinic Visit 3, the patient should receive the drug card labelled with their SIC and marked card 3 of 3.

Table 4 shows the number of SPI-1005 and placebo subjects in each cohort. Table 5 shows the number and type of capsules for each dose in each treatment group.

Table 4 Number of subjects randomized in each dose-escalation cohort

	SPI-1005 (200 mg bid)	SPI-1005 (400 mg bid)	SPI-1005 (600 mg bid)	Placebo
Cohort 1	10			3
Cohort 2		10		3
Cohort 3			10	4
Total	10	10	10	10

Table 5 Number and type of capsules per dose in each treatment group

	SPI-1005 (200 mg bid)	SPI-1005 (400 mg bid)	SPI-1005 (600 mg bid)	Placebo
Number of 200 mg SPI-1005 capsules/dose	1	2	3	0
Number of placebo capsules/dose	2	1	0	3

6.12 Access to Patient Identification and Randomization

If a patient experiences a serious adverse event that requires unblinding, the Principal Investigator will request decoding of the patient's group assignment and drug product information through SPI. The list of subjects will contain emergency contact information for the patients for use as needed by the clinical investigators and the appropriate personnel at SPI, and will be made immediately available to FDA personnel upon request.

6.13 Assessment of Safety and Efficacy: Credentials, Equipment, and Methods

Medical

History and physical examinations, vital signs and analysis of lab reports will be performed to evaluate the safety of SPI-1005. A licensed Medical Doctor (MD) or Physician Assistant (PA) will perform physical examinations using standard clinical equipment at the appointed study intervals. Blood test results will be analyzed according to currently established laboratory norms. Patients will be asked about adverse events at each clinic visit.

Laboratory

Blood testing will be performed at specified intervals to evaluate the safety of SPI-1005. A qualified medical laboratory technician will perform laboratory testing using standard equipment and established universal safety precautions for collecting and handling blood samples. Blood tests

performed include CBC and Chem-20. Blood will be collected and shipped to a designated CRO(s) to quantify ebselen, ebselen metabolite, and total selenium.

Audiology

Audiological evaluations will be performed at specified intervals to evaluate the efficacy of SPI-1005. Tests include otoscopy, tympanometry, pure-tone audiometry, bone conduction and speech discrimination performed by physician or qualified audiologist (Wilson & Burks, 2005). ECoG will be performed at specified intervals by a physician specialist. Patient-reported outcomes by self-administered questionnaire will include the VSS (Yardley, Donovan-Hall et al., 2004) and the TFI (Meikle, Henry et al., 2012). These will be scored by study personnel.

6.14 Early Termination of Patients

Patients who are enrolled in this study may terminate at will. Patients that have started SPI-1005 treatment and are discontinued from the study for any reason will continue to be monitored for safety for 28 days after the last dose of treatment. Investigators may terminate a patient who:

- Experiences unacceptable toxicity;
- Is pregnant;
- Or has non-compliance issues including:
 - Patient's inability to keep appointments for required test intervals.
 - *Note: If patient misses two or more of the Clinic Visits, the patient will be discontinued from the study.*
 - Patient's inability to follow the dosing regimen.
 - *Note: Patients that do not take more than 10 doses (30 capsules) at any time during the treatment period will be discontinued.*
- Patient reports use of potentially ototoxic medications during the study period.
- Patient found to be in violation of Inclusion or Exclusion Criteria.

Every effort will be made by the investigational site to maintain contact with patients who are discontinued, including those discontinued based on non-compliance issues, for at least 28 days following their last dose taken in order to monitor for safety.

All patients receiving at least one 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 patients or revealed upon examination or lab testing will be included in the analysis.

6.15 Statistical Analysis of Study Endpoints

Adverse events will be coded using MedDRA (Version 18.1 or higher) and summarized by each dose level (placebo, 200, 400 and 600 mg BID) for the number of adverse events. Comparisons will be made between baseline, while on treatment, and 7-day and 28-day follow-up values.

Vital signs and clinical laboratory results will be summarized for each dose level. Comparisons will be made between baseline, on treatment, 7-day and 28-day follow-up values. Abnormal values will be identified and categorized for severity.

