CLINICAL RESEARCH PROTOCOL

DRUG:	SPI-1005
STUDY NUMBER(S):	SPI-3005-501
PROTOCOL(S) TITLE:	A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, AND EFFICACY OF SPI-1005 IN CYSTIC FIBROSIS PATIENTS WITH ACUTE PULMONARY EXACERBATION RECEIVING IV TOBRAMYCIN AT RISK FOR OTOTOXICITY
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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPl-1005 IN CYSTIC FIBROSIS PATIENTS WITH ACUTE PULMONARY EXACERBATION RECEIVING IV TOBRAMYCIN AT RISK FOR OTOTOXICITY

Study No: SPI-3005-501

Original Protocol Date: 08 February 2017

Protocol Version No: 5.0

Protocol Version Date: 06 December 2018

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: Liza Wallace, Vice President	Yes No [X] [ ]		
Medical Lead: Jonathan Kil, CMO	Yes No [X] [ ]		

SPI-3005-501

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, AND EFFICACY OF SPI-1005 IN CYSTIC FIBROSIS PATIENTS WITH ACUTE PULMONARY EXACERBATION RECEIVING IV TOBRAMYCIN AT RISK FOR OTOTOXICITY

Confidentiality and investigator statement

The information contained in this protocol and all other information relevant to SPI-1005 are the confidential and proprietary information of Sound Pharmaceuticals, Inc. (SPI), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of SPI.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel (APPENDIX I – Names of Study Personnel) under my supervision copies of the protocol and any amendments, and access to all information provided by Sound Pharmaceuticals, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about SPI-1005 and the study.

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

1 STUDY SUMMARY

Protocol Number: SPI-3005-501

Investigational Product: SPI-1005

IND Number: 128939

Title: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN CYSTIC FIBROSIS (CF) PATIENTS WITH ACUTE PULMONARY EXACERBATION (APE) RECEIVING IV TOBRAMYCIN AT RISK FOR OTOTOXICITY

Study Centers:
Approximately 10 and up to 20 sites in the U.S

Study Objectives:

Primary Objectives are the safety and efficacy of SPI-1005 treatment determined by:

- Determination of sensorineural hearing loss using pure-tone audiometry comparing baseline to post-treatment.
- Change in distortion product otoacoustics emissions (DPOAE) comparing baseline to post-treatment.
- Change in word recognition scores using the Words-in-Noise test (WINT) comparing baseline to post-treatment.
- Severity or development of tinnitus using the Tinnitus Functional Index (TFI) comparing baseline to post-treatment.
- Severity or development of vertigo using the Vertigo Symptoms Scale (VSS) comparing baseline to post-treatment.
- Spirometry performance assessing baseline to post-treatment.
- Pharmacokinetics of SPI-1005 in CF patients.
- Physical examinations including vital signs.
- Adverse event monitoring using MedDRA coding (version 18.1 or higher).
- Clinical Laboratory tests (CBC, serum chemistry, and urinalysis).

Exploratory Objectives:

- Pharmacogenomics analysis will explore SPI-1005 as an inducer of gene expression for Nrf2, glutathione peroxidase-1, hemeoxygenase-1, and thioredoxin class of redox proteins.
- Pharmacodynamics analysis will explore SPI-1005 on the level of Nrf2 (nuclear translocation from cytosol), Glutathione (GSH reduced and GSSG oxidized), cysteine and cystine.

Study Design: An interventional Phase 2 randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of SPI-1005 in adult CF patients with APE receiving IV tobramycin. Where feasible, baseline assessments will be obtained prior to the start of IV tobramycin. Otherwise; baseline assessments will be obtained within 48 hours of initiating IV tobramycin treatment, but prior to initiating treatment with SPI-1005. SPI-1005 treatment will start concomitant with or within the first 48 hours of the start of IV tobramycin treatment. Patients will have their audiologic and vestibular function assessed at baseline and at two post-treatment intervals. Post-treatment PK and PD samples will be analyzed and compared to baseline values.

Number of Patients:
The study aims to enroll approximately 80 adult male or female patients with CF receiving IV tobramycin for APE.

Inclusion Criteria:

1. CF patients about to receive IV tobramycin (or within 48 hours of initiating IV tobramycin) for a planned minimum of 10 days for the treatment of acute pulmonary exacerbation (APE).
2. Voluntarily consent to participate in the study.
3. Age ≥18 years of age at the time of informed consent.
4. Male patients that are willing to use condoms throughout the study period and 90- days following study completion even if not fertile.
5. Females of childbearing potential should be using and committed to continue using one of the following acceptable birth control methods:
    a) Sexual abstinence (inactivity) for 14 days prior to screening through study completion; or
    b) IUD in place for at least 3 months prior to study through study completion; or
    c) Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or
    d) Stable hormonal contraceptive for at least 3 months prior to study through study completion.
6. Ability to perform all study related procedures.

Exclusion Criteria:

1. Use within 60 days of study enrollment any of the following IV ototoxic medications: aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin); platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or loop diuretic (furosemide).
2. Sensorineural hearing loss ≥70 dB at (air conduction) at conventional frequencies ≤4 kHz at baseline.
3. Severe lung disease with FEV_1 <40% predicted at baseline or Day 1, or Investigator discretion in consultation with sponsor for FEV_1 <40% predicted.
4. History of idiopathic sensorineural hearing loss, otosclerosis, or vestibular schwannoma.
5. History of middle ear or inner ear surgery.
6. Current conductive hearing loss or middle ear effusion.
7. Significant cardiovascular, renal, hematologic, immunologic, or psychiatric disease.
8. Patients with liver function testing (ALT, AST or GGT) results ≥3x the upper limit of normal.
9. History of hypersensitivity or idiosyncratic reaction to compounds related to ebselen or selenium.
10. Participation in another investigational drug or device study within 30 days prior to study enrollment.
11. Female patients who are pregnant or breastfeeding.
12. Subject has any other illness or other condition that, in the opinion of the investigator would prohibit the subject from participating in the study.

Dosage Forms
Capsules
- SPI-1005 containing 200 mg of ebselen
- Matching placebo

Dose and Regimen
Patients will be randomized to one of three dose levels of SPI-1005 or randomized to matching placebo.
Dose Group 1: 200 mg PO BID (n=20) for 21 days
Dose Group 2: 400 mg PO BID (n=20) for 21 days
Dose Group 3: 600 mg PO BID (n=20) for 21 days
Dose Group 4: Placebo mg PO BID (n=20) for 21 days

Safety Parameters
An interventional study with repeat physical examinations, vital signs, adverse events (AE's) monitoring, CBC, serum chemistry and urinalysis assessments.
AEs will be coded using MedDRA (version 18.1 or greater) and summarized by each dose level for the number of adverse events by body-system-organ class. Comparisons will be made between baseline, at the end of treatment 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, and the end of treatment and 28-day follow-up values.
The investigator(s) will contact SPI medical monitor for a loss in air conduction hearing threshold ≥40 dB at any frequency during the study.

Pharmacokinetic Assessments
Study Participant PK: The peak and trough plasma levels of SPI-1005 and its major metabolite will be determined by LCMS. The corresponding peak and trough total plasma selenium levels will be determined by ICP-MS. PK results will be summarized for each dose level and compared.

Pharmacodynamic Assessments
PD consists of audiometric, vestibular, respiratory and PGx profiles.