Audiometric data will be collected in the form of categorical and continuous variables. Categorical data will be analyzed using the chi-square distribution. 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. Backwards stepwise regression will be used to determine the final model including only variables with significance at a .05 level. No interim statistical analyses are planned. The sample size of 40 patients is sufficient to provide safety, PK and PD results to guide future dose selection.

Criteria for termination of the study include any significant adverse effect related to treatment that is deemed to merit discontinuation of the study by the IRB or Sponsor.

While every attempt will be made to completely capture all data elements in the Case Report Form, any unavoidably missing, unused or spurious data will be noted in the data listings in the Clinical Study Report.

Deviations from the original statistical plan will be described and justified in the Clinical Study Report, as appropriate. The selection of patients to include in the analyses include all randomized patients, all dosed patients, all eligible patients, and all evaluable patients. The population used for a given analysis will be identified in the Clinical Study Report.

7 ADVERSE EVENTS

An Adverse Event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any patient/subject has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by Sound Pharmaceutical, Inc.

7.1 Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any patient/subject has been enrolled, before treatment, during treatment, or within 28 days following the cessation of treatment, whether or not they are related to the study,

must be recorded on forms provided by SPI.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

If one patient develops a Grade 3 or 4 systemic or major organ toxicity thought to be related to SPI-1005, the patient will be offered supportive care and the IRB will follow its protocol for investigating the incident to determine if stopping the study is warranted. The study may be stopped at the investigator's or sponsor's discretion.

Any serious or unexpected 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 four weeks of the patient's last treatment must be reported within 24 hours to SPI, even if the event appears unrelated to the treatment.

Sound Pharmaceuticals, Inc. (SPI) contact information:

Jonathan Kil, MD
Sound Pharmaceuticals, Inc.
4010 Stone Way N. Suite 120
Seattle, WA
(206) 634-2559 (office)
jkil@soundpharma.com

SPI evening, weekend, and holiday contact information:

Jonathan Kil, MD
3404 East Yesler Way
Seattle, WA 98122
(206) 420-2929 (home)
(206) 769-4820 (cell)

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 patient during the informed consent process.

7.2 Relationship to Treatment

An Investigator who is qualified in medicine must make the determination of relationship to the treatment for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the treatment. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the treatment and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE and the treatment is determined to be “possible” or “probable” the event will be considered to be related to the treatment for the purposes of expedited regulatory reporting.

7.3 Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs since they will be captured in those data listings. However, abnormal values that constitute an SAE or lead to discontinuation of administration of treatment must be reported and recorded as an AE. Information about AEs will be collected from the signing of the consent form until the end of the study. Serious Adverse Event information will be collected from signing of the consent form until 28 days following the last dose of treatment. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under the Section above entitled Serious Adverse Event. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded in the source documents and Medical History form in the Case Report Form. 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 patient 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 handled as AEs.

7.4 Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until 28 days following the end of treatment. Any SAEs considered possibly or probably related to the treatment and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Sound Pharmaceuticals within one business day 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 Sound Pharmaceuticals, Jkil@soundpharma.com.

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.

Sound Pharmaceuticals is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

8 INVESTIGATIONAL RECORD KEEPING

All study records including disposition of the drug (i.e., dates, quantity, use by patients, and unused supplies) and patient Case Report Forms (CRFs), source documents, consent forms, and chart notes will be maintained and retained in accordance with federal regulations set forth by 21 CFR, Part 312.62. Each patient case history will contain documentation confirming that informed consent was obtained for the patient prior to participation in the study. All personnel associated with this study will make their best effort to ensure anonymity and confidentiality of patient records. Individual CRFs will be collected for each patient. A copy of each CRF will be retained at the clinical site in the investigator's files until further notice from SPI. All original CRFs will be transferred to SPI or its appointed agent for analysis and storage.

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.

8.1 Protocol Deviations and Amendments

Any deviation from protocol deemed appropriate due to potential harm it may cause an individual patient 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 occurrence.