Clinical Laboratory Assessments

Hematology	Chemistry		Urinalysis
RBC	Sodium	Albumin	pH
Hematocrit	Potassium	AST (SGOT)	Specific gravity
Hemoglobin	Chloride	ALT (SGPT)	Protein
Platelets	Bicarbonate	GGT	Glucose
WBC	Glucose	Total bilirubin	Ketones
Neutrophils	Blood urea nitrogen (BUN) or Urea	Alkaline phosphatase	Blood
Lymphocytes	Creatinine	Uric acid	Microscopic exam only if indicated
Monocytes	Calcium	LDH	Beta-Human Chorionic Gonadotropin (β-HCG) for women of childbearing potential
Basophils	Magnesium	Cholesterol	
Eosinophils	Inorganic phosphorus	Triglycerides	
	Total protein		

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 test 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 variables with significance at 0.05 level.

1.1 Schedule of Assessments

Table 1 Schedule of Assessments

	Screen & Baseline	**Start SPI-1005**	**Safety Eval**	**Safety Eval**	**Safety Eval**	**End of Study**
Clinic Visit	**-3 to 0**	**1**	***2**	***3**	**4**	**5**
Study Treatment Day	0	1	7-10	10, 14 or 21	24, 28, or 35	38, 42, or 49
Visit Interval	-3	0	±2	±3	±3	±3
Assessment						
Informed Consent	X					
Demographics	X					
Height	X					
Weight/BMI	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Medical History	X					
CF History	X					
Detailed Ototoxic Medication History	X					
PE-Comprehensive	X					X
PE-Routine			X	X	X	
Serum chemistry	X		X	X	X	X
CBC	X		X	X	X	X
Urinalysis	X		X	X	X	X
Urine pregnancy[1]	X[1]					
Spirometry	X		X	X	X	X
Randomization[2]	X[2]	X[2]				
SPI-1005 treatment		X[3]	X	X		
TFI/VSS	X				X	X
Otoscopy/Tymp	X				X	X
DPOAE	X				X	X
Audiometry/WINT	X				X	X
AE Assessment	X	X	X	X	X	X
Con Med Review	X	X	X	X	X	X
PG /PD	X				X	
SPI-1005 PK[4]			X[4]	X	X	

* Clinic visits 2 and 3 can be combined if these visits overlap between 8-13 days.

1 Women of child bearing potential

2 Randomization: after all inclusion/exclusion criteria are met. Local labs of equivalent parameters may be used for randomization. Central labs will be completed regardless of laboratory source for screening.

3 SPI-1005 for 21 days will be dispensed at this visit.

4 SPI-1005 PK samples will consist of blood samples for SPI-1005, SPI-1005 major metabolite and selenium collected before the morning dose when feasible, and time of last dose documented.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Meaning
AAA	American Academy of Audiology
AE	Adverse event
AMG	Aminoglycoside
ANOVA	Analysis of Variance
ANSI	American National Standards Institute
APE	Acute pulmonary exacerbation
ASHA	American Speech, Language, and Hearing Association
ATS	American Thoracic Society
AUC0-t	Area under the curve time 0 to time t
BID	Twice daily dosing
CBC	Complete Blood Count
CCC-A	Certificate of Clinical Competence in Audiology issued by ASHA
CF	Cystic fibrosis
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
Cl	Clearance
Cmax	Maximum concentration
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRISS	Chronic Respiratory Infection Symptom Scale
CRO	Contract Research Organization
CSC	Controlled Sound Challenge
CV	Clinic Visit
dB	deciBel, $1/10^{th}$ of a Bel—measure of ratios on a log scale
dB HL	decibels of hearing loss (also decibels of hearing level)
DPOAE	Distortion Product Otoacoustics Emission
DMC	Data Monitoring Committee
ER	Etymotic Research
EQ-5L-5D	Euro QOL Group–5 Level–5 Dimension
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
GPx	Glutathione Peroxidase
GSH	Glutathione
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
hr	Hour
Hz	Hertz—unit of measure for frequency
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee

IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
kHz	Kilohertz
LCMS	Liquid chromatography mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
ml	milliliter
NCRAR	National Center for Rehabilitative Auditory Research
ng	nanogram
PA	Physician Assistant
PD	Pharmacodynamics
PE	Pulmonary exacerbation
PGx	Pharmacogenomics
PI	Principal Investigator
PK	Pharmacokinetics
Po	By mouth
PTA	Pure tone audiometry
R^2	Correlation coefficient
RN	Registered Nurse
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SAE	Serious adverse event
SC	Study Coordinator
Se	Selenium
SNR	Signal-to-noise ratio
SPI	Sound Pharmaceuticals, Inc.
SPI-1005	Sound Pharmaceuticals, Inc. proprietary oral formulation of ebselen
SRO	Sensitive range for ototoxicity
T1/2	Half life
TFI	Tinnitus Functional Index
Tmax	Time of maximum concentration
TTS	Temporary Threshold Shift
VS	Vital signs
VSS	Vertigo Symptom Scale
WINT	Words-in-Noise Test

2 BACKGROUND

Currently, there are no FDA approved treatments that prevent or treat ototoxicity, or any other type of sensorineural hearing loss. SPI-1005, is a proprietary capsule that contains ebselen, a novel small molecule that mimics the activity of Glutathione Peroxidase (GPx). GPx activity is critical to several inner ear structures including auditory and vestibular sensory hair cells. Inner ear hair cells are injured or destroyed following acute and repeated exposures to noise or ototoxic agents such as platinum and aminoglycosides. SPI-1005 is being tested investigated to prevent and treat acute forms of sensorineural hearing loss, tinnitus, and ototoxicity under INDs 068443, 078348, and 127540. A Phase 1 safety and pharmacokinetic clinical trial with 32 healthy volunteers has been completed. A Phase 2 safety and efficacy clinical trial with 83 young adults was completed (SPI-1005-202). The SPI-1005-202 study demonstrated that SPI-1005 could prevent the incidence, severity and duration of an acute noise induced hearing loss with 4 days of treatment. SPI-1005 was well safe and well tolerated. The mechanism of action of SPI-1005 indicates that it may be useful in preventing and treating aminoglycoside-induced ototoxicity which has a very similar pathophysiology. In support of this, ebselen treatment was shown to prevent both auditory and vestibular hair cell injury and loss induced by acute gentamicin injection in a guinea pig model of ototoxicity. The observational and interventional clinical studies detailed here will determine if SPI-1005 can prevent and treat aminoglycoside-induced ototoxicity in CF patients receiving IV aminoglycosides using five different measures of auditory and vestibular function.

2.1 Class or Type of Drug Being Studied/Description of Drug

SPI-1005 is a proprietary formulation of ebselen (2-Phenyl-1,2-benzisoselenazol-3(2H) one) for oral delivery. SPI-1005 is a seleno-organic small molecule mimic of GPx, an endogenous enzyme with catalytic antioxidant activity. GPx reduces reactive oxygen species (ROS) by the binding of free radicals to its selenium (Se) moiety and the subsequent transfer to glutathione (GSH). By reacting with GSH, GPx limits free radical toxicity, exhibiting strong activity against peroxynitrite ($ONOO^-$). It has been shown to reduce cytochrome-C release from mitochondria and nuclear damage during lipid peroxidation. Agents that reduce the activity of ROS, or free radicals, can attenuate the deleterious effects of noise on hearing. The unique properties of SPI-1005 make this compound a very promising candidate to be the first orally delivered pharmaceutical agent or drug for otoprotection.

2.2 Preclinical Profile

Sound Pharmaceuticals has conducted 13 nonclinical studies evaluating the potential genetic toxicity and preclinical safety of SPI-1005. Results are summarized below; see the Investigator's Brochure in module 1.14.4.1 for detailed information.

2.2.1 Preclinical Toxicology

Genotoxicity and mutagenicity studies performed to date indicate SPI-1005 does not have genotoxic or mutagenic properties under the conditions tested. In the genetic toxicology studies, dose levels were limited by cytotoxicity in bacterial reverse mutation assays and in the in vitro chromosomal aberrations assay. SPI-1005 has shown no evidence of genetic toxicity in assays for bacterial reverse mutation, in vitro mammalian chromosomal aberrations, or in vivo bone marrow micronucleus formation. In each study, maximum feasible doses were administered, and assays were determined to be valid based upon positive and negative control responses.

Safety pharmacology studies indicate no cardiovascular effects in minipigs when dosed orally up to 1000 mg/kg. In neurobehavioral studies performed in rats, a NOAEL was determined at the highest dosed tested of 1000 mg/kg oral. No pulmonary effects were observed up to 100 mg/kg oral in rats, while the doses of 1000 mg/kg produced decreases in respiratory rate and minute volume.

General toxicity has been examined following acute and repeated (28 day) oral gavage toxicology studies in rats, mini-pigs and monkeys. SPI-1005 toxicity was also evaluated in acute intravenous studies in rats and mini-pigs.

Acute toxicity has been examined in oral studies with rat and minipig up to 2000 mg/kg. SPI-1005 is a poorly water-soluble molecule and posed challenges administering high oral doses by gavage. The use of a 200-250 mg/mL suspension of SPI-1005 in 0.5% carboxymethylcellulose vehicle resulted in a thick suspension that was difficult to gavage by mouth. This high concentration was chosen in order to stay within generally accepted volume guidance for oral gavage in rats (8-10 ml/kg) and be able to deliver doses at up to 2000 mg/kg.

In minipigs given a single oral dose of SPI-1005 at 2000 mg/kg, slight hematologic alterations occurred along with changes in urine volume. Rats dosed up to 2000 mg/kg oral SPI-1005 exhibited no evidence of acute or delayed toxicity. Single dose, oral administration of SPI-1005 to rats and mini-pigs at doses of up to 2000 mg/kg was not associated with evidence of acute or delayed toxicity in these species. In rats, systemic exposure to SPI-1005 was dose-proportional. Glucuronidated, methylated, and parahydroxy metabolites of SPI-1005 were observed in this species. In mini-pigs, systemic exposure to SPI-1005 was observed in treated animals, as was significant exposure to a glucuronidated metabolite. There was no significant exposure to methylated or parahydroxylated metabolites in mini-pigs. The acute oral no-observable-adverse-effect level (NOAEL) in each species was 2000 mg/kg.

Acute toxicity of intravenously delivered SPI-1005 was studied in rats and minipigs. Given the highly hydrophobic nature of SPI-1005, it was dissolved in DMSO then mixed with saline for injection. During formulation, flocculent material was observed to precipitate from solution. Significant mortality was observed in rats and mini-pigs receiving intravenous SPI-1005. Drug induced mortality occurred at every dose tested. In rats,

plasma SPI-1005 exposure was minimal and short-lived across all doses. Systemic exposure to SPI-1005's metabolites was minimal or below detectable levels in surviving rats. Analysis of plasma from surviving mini-pigs demonstrated that all pigs had systemic exposure to SPI-1005 and glucuronidated SPI-1005 at 30 mg/kg IV dose. Systemic exposure to SPI-1005 was greater than that of glucuronidated SPI-1005. Exposure to the other metabolites was minimal or undetectable in pigs. The maximal measured plasma concentration of SPI-1005 in IV dosed pigs was approximately 6.5X the C_{max} following single oral dosing at 2000 mg/kg in this species. Gross and microscopic findings in pigs following intravenous dosing were suggestive of microvascular compromise, most likely associated with intravenous precipitation of SPI-1005 as formulated. This hypothesis is supported by the presence of foreign material found in many of the lungs of mini-pigs that died prematurely. Microscopic examination was not performed in rats.

General toxicity has been examined following repeated (28 day) oral gavage toxicology studies in rats, mini-pigs and monkeys dosed orally up to 2000 mg/kg. Gavage-related injury occurred to at least six rats and one pig in the 28-day repeat dose studies. Repeated 28-day oral dosing of SPI-1005 to rats was associated with systemic exposure to SPI-1005 as well as its glucuronidated, methylated, and parahydroxy metabolites. Repeated 28-day dosing of SPI-1005 to mini-pigs resulted in systemic exposure to SPI-1005 and glucuronidated SPI-1005 in a dose-dependent manner.

In the 28-day toxicity study in rat, changes in liver and thyroid weights were observed in rats at all dose levels (100, 500, and 2000 mg/kg/day). These changes were accompanied by an apparent treatment related hepatic toxicity [minimal to mild multifocal eosinophilic inclusions in the hepatocytes] in the high dose males and thymic toxicity [atrophy and/or apoptosis] at all doses (100, 500, 2000 mg/kg/day), microscopic evidence of hepatocellular hypertrophy and thyroid follicular cell hypertrophy. Microscopic and organ weight changes in the liver coupled with a significant glucuronide metabolite suggest that these findings are likely due to induction of biotransforming enzymes in the liver. Although no observable effect level (NOEL) was identified in this study, treatment-related changes in all groups were considered either secondary to induction of hepatic biotransforming enzymes or to difficulty in administering the test material.

In the 28-day toxicity study in mini-pigs, doses up to 2000 mg/kg yielded no treatment-related changes, but the study was complicated by histopathology lung findings in treated and untreated animals. The potential for lung toxicity in minipigs dosed at 100, 500, and 2000 mg/kg/day could not be excluded due to the presence of minimal to marked edema, mild to moderate multifocal hemorrhage and minimal congestion in the lungs of all groups including vehicle controls. This finding may have obscured important toxicological observations in the lung on this study. The conclusion of the study director was that the observed lung findings were not test article related.

Subsequent to the rat and mini-pig studies, a 28-day study of SPI-1005 delivered via nasogastric gavage to monkeys was conducted without gavage-related injury and no test article related effects were observed up to the highest dose tested (NOAEL = 2000 mg/kg). To reduce the gavage-associated difficulty with high dose SPI-1005, SPI evaluated oral