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

Both SPI and clinical investigators must be in concurrence about any formal amendment to the protocol, and such an amendment must be approved by the IRB if it has the potential to impact a patient's safety. Potential impact on any of the following requires making a formal amendment to the protocol:

- Number of patients required for the study
- Selection criteria
- Drug dosage or duration of treatment
- Experimental design

- Scope of the investigation
- Scientific quality of the investigation

Other modifications to the protocol that may not require IRB approval but do require being written up as protocol amendments include the following:

- Changes that do not impact patient safety
- Changes in the methods of statistical analysis
- Additional lab tests performed on stored samples

8.2 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 to 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.

8.3 Study Monitoring

Before an investigational site can enter a patient 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 Study 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 patient'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 patient (e.g., clinic charts).
- CRFs are sent to SPI or its designated agent for entry into the Study Database 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 forwarded to the IRB.

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

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

8.4 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 stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

8.5 Retention of Records

The Principal 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.

9 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 IRB for this study will be Western Institutional Review Board (WIRB). The Principal Investigator must verify that WIRB has approved the protocol, consent form and recruitment materials for the investigation prior to conducting study evaluations. Initial IRB approval, and all materials approved by the IRB for this study including the Informed Consent Form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Principal 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 Principal 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 Principal Investigator.

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

9.1 Ethical Conduct of the Study

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.

9.2 Written Informed Consent

The Principal Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

10 LIST OF REFERENCES

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11 APPENDICES

Appendix 1: FDA Form 1572

On following pages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See instructions on reverse side.)			Form Approved: OMB No. 0910-0014 Expiration Date: April 30, 2015 See OMB Statement on Reverse NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).	
1. NAME AND ADDRESS OF INVESTIGATOR Name of Principal Investigator May Y. Huang, MD, FACS				
Address 1 Northwest Ear, Inc.		Address 2 1221 Madison Street		
City Seattle	State/Province/Region WA	Country USA	ZIP or Postal Code 98104	
2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (Select one of the following.) ☒ Curriculum Vitae ☐ Other Statement of Qualifications				
3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED				CONTINUATION PAGE for Item 3
Name of Medical School, Hospital, or Other Research Facility Northwest Ear, Inc.				
Address 1 1221 Madison Street		Address 2		
City Seattle	State/Province/Region WA	Country USA	ZIP or Postal Code 98104	
4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY				CONTINUATION PAGE for Item 4
Name of Clinical Laboratory Facility LabCorp of America				
Address 1 7800 W 110th St		Address 2		
City Overland Park	State/Province/Region KS	Country USA	ZIP or Postal Code 62210	
5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)				CONTINUATION PAGE for Item 5
Name of IRB Western Institutional Review Board				
Address 1 1019 39th Avenue SE		Address 2 Suite 120		
City Puyallup	State/Province/Region WA	Country USA	ZIP or Postal Code 98374-2115	
6. NAMES OF SUBINVESTIGATORS (If not applicable, enter "None") None				
				CONTINUATION PAGE – for Item 6
7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR SPI-1005-151				

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. (Select **one** of the following.)

- ☒ For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
- ☐ For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR**

- Complete all sections. Provide a separate page if additional space is needed.
- Provide curriculum vitae or other statement of qualifications as described in Section 2.
- Provide protocol outline as described in Section 8.
- Sign and date below.
- FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR.** The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). **INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.**

10. DATE (mm/dd/yyyy)

11-12-15

11. SIGNATURE OF INVESTIGATOR

Sign



(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

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Office of Chief Information Officer
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**DO NOT SEND YOUR COMPLETED FORM
TO THIS PRA STAFF EMAIL ADDRESS.**

Appendix 2: Principal Investigator Curriculum Vitae

MAY Y. HUANG, M.D., FACS
Curriculum Vitae

Office Address: Northwest Ear, Inc, PS
1221 Madison St, Suite 1410
Seattle, Washington 98104

Past Positions: Seattle Ear Clinic
801 Broadway # 830
Seattle, Washington 98122
December 1999- April 2005

Director, Section of Neurotology and Otology
Assistant Professor of Surgery
Milton S. Hershey Medical Center
Pennsylvania State University College of Medicine
Hershey, Pennsylvania
July 24, 1995 – December 31, 1999