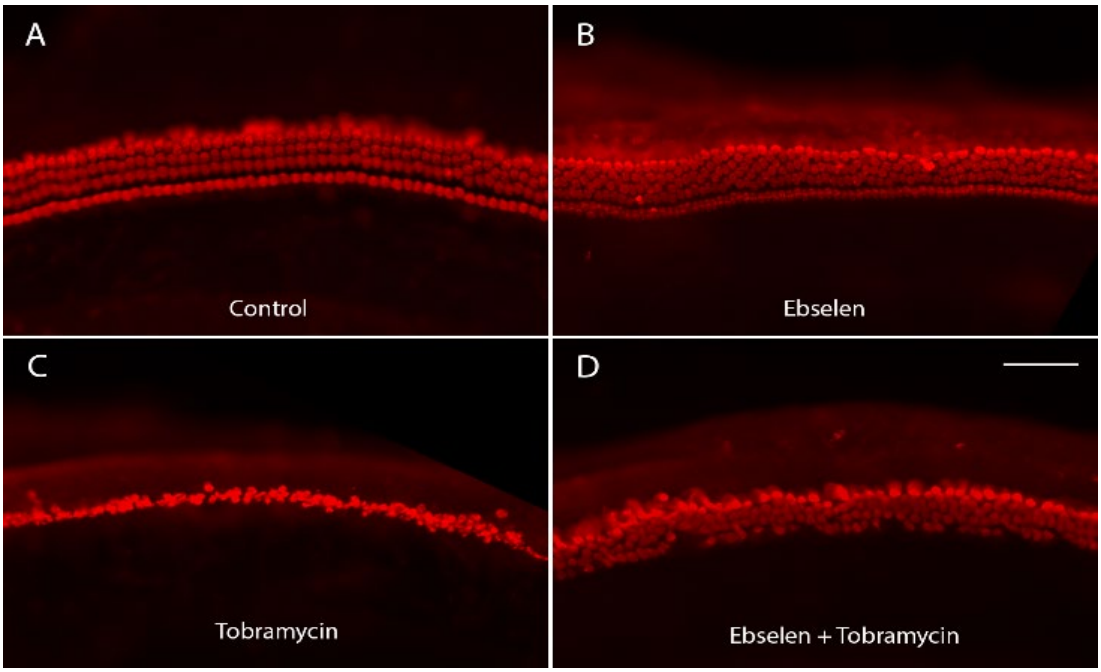
formulations in Cynomolgus monkeys via nasogastric tube. Of the formulations documented for appropriate physical and chemical characteristics, 0.5% carboxymethylcellulose (CMC) and 5% gum Arabic were selected for evaluation in monkeys. This study indicated that 0.5% CMC was an appropriate formulation tested in monkeys. No dosing procedural mortality occurred in the 28-day monkey toxicity study. This study demonstrated an apparent treatment-related increase in minimal cellular aggregate of the liver with an incidence of 1/6, 4/6, 4/6, and 6/6 for the control, 100, 500, and 2000 mg/kg/day dose groups respectively. Notably, no treatment related pathologic or histological findings in lungs were observed at any dose level.

2.2.2 Preclinical Pharmacology

Several preclinical animal studies conducted by Sound Pharmaceuticals, Inc. (SPI) and other independent laboratories have demonstrated the efficacy of SPI-1005 at preventing and treating different acquired forms of sensorineural hearing loss (Kil et al., 2007). SPI-1005 is a novel anti-inflammatory compound with glutathione peroxidase 1 (GPx1) activity. GPx1 is the dominant catalytic antioxidant enzyme in the mammalian inner ear, and its activity is decreased after ototoxic insult. SPI-1005 treatment has been shown to prevent or reverse the pathologic changes in the cochlea following noise- or ototoxin-induced injury.

In vitro studies show that murine cochlear hair cells pre-incubated with SPI-1005 at 6.25-50 μM concentrations for 30 minutes, were protected from the ototoxic destruction of the inner and outer hair cells following incubation for 48 hours with tobramycin or amikacin at 0.5 or 1.0 mM, respectively (Figure 1). These data support the otoprotective capacity of SPI-1005 and show that it is similar to the level of chemoprotection observed by SPI-1005 pre-treatment in cisplatin-induced ototoxicity (Kim et al., 2009).

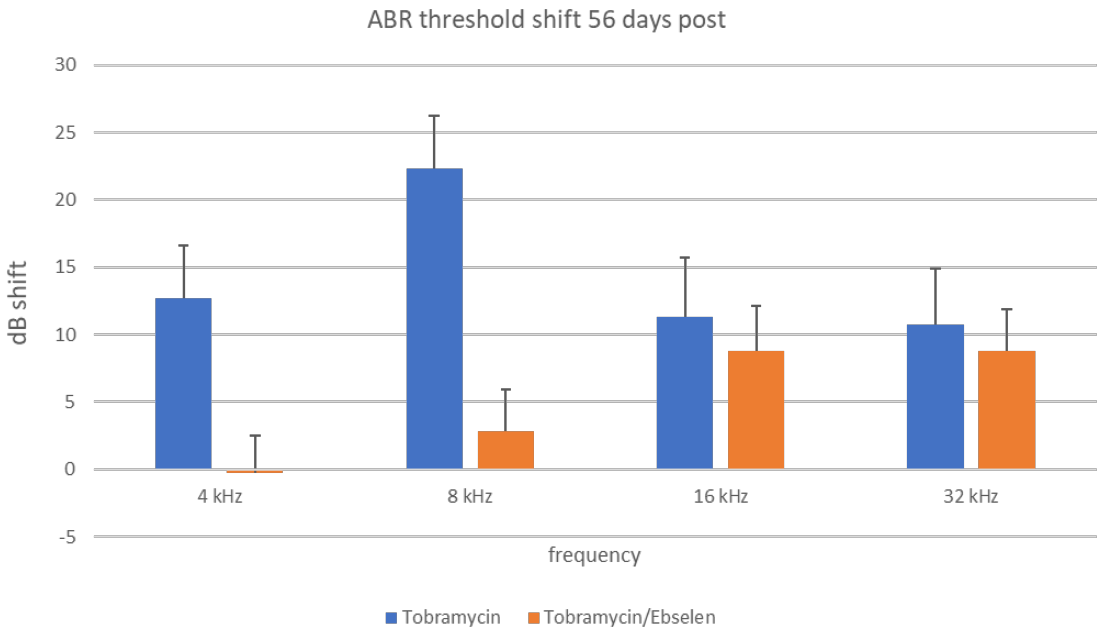
Figure 1 SPI-1005 prevents aminoglycoside toxicity to inner and outer hair cells in vitro.



Whole mount epifluorescence images of mouse cochlea demonstrate the ototoxic effects of tobramycin. ***A.*** *Cochlea in control media possess one row of myosin-VIIa-positive inner hair cells (IHC) and three rows of outer hair cells (OHC).* ***B.*** *SPI-1005 treatment (50 µM) for 48 hours is not ototoxic to either IHCs or OHCs.* ***C.*** *Tobramycin at 0.5 mM for 48 hours was highly ototoxic to both IHCs and OHCs resulting in a complete loss of hair cells in the basal turn (high-frequency region) of the cochlea and a complete loss of OHCs in the apical turns of the cochlea (low-frequency region).* ***D.*** *SPI-1005 treatment 30 minutes prior to the aminoglycoside treatment prevented the ototoxicity induced by tobramycin. Similar results (not shown) were generated for amikacin 1 mM and for SPI-1005 25 µM. (Sound Pharmaceuticals, unpublished data).*

Ebselen has been reported to prevent damage to the organ of Corti and the vestibular organ induced by intratympanic gentamicin, and aminoglycoside antibiotic, in guinea pigs (Takumida et al., 1999). The sensory hairs near the striola portion of the maculae and central portion of cristae had severe changes, ranging from fusion of individual sensory hairs to, in some cases, even complete loss of the sensory hairs (Figure 2). When oral ebselen was given after the gentamicin, there was lessening of the damage severity. In the organ of Corti, the hair bundles in all rows maintained stereocilia rigidity and there was only minimal disruption. In the vestibule, damage to sensory cells was limited and less severe.