Education: University of Virginia/ Echols Scholar
Bachelor of Arts with Distinction, Biological Chemistry
Charlottesville, Virginia
1979 - 1983

University of North Carolina School of Medicine
Doctor of Medicine, Class President
Chapel Hill, North Carolina
1983 - 1987

University of Michigan Rackam School of Graduate Studies
Master of Science, Biological Chemistry
Ann Arbor, Michigan
1988 - 1989

Internship: General Surgery
St. Joseph Mercy Hospital/U of Michigan Medical Center Affiliate
Ann Arbor, Michigan
1987 - 1988

Residency: Otorhinolaryngology-Head and Neck Surgery
Department of Otorhinolaryngology
University of Michigan Medical Center
Ann Arbor, Michigan
1988 - 1993

Fellowship (Research): Postdoctoral NIH Research Training Fellowship

Kresge Hearing Research Institute and
Department of Otorhinolaryngology
University of Michigan Medical Center
Ann Arbor, Michigan
1988 - 1990

Postdoctoral Otology Research Fellowship
(Paul R. Lambert, MD and Jeffrey T. Corwin, PhD)
Departments of Neuroscience and Otolaryngology
University of Virginia Health Sciences Center
Charlottesville, Virginia
1993 - 1994

Fellowship (Clinical): Neurotology and Otology Fellowship
(Paul R. Lambert, MD)
Department of Otolaryngology
University of Virginia Health Sciences Center
Charlottesville, Virginia
1994 - 1995

Certification: National Board of Medical Examiners, 1987
American Board of Otolaryngology, 1995
Neurotology- Otology Subspecialty/ ABO, 2012

Licensure: Washington MD00038100

Organizations: American Academy of Otolaryngology-Head & Neck Surgery, 1988-
American Neurotology Society, 1997-
Northwest Academy of Otolaryngology/ HNS, 1999-
Washington State Medical Association, 2000-
King County Medical Society, 2000-
Vestibular Disorders Association, 1997-
American Speech-Language-Hearing Association, 1996-2001
American Tinnitus Association, 1996-2001

Scientific publications (peer-reviewed):

Huang, MY, Schacht, J: Drug-induced ototoxicity: pathogenesis and prevention. *Med Toxicol Adv Drug Exper* 4 (6): 452-467, 1989.

Huang, MY, Schacht, J: Outer hair cells as potential targets of inflammatory mediators. *Ann Otol Rhinol Laryngol* 99 (6, Part 2, Suppl 148): 35-38, 1990.

Huang, MY, Schacht J: Formation of a cytotoxic metabolite from gentamicin by liver. *Biochem Pharmacol* 40: R11-R14, 1990.

Crann, SA, Huang, MY, McLaren, JD, Schacht, J: Formation of a toxic metabolite from gentamicin by a hepatic cytosolic fraction. *Biochem Pharmacol* 43(8):1835-1839, 1992.

Huang, MY, Schacht, J: Drug-induced ototoxicity. *New Ethicals* 29(1):105-109, April 1992.

Levin, RJ, Hamill, NJ, Huang, MY: Management of dopamine-secreting glomus vagale: Case report and histopathologic correlation. *Head & Neck Surgery* 20(8): 753-757, 1998.

Hunter, CJ, Huang, MY: Histopathology of petrous apex cholesterol granuloma. *American Journal of Otology/ Pathology Case of the Month*, submitted, 1999.

Huang MY, Vermeulen S: Clinical perspectives regarding patients with internal auditory canal or cerebellopontine angle lesions: surgical and radiation oncology perspectives, *Seminars in Ultrasound, CT and MRI* 24 (3):124-132, 2003.

Haynes D, Huang MY, Roland PS: Cochlear implants, SiPac, First Edition, AAO- HNS, 2006.

Book Chapters:

Huang, MY, Schacht, J: Drug-induced ototoxicity. In Mammen GJ (Ed), *Clinical Pharmacokinetics*, ADIS Press Ltd., 1990.

Huang, MY, Lambert, PR: Temporal bone trauma. In Hughes G, Pensak M (Eds), *Clinical Otology*, 2nd Edition, Thieme Medical Publishers, 1997.

Huang, MY: Neurotology. In *Surgery Pearls of Wisdom Board Review Text*, Boston Medical Publishing, 1998.

Huang, MY: Temporal Bone Tumors/ Acoustic Neuromas/ Surgery--Middle Cranial Fossa Approach. In *YourDoctor.com*. 2000.

Huang MY: Temporal Bone Tumors/ Cholesteatoma/ Petrous Apex. In *YourDoctor.com*, 2000.

Huang MY: Facial Nerve Schwannoma. In DeSouza C (Ed), *Otolaryngology-Head and Neck Surgery*, 2013.

O'Connell. Lambert P and Huang MY: Temporal Bone Trauma. In Pensak M and Choo D (Eds), *Clinical Otology*, 4th Ed, Thieme Publishers, 2014.

Book Reviews:

Otoneurosurgery and Lateral Skull Base Surgery, (Eds. Fabrizio Salvinelli and Antonio De la Cruz, W.B. Saunders, Philadelphia, 1996), *Laryngoscope*, 1997.

Pediatric Neurotology and Otology, (Eds. Anil K Lalwani and Kenneth M. Grundfast, Lippincott-Raven, Philadelphia, 1998), *Head and Neck Surgery*, 1999.

Abstract/Scientific Presentations:

Huang, MY, Schacht, J: Isolated cochlear hair cells as an assay for the ototoxicity of drugs.

American Academy of Otolaryngology--Head and Neck Surgery Research Forum No. 14, New Orleans, LA, September 24-28, 1989. *Otolaryngol Head Neck Surg* 101(2):200, 1989.

Huang, MY, Schacht J: Potential involvement of aminoglycoside metabolites in the pathogenesis of ototoxicity. Association for Research in Otolaryngology, Thirteenth Midwinter Research Meeting, St. Petersburg, FL, February 4-8, 1990.

Huang, MY, Schacht, J: Involvement of metabolite in ototoxicity of aminoglycoside antibiotics. Twenty-seventh Workshop on Inner Ear Biology, Stockholm, Sweden, June 17-20, 1990.

Huang, MY, Adcock, SE, Hammel, L, Schacht, J: Cytosolic enzymes convert gentamicin into toxic metabolite. Association for Research in Otolaryngology, Fourteenth Midwinter Research Meeting, St. Petersburg, FL, February 3-7, 1991.

Huang, MY, Schacht, J: Non-microsomal metabolites of aminoglycosides are cytotoxic to cochlear outer hair cells. American Academy of Otolaryngology--Head and Neck Surgery Research Forum, Kansas City, KS, September 22-26, 1991. *Otolaryngol Head Neck Surg* 105(2): 191, 1991.

Huang, MY, Koopman, CF, Jr: Pediatric tumors of the infratemporal fossa. American Society of Pediatric Otolaryngology, Eighth Annual Meeting, Los Angeles, CA, April 19-22, 1993.

Huang, MY, Goldstein, BJ, Corwin, JT: Regenerative proliferation in the guinea pig utricle *in vivo*. Association for Research in Otolaryngology, Seventeenth Midwinter Research Meeting, St. Petersburg, FL, Feb 6-10, 1994.

Huang, MY, Goldstein, BJ, Corwin, JT: Evidence for regenerative proliferation of vestibular sensory epithelium *in vivo*. Annual Meeting of the Virginia Society of Otolaryngology--Head and Neck Surgery, Tysons Corner, VA, April 21-23, 1994.

Huang, MY, Corwin, JT: A rapid method for photoablation of hair cells in otic sensory epithelia. American Academy of Otolaryngology-Head and Neck Surgery Research Forum, San Diego, CA, September 18-22, 1994.

Corwin, JT, Jones, JE, Goldstein, BJ, Gu R., Huang, MY, Katayama A, Kelley, MW, Lambert, PR, Warchol, ME, Xu, XM: Mechanisms of hair cell regeneration in fish, amphibians, birds and mammals. Auditory Plasticity and Regeneration: Scientific and Clinical Implications, Trento, Italy, May 4-7, 1994.