Figure 2 SPI-1005 prevents ototoxicity 56 days post treatment



200 mg/kg Tobramycin 20 mg/kg Ebselen

2.3 Potential for Drug-Drug Interactions

The in silico predictive model, admetSAR®, was used to evaluate potential interactions of SPI-1005 with cytochrome P450 (CYP450) (Shen et al., 2010). The CAS number (60940-34-3) was used to identify ebselen, the active ingredient in SPI-1005, and the model then predicted absorption and metabolic profiles from the molecular structure. Only interactions with a probability of 0.6 or greater were considered meaningful. The theoretical profile for SPI-1005 includes inhibition of CYP450 types 1A2, 2C9, 2D6, and 2C19 with high CYP inhibitory promiscuity. SPI-1005 is predicted to be a substrate for CYP450 type 3A4. In silico modeling predicted a lack of interaction with P-glycoprotein and renal organic cation transporter.

Ebselen interaction with cytochrome P450 rat liver microsomes was tested in vitro. The addition of ebselen converted maximally 50% of the cytochrome P450 to P420 in a time-dependent fashion. The effect was half-maximal at 50 µM using a cytochrome P450 concentration of 1 nmol/mL (Kuhn-Velten & Sies, 1989).

Bovine serum albumin at physiologic concentrations and sulfhydryl compounds are effective in preventing this cytochrome P450 inactivation by ebselen (Kuhn-Velten & Sies, 1989; Sies, 1989). In vivo, ebselen is largely bound to plasma proteins. This may contribute to the previously reported low toxicity of the compound (Parnham & Graf, 1987) and may mean that CYP450 inhibition by ebselen is not clinically relevant. See the SPI-1005 Investigator's Brochure in module 1.14.4.1 for additional information.

2.4 Clinical Profile

Sound Pharmaceuticals has completed a Phase 1 study in healthy normal subjects (SPI-1005-101). In the Phase 1 study, there were no treatment- or dose-related trends in overall AE incidence. SPI has completed a Phase 2 study in healthy normal subjects (SPI-1005-202) exposed to a Controlled Sound Challenge (CSC). In the Phase 2 study there were no treatment- or dose-related trends in overall AE incidence. SPI-1005 was found to be effective in reducing the incidence, severity and duration of the temporary threshold shift induced by the CSC. In addition to these, SPI sponsored studies, Rhone-Poulenc sponsored and published limited PK and metabolism studies using ebselen in healthy volunteers in which no AEs were reported. Daiichi Pharmaceuticals sponsored 3 safety and efficacy studies in Japan for the indication of acute stroke. SPI has completed a Part 1 observational study in 20 adult subjects being treated with IV tobramycin (10 mg/kg once a day for 10-21 days) and a sentinel PK study in 5 adult subjects receiving IV tobramycin with steady state dosing (10 mg/kg once a day) during the period of concomitant SPI-1005 treatment (3 oral doses of 600 mg BID). In the observational study at 2 and 4 weeks post tobramycin, PTA and DPOAEs showed a robust level of cochleotoxicity, WINT showed cochleotoxicity, TFI and VSS showed cochlear and vestibular toxicity. In the sentinel PK study, SPI-1005 did not significantly impact serum tobramycin levels. See the Investigator's Brochure for details on SPI and external studies.

2.5 Pharmacokinetics

SPI-1005 capsules have been administered in a single oral dose of 200 mg to 1600 mg to 24 healthy male and female subjects (SPI-1005-101). Following the administration of escalating oral doses of SPI-1005:

- CL/F (L/hr) values ranged from 52 mL/hr to 113 mL/hr,
- C_{max} values ranged from 30.3 ng/mL to 83.4 ng/mL,
- AUC_{0-t} values ranged from 117.4 ng*hr/mL to 880.6 ng*hr/mL,
- T_{max} values ranged from 1.5 hours to 2.3 hours, and
- $t_{1/2}$ values ranged from 6.4 hours to 16.7 hours.

The maximum peak plasma concentrations (C_{max}) and total exposure (AUC_{0-t}) increased with increasing doses of SPI-1005. As the SPI-1005 dose administered increased by 1:2:4:8, the corresponding SPI-1005 AUC_{0-t} changed 1:3.2:5.9:7.5, indicating that ebselen exposure did not change in a dose-proportional manner. Less than 11% of the administered dose was excreted in urine as the parent drug and its metabolites. The predominate metabolite of SPI-1005 was the 2-glucuronyl selenobenzanilide moiety in plasma and urine.

The combined plasma SPI-1005 and metabolites concentrations demonstrated a strong positive correlation with selenium plasma concentrations across all dose groups (R^2 = 0.8120). The R^2 values for combined plasma SPI-1005 and metabolites concentrations versus selenium plasma concentrations per dose group following the administrations of 200 mg, 400 mg, 800 mg, and 1600 mg were 0.9317, 0.8540, 0.7809, and 0.7648, respectively.

In a Phase 2 trial, SPI-1005-202, the safety and efficacy of SPI-1005 was evaluated in subjects, age 18 - 31 years, who experienced a temporary auditory threshold shift (TTS). Subjects received SPI-1005 in one of three dose levels (200, 400, or 600 mg) or placebo delivered orally twice daily (bid) for 4 days.

Blood samples were collected on Day 3 (Clinic Visit or CV2) before and two hours following the morning SPI-1005 dose (fifth dose out of eight) for determination plasma concentrations of selenium, SPI-1005 and three SPI-1005 metabolites (2-glucuronyl selenobenzanilide, N-(4-hydroxyphenyl)-2-methylselenobenzamide, and 2-methyl selenobenzanilide). Samples were also collected for selenium at screening (CV1) and Day 10 (CV4).

Peak and trough concentrations increase with increasing dose. A statistical test was performed to evaluate dose proportionality. The natural log of concentration was plotted versus the natural log of dose and the slope and 95% confidence interval was determined. Both peak and trough concentrations were considered proportional to dose because the 95% confidence interval included 1.0. In contrast to the dose proportionality of trough SPI-1005 concentrations, there is not a consistent pattern of trough concentrations with respect to dose for the metabolites. Overall, exposure is greatest to the glucuronide metabolite followed by N-(4-hydroxyphenyl) -2-methylselenobenzamide. Exposure to SPI-1005 and 2-(methylseleno)-benzanilide are lower than the other two metabolites.

Table 2 SPI-1005-202: Pharmacokinetic Parameters for SPI-1005 and Metabolites

	Median Plasma Conc. (nmol/mL)			
	SPI-1005	**SPI-1005 Glucuronide**	**2-(Methylseleno)-Benzanilide**	**N-(4-hydroxyphenyl)-2-Methylselenobenzamide**
200 mg BID (n=22)				
C_{min}	0.066	0.430	0.083	0.385
C_{max}	0.138	1.708	0.146	0.696
400 mg BID (n=20)				
C_{min}	0.149	1.351	0.082	0.764
C_{max}	0.272	3.368	0.231	1.138
600 mg BID (n=21)				
C_{min}	0.165	1.019	0.078	0.718
C_{max}	0.399	4.930	0.326	1.439
C_{min} measured prior to morning dose on Clinic Visit 2. C_{max} measured 2 hours post dose on Clinic Visit 2.				

2.6 Clinical Adverse Event Profile

To date, adverse events reported in the two completed Sound Pharmaceuticals clinical trials with SPI-1005 have been mild to moderate (SPI-1005-101 and SPI-1005-202). No SAEs have been reported to date. Events have consisted primarily of resolving headaches of mild

to moderate severity. See the Investigator's Brochure for additional information on clinical adverse event profile.