Gallagher, JE, Huang, MY, Levin, RJ: Decompression for facial nerve paralysis secondary to temporal bone fracture. American College of Surgeons, Pennsylvania Committee on Trauma, Residents' Trauma Paper Competition, Honorable Mention, Hershey Medical Center, Hershey, PA, November 13, 1996.

Huang, MY, Mundok, M: Electrocochleography and Vestibular Hydrops. American Auditory Society, Phoenix, AZ, March 5-6, 1999.

Levin, RJ, Malone, JP, Huang, MY, Fedok, FG: Unusual Second Primary Malignancies after

Successful Treatment of Nasopharyngeal Carcinoma. North American Skull Base Society, Chicago, IL, May 28-31, 1999.

Huang, MY, Levin, Roger J: Facial Nerve Decompression after Temporal Bone Fracture. North American Skull Base Society, Chicago, IL, May 28-31, 1999.

Huang, MY: Complications of inadequate mastoid cavity care. Pennsylvania Academy of Otolaryngology-Head and Neck Surgery, Hershey, PA, June 18-1999

Clinical Studies:

"A Multicenter, Randomized, Evaluator-Blind Study Comparing the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin Otic Solution in the Treatment of Acute Otitis Externa in Adults" Daiichi Pharmaceutical Corporation
University of Virginia Health Sciences Center
Sub-Investigator, July - October, 1994

"Treatment for Unilateral Sudden Sensorineural Hearing Loss with Systemic Steroids and Valacyclovir" Duke University,
Clinical Research Institute Investigator, July 1998 – 2000

"Genetic basis of familial non-syndromic hearing loss"
University of Michigan Medical Center Ann Arbor, Michigan
Co- Investigator, February 1999 - 2000

Research Grants:

"Multichannel Cochlear Implant Device" University Physicians Practice Site Fund
Milton S. Hershey Medical Center July 1996 - July 1997

"Pediatric Cochlear Implants" Children's Miracle Network, October 1996 - August 1997

"Function of the Central Auditory Pathway after Auditory Deprivation in Rats"
Department of Surgery, Penn State Geisinger Health System, July 1997 - June 1998

"Brainstem Auditory Pathway Function After Reversible Deafness" Pennsylvania Lions Hearing Research Foundation, June 1998-June 1999

"Brainstem Auditory Pathway Function After Reversible Deafness"
Department of Surgery, Penn State Geisinger Health System, June 1998 - June 1999

"Hearing Loss and the Central Auditory Pathway" Faculty Mentor/ Alpha Omega Alpha Student Research Fellowship, March 1999- December 1999

"Auditory Plasticity after Postnatal Cochlear Implant" Children's Miracle Network, July 1999-August 2000

"Protein Expression after Hearing Restoration in Postnatal Rat Auditory Nuclei" Department of

Surgery, Penn State Geisinger Health System, July 1999-June 2000

“Vestibular Regulation of Blood Pressure Sympathetic Nerve Activity in Humans: Effect of Aging and Vestibular Deficiency” Departments of Surgery, Cardiology and Medicine (Chet Ray, Ph.D.), Dean’s Feasibility Grant, Co-investigator, Penn State College of Medicine, July 1999-June 2000

Appendix 3: Diagnostic Criteria for Meniere's Disease

Diagnosis of Meniere's Disease

Possible Meniere's disease

Episodic vertigo of the Meniere's type without documented hearing loss, or
Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without definitive
episodes
Other causes excluded

Probable Meniere's disease

One definitive episode of vertigo
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other causes excluded

Definite Meniere's disease

Two or more definitive spontaneous episodes of vertigo 20 minutes or longer
Audiometrically documented hearing loss on at least one occasion
Tinnitus or aural fullness in the treated ear
Other cases excluded

Certain Meniere's disease

Definite Meniere's disease, plus histopathologic confirmation

American Academy of Otolaryngology-Head and Neck Foundation, Inc. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg. 1995 Sep;113(3):181-5.

Thorp MA, Shehab ZP, Bance ML, Rutka JA; AAO-HNS Committee on Hearing and Equilibrium. The AAO-HNS Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease: have they been applied in the published literature of the last decade? Clin Otolaryngol Allied Sci. 2003 Jun;28(3):173-6.

Appendix 4: 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	

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

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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, #21, #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.