In the SPI-1005-101 study, there were no treatment- or dose-related trends in AE incidence. No serious AEs occurred and none of the subjects were discontinued from the study treatment due to an AE. All AEs in this study were mild or moderate in severity and resolved without sequelae. Although 14 (44%) of the 32 subjects exhibited insufficient orthostatic compensation during at least one time point in the study, there were no treatment- or dose-related trends.

Adverse events reported in at least 5% of subjects that were considered possibly related to study drug included mild or moderate headache (6 subjects on study drug; 5 subjects on placebo); moderate dizziness (2 subjects on study drug); and mild postural dizziness (1 subject on study drug; 1 subject on placebo). All events resolved and may possibly be attributed to the prolonged overnight fast. These events were not repeated in the SPI-1005-202 clinical study.

In the SPI-1005-202 study, treatment with SPI-1005 was well tolerated and no significant adverse events related to study drug were reported or observed for any safety measurement (history, physical finding, hematology, serum chemistry, or chest x-rays) in the 83 enrolled subjects. In total, 63 subjects received at least one dose of SPI-1005: 22 subjects received 200 mg; 20 subjects received 400 mg, and 21 subjects received 600 mg twice daily for 4 days. 20 subjects were randomized to placebo which was delivered by the same schedule. No significant or clinically relevant changes were observed in either treatment group. There were no serious adverse events. The adverse events that occurred in at least 5% of subjects that were considered possibly related to study drug were all mild in severity and included upper abdominal discomfort (3 subjects: two at 400 mg, one placebo); cough (2 subjects); hot flush (1 subject); sunburn (1 subject); and allergic rhinitis (1 subject). All events resolved without complication or sequelae.

In the SPI-1005-151 study, 42 adult subjects were randomized and oral dosing for 21 days was well tolerated with no adverse events due to study drug.

2.6.1 Potential Risk to Fetal Development

Sound Pharmaceuticals has not conducted preclinical fetal development toxicology studies.

3 STUDY RATIONALE

3.1 Therapeutic Rationale

Ototoxic drugs with the potential to cause toxic reactions impart damage to structures of the inner ear, including the cochlea, vestibule, semicircular canals, and otoliths, is considered ototoxic (Govaerts et al., 1990). Drug-induced damage affecting the auditory and vestibular systems can be called, respectively, cochleotoxicity and vestibulotoxicity. The benefits of ototoxic drugs must be weighed against their potential for permanent damage to the inner ear. In selecting treatment protocols, the role of hearing and balance in maintaining quality of life should be considered. Permanent hearing loss or balance disorders caused by ototoxic drugs can have serious vocational, educational, and social consequences. These effects may be minimized if the ototoxic process is detected early during treatment. An effective monitoring program should detect ototoxic damage before the patient becomes aware of ototoxic symptoms (ASHA, 1994).

Several classes of therapeutic agents including aminoglycoside antibiotics and cancer chemotherapy drugs can cause oxidative stress in the inner ear resulting in cellular injury or irreversible cell death. Hearing loss due to ototoxic medications is sensorineural and usually presents initially at the high frequencies and subsequently progresses to the lower frequencies (S.A. Fausti & Frey, 1993; S. A. Fausti, Frey, et al., 1992; S. A. Fausti et al., 1994). Hearing loss due to ototoxicity can be temporary, but usually is permanent. Because aminoglycosides are cleared more slowly from inner ear fluids than from plasma, there may be a significant latency to the ototoxic effect of aminoglycosides (Gatell et al., 1984; Lerner & Matz, 1979; Meyerhoff et al., 1989). Clinical symptoms of ototoxicity involve one or more of the following: hearing loss, tinnitus, difficulty understanding speech, vertigo and/or dizziness.

In a prospective study of several different ototoxic medications, intravenous aminoglycoside antibiotics showed a high incidence of new onset tinnitus of 19% following a single course of treatment. However, this study's exclusion criteria may have resulted in an underestimation of aminoglycoside-induced tinnitus in the general population due to the high baseline rates of tinnitus in this veteran based population (Dille et al., 2010). The frequency of cochleotoxicity associated with specific drugs is unclear because of the inconsistencies in the treatment of specific study populations. In support of this, the incidence of aminoglycoside-induced cochleotoxicity has been reported to range from 0% to 63% (Pedersen et al., 1987; Tablan et al., 1984).

Intravenous aminoglycosides, widely used in patients with cystic fibrosis, are known to induce ototoxic complications. Patients with greater number of courses of intravenous aminoglycosides are at higher risk (Al-Malky et al., 2014). In this series of 63 CF patients who received IV aminoglycosides, 24% had ototoxicity detected using pure tone audiometry including extended high frequency testing. Since the cochleotoxic effect of aminoglycosides is initially confined to the high frequencies, extended high-frequency testing (>8 kHz) is more sensitive for clinical monitoring (Al-Malky et al., 2011). A cellular

mechanism connected with aminoglycoside ototoxicity involves imbalance with reactive oxygen and reactive nitrogen species (ROS/RNS).

In the Part 1 observational study, PTA, DPOAEs and WINT showed cochleotoxicity at 2 and 4 weeks post IV tobramycin

3.2 Study Design Rationale

This is the fifth clinical trial for SPI-1005 (SPI-1005-101, SPI-1005-202 and SPI-1005-151 completed, SPI-1005-251 ongoing). The primary goal is to assess the safety and efficacy of SPI-1005 at three doses compared to placebo in CF patients with acute pulmonary exacerbation (APE).

Safety is a primary concern throughout the study. Safety concerns may arise from the pharmacological properties of the drug in humans or from findings during the toxicology studies. The primary pharmacology or mechanism of action of SPI-1005 is as a GPx mimic that corrects or augments redox-balance. From two prior clinical studies, the dose tested has been safe and well tolerated.

The CF population selected for enrollment in this clinical trial will receive IV aminoglycoside antibiotics for the empirical and/or targeted treatment of lung infections. For CF patients, the majority of these treatment episodes with aminoglycoside antibiotics are empirical with pretreatment cultures negative, and of fixed duration (Bhatt, 2013; Flume et al., 2009). The duration of treatment ranges from 8 to 15 days with an IV aminoglycoside, and there is lack of consensus on optimal duration within the CF community (Flume et al., 2009).

In this study, SPI-1005 treatment will be initiated in close proximity to initiation of IV aminoglycoside treatment for APE. Assessments of baseline and post-treatment hearing sensitivity will be performed in conjunction with a battery of safety assessments. Dosing with SPI-1005 will continue concomitantly with IV tobramycin treatment and end at 21 days. For patients receiving 10 or 14 days of tobramycin IV, dosing will continue 11 to 7 days following the discontinuation of IV tobramycin. For patients receiving 21 days of IV tobramycin, treatment with SPI-1005 will mirror patient treatment for APE.

3.3 Dose Rationale

Doses of 200, 400 and 600 mg will be used in this trial, based on prior clinical experience and supporting preclinical toxicokinetic data. Dose selection for this proposed study is based on prior clinical trials conducted by SPI: a single dose escalating trial (SPI-1005-101) and a multiple dose trial (SPI-1005-202). Doses of 200, 400, 800 and 1600 mg were safe and well tolerated in the Phase 1 SPI-1005-101 trial. Doses selected in the SPI-1005-101 clinical trial utilized preclinical toxicokinetic results to set the maximum dose (Section 2.2.1). Doses selected in the SPI-1005-202 study, employed doses of 200, 400, and 600 mg twice daily for 4 days that were safe and well tolerated. In addition, the ongoing SPI-1005-151 clinical trial for the treatment of Meniere's disease involves testing 200, 400 and 600 mg twice daily for 21 days.

3.4 Dosing Regimen

Blinded: All patients will be randomized to one of three dose levels of SPI-1005 or randomized to matching placebo.

- Dose Group 1: 200 mg PO BID (n=20) for 21 days
- Dose Group 2: 400 mg PO BID (n=20) for 21 days
- Dose Group 3: 600 mg PO BID (n=20) for 21 days
- Dose Group 4: Placebo mg PO BID (n=20) for 21 days

Patients will take their treatment twice daily for 21 days. Capsules will be taken orally with water (with or without food) in the am and pm (approximately 12 hours apart).

4 STUDY OBJECTIVES

The data from the proposed Phase 2 clinical trial will be used to determine whether SPI-1005 is safe and efficacious in a CF population undergoing IV tobramycin treatment, and whether SPI-1005 can mitigate aminoglycoside-induced ototoxicity.

4.1 Primary Objectives

The safety and efficacy of SPI-1005 treatment in CF patients with APE receiving IV tobramycin will be determined through the following assessments.

- Determination of sensorineural hearing loss using pure-tone audiometry comparing baseline to post-treatment.
- Change in distortion product otoacoustics emissions (DPOAE) comparing baseline to post-treatment.
- Change in word recognition scores using the Words-in-Noise test (WINT) comparing baseline to post-treatment.
- Severity or development of tinnitus using the Tinnitus Functional Index (TFI) comparing baseline to post-treatment.
- Severity or development of vertigo using the Vertigo Symptoms Scale (VSS) comparing baseline to post-treatment.
- Spirometry performance assessing baseline to post-treatment.
- Pharmacokinetics of SPI-1005 in CF patients and drug-drug interaction analysis of SPI-1005 and tobramycin.
- Physical examinations including vital signs
- Adverse event monitoring using MeDRA coding (version 18.1 or higher)
- Clinical Laboratory tests (CBC, serum chemistry, and urinalysis)

4.2 Exploratory Objectives

- Pharmacogenomics analysis will explore SPI-1005 as an inducer of gene expression for Nrf2, glutathione peroxidase-1, hemeoxygenase-1, and thioredoxin class of redox proteins.

- Pharmacodynamics analysis will explore SPI-1005 on the level of Nrf2 (nuclear translocation from cytosol), Glutathione (GSH reduced and GSSG oxidized), cysteine and cystine.

5 STUDY PLAN

This is a randomized, double-blind, placebo-controlled multi-center study. Patients with cystic fibrosis will receive one of three oral doses of SPI-1005 or matching placebo within 48 hours of starting IV tobramycin treatment. Patients will have repeated safety and pharmacodynamic assessments, including specific audiometric testing to determine the incidence and severity of ototoxicity using academy criteria (ASHA, 1994). Extended high-frequency hearing tests and distortion product otoacoustic emissions (DPOAEs) testing will be conducted at the start of and after IV aminoglycoside treatment as well as patient reported outcomes (PRO) of tinnitus and vertigo severity using clinically validated PROs.

5.1 Study Design

80 adult CF participants will be enrolled in a multicenter, randomized, double-blinded, placebo-controlled study of SPI-1005. Patients, aged ≥18 years of age, will have screening ototoxicity testing performed. Patients meeting all enrollment criteria will be randomized to a dose of SPI-1005 or placebo within two days of initiating IV tobramycin. Patients will have safety assessments performed at baseline and through study duration according to schedule of assessments in Section 1.1. Female subjects of child bearing potential will receive pregnancy testing at screening, and those found to be pregnant will be excluded or discontinued from the study and monitored for adverse events. Patients will continue with SPI-1005 or placebo for a total of 21 days of treatment.

SPI-1005 treatment will be evaluated for safety by vital signs, physical examinations, clinical laboratory tests (CBC, serum chemistry, and urinalysis), spirometry, and adverse events see Section 1.1. Additionally, criteria have been implemented to report changes in audiological PTA exceeding specified values.

Pharmacokinetics will evaluate repeated trough levels of total selenium, ebselen SPI-1005 and its major metabolite in the plasma. Plasma will be analyzed by ICP-MS for total selenium, and by LCMS for SPI-1005 and its major metabolite.

Pharmacodynamic (PD) and pharmacogenomic (PGx) samples will be collected according to the schedule of assessments in Section 1.1. Exploratory PD analysis will include Glutathione (GSH reduced and GSSG oxidized), cysteine and cystine. PGx analysis will explore SPI-1005 as an inducer of gene expression for glutathione peroxidase-1, Nrf2 (nuclear translocation from cytosol), hemeoxygenase-1, and thioredoxin class of redox proteins.

PGx samples may be retained for future exploratory analysis guided by: The DNA sample(s) collected in the current trial will be used to study various genetic causes for how subjects may respond to a drug. The DNA sample(s) will be stored to provide a resource for future studies conducted by Sound Pharmaceuticals, Inc. focused on the study of genes

responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. All samples will be used by Sound Pharmaceuticals or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

5.2 POPULATION

The diagnosis of acute pulmonary exacerbation will be made by the physician's decision to treat a pulmonary exacerbation and with IV antibiotics (i.e. tobramycin). Guidelines on the use of antibiotics based on cultures obtained over the last 2 years are recommended. Concurrent treatment decisions are relegated to the treating clinician and should be maximized for airway clearance per protocol. In general, patients are to continue with their chronic therapies (e.g. bronchodilators, macrolides, Pulmozyme, inhaled antibiotics). The use or prohibition of other concomitant medications shall follow the physician's decision and per protocol. Note, very sick patients are excluded from consideration (e.g. ICU care, massive hemoptysis, IV antibiotics in the last 60 days).

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

5.3 Number of Subjects

The study aims to enroll approximately 80 male or female patients with CF receiving IV tobramycin for APE.

After consultation with the sponsor and the principal investigator, enrollment may be extended to replace patient(s) discontinued during the study for non-safety reasons.

5.4 Inclusion Criteria

1. CF patients about to receive IV tobramycin (or within 48 hours of initiating IV tobramycin) for a planned minimum of 10 days for the treatment of acute pulmonary exacerbation (APE).
2. Voluntarily consent to participate in the study.
3. Age ≥18 years of age at the time of informed consent.
4. Male patients that are willing to use condoms throughout the study period and 90-days following study completion even if not fertile.
5. Females of childbearing potential should be using and committed to continue using one of the following acceptable birth control methods:
    a. Sexual abstinence (inactivity) for 14 days prior to screening through study completion; or
    b. IUD in place for at least 3 months prior to study through study completion; or
    c. Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or
    d. Stable hormonal contraceptive for at least 3 months prior to study through study completion.
6. Ability to perform all study related procedures.

5.5 Exclusion Criteria

1. Use within 60 days of study enrollment of any of the following IV ototoxic medications: aminoglycoside antibiotics (gentamicin, tobramycin, amikacin, streptomycin); platinum-containing chemotherapies (cisplatin, carboplatin, oxaliplatin); or loop diuretic (furosemide).

2. Severe lung disease with FEV_1 <40% predicted, or Investigator discretion for FEV1% predicted.
3. Sensorineural hearing loss ≥70 dB at (air conduction) at conventional frequencies ≤4 kHz at baseline.
4. History of idiopathic sensorineural hearing loss, otosclerosis, or vestibular schwannoma.
5. History of middle ear or inner ear surgery.
6. Current conductive hearing loss or middle ear effusion.
7. Significant cardiovascular, renal, hematologic, immunologic, or psychiatric disease.
8. Patients with liver function testing (ALT, AST or GGT) results ≥3x the upper limit of normal.
9. History of hypersensitivity or idiosyncratic reaction to compounds related to ebselen or selenium.
10. Participation in another investigational drug or device study within 30 days prior to study enrollment.
11. Female patients who are pregnant or breastfeeding.
12. Subject has any other illness or other condition that, in the opinion of the investigator would prohibit the subject from participating in the study.

5.6 Deviation from Inclusion/Exclusion Criteria

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 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.

6 STUDY CONDUCT

6.1 General Instructions

Patients will participate in this clinical trial for approximately 38 to 49 days after initiation of study treatment. Patients will remain on study approximately four weeks after the completion of IV tobramycin. Each patient will have up to six clinical visits during this study. Details regarding pulmonary monitoring (spirometry, pulse oximetry, collection of pulmonary-related adverse events) will be performed in accordance with schedule of assessments, Section 1.1.

6.2 Study Procedures by Time Point

6.2.1 Clinic Visit -3 to 0 – Initial Screening (Study day 0)

Subjects will be briefed and informed consent for study participation obtained before study evaluations are conducted. CF disease history, safety, audiometric, PK and PD assessments will be made according to the schedule of assessments, Section 1.1. Each subject will be interviewed regarding hearing and health to reveal any history of hearing loss, tinnitus, known ear pathology, or use of any potentially ototoxic medications (i.e., diuretics, aminoglycosides). After fulfilling all inclusion and exclusion criteria, blinded randomization to placebo or treatment group will be done and clinical supply will be provided. Local laboratory results are allowed to determine inclusion and exclusion criteria. If used, these results will be recorded in source and available for review. Central lab results must be collected regardless of use of local labs.

6.2.2 Study Visit 1 (Study Day 1)

Randomization will occur on Visit 1 if local labs were not used to determine eligibility at Visit 0. Additionally, vital signs and safety assessments will be performed according to schedule of assessments in Section 1.1.

6.2.3 Study Visit 2 (Study Day 7 to 10)

Safety, audiometric, and PK assessments will be completed according to the schedule of assessments, Section 1.1.

Note: Clinic Visits 2 and 3 can be combined if these visits overlap between 8-13 days.

6.2.4 Study Visit 3 (Study Day 10, 14 or 21)

Safety, audiometric, PD and PK assessments will be completed according to the schedule of assessments, Section 1.1.

6.2.5 Study Visit 4 (Study Day 24, 28 or 35)

Safety, audiometric, and PK assessments will be completed according to the schedule of assessments, Section 1.1.

6.2.6 Study Visit 5 (Study Day 38, 42 or 49)

Safety, audiometric, PD and PK assessments will be completed according to the schedule of assessments, Section 1.1.

6.3 Premature Discontinuation

6.3.1 Early Permanent Discontinuation of study Treatment

A subject may be permanently discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for early permanent discontinuation of study treatment:

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

If a subject is permanently discontinued from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who permanently discontinue study treatment early should come in for an early permanent discontinuation of study treatment visit as soon as possible and then should be encouraged to remain on-study and complete all remaining scheduled visits and procedures.

6.3.2 Early Withdrawal of Subjects from the Study

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. This may include subjects who withdraw from study treatment early and who decline to continue to come in for remaining follow-up visits or it may include subjects who completed treatment and decline to come in for remaining follow-up visits.

Reasonable attempts will be made by the investigator to provide a reason for early subject withdrawals. The reason for the subject's early withdrawal from the study will be specified in the subject's source documents and recorded on the Case Report Form (CRF). Subjects who withdraw early from the should be encouraged to come in for a final end of study visit (Section 1.1).

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 final study visit are performed.

At a minimum collect the following information when a patient discontinues:

- The reason the patient 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 final trial visit (see Section 1.1)

7 DESCRIPTION OF STUDY PROCEDURES

Patients selected for the trial will undergo assessments and testing according to the schedule in Section 1.1. Procedures will be performed according to sequence of events and standards described below.

7.1 Informed Consent

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 before performing any study-related procedure. A copy of the informed consent will be given to the subject.

A separate consent will be provided for the PGx portion of this study.

7.2 Screening Number Assignment

Following completion of the study-specific informed consent by the subject, a screening number may be assigned to the subject by the site in sequential order starting with 001. Screening numbers will be recorded on the CRF.

7.3 Randomization Number Assignment

Prior to the administration of SPI-1005 treatment, a randomization number will be assigned to each subject by the site using the Subject Identification Code (SIC) provided in Section 8.4.

7.4 Demographics

The demographic profile required by the study CRF and permitted by local regulations should be entered. This information may include the subject's age (at baseline), ethnicity, gender and race.

7.5 Record Adverse Events and Concomitant Medications

See Section 9.1, Documenting Adverse Events; Section 10.3, Reporting Serious Adverse Events; and Section 6.3, Premature Discontinuation.

Concomitant medications will be collected at baseline and for all treatments received following informed consent. Data will include drug, dose, route, duration of use and indication.

Concomitant use of the following medications other than IV tobramycin are prohibited:

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

7.6 Height and Weight

Body height and weight measurements should be obtained and recorded to the nearest kg and cm in source and captured on the CRF.

7.7 BMI

BMI should be calculated using the following formula and recorded in the source document and auto-calculated on the CRF: BMI = Weight (kg)/Height $(m)^2$.

7.8 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. Systolic and diastolic blood pressure (mm Hg), pulse rate (bpm) (manually assessed and recorded in source, body temperature and the actual clock time 24:00) will be recorded in source and captured on the CRF. All vital signs should be measured consistently using the same approach. 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.

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.

7.9 Medical History

A detailed medical history will be obtained by the investigator or qualified designee. Subject history should include information on clinically significant family and personal history, birth control history, smoking history, and history of diseases (including past history of hepatitis, allergies or reactions to medications and food, seizures, previous

surgery, trauma, syncope, and arrhythmias). Any clinically relevant changes found at any time during the study will be recorded as an adverse event and captured on the CRF.

7.10 Cystic Fibrosis History

In addition to the routine medical history, a cystic fibrosis history will capture the following elements:

- CF Foundation Registration Number
- CF Genotype
- Age of CF diagnosis
- Age of onset chronic Pseudomonas aeruginosa
- Pancreatic insufficiency (enzyme usage) history
- CF related diabetes history

7.11 Detailed Ototoxic Medication History

Use of ototoxic medications will be collected and will be documented in source and captured on the CRF. Specifically, ototoxic medications such as aminoglycosides, loop diuretics, and platinum-based antineoplastic agents should be documented

7.12 Physical Examination-Comprehensive

The principal investigator or designee will perform a physical examination of the following organ systems at the times specified in Section 1.1: Eyes, ears, nose, head, oropharynx, thyroid, respiratory system, cardiovascular system, endocrine system, abdomen (gastrointestinal/genitourinary), skin, extremities, lymph nodes (including cervical, axillary and femoral), and musculoskeletal reflexes. Clinically significant changes from the Screening and/or Baseline physical examinations will be recorded as adverse events. For abnormal findings, the investigator will comment on clinical significance; clinically significant or not clinically significant.

7.13 Physical Examination-Routine

The principal investigator or designee will perform a physical examination of the following organ systems at the times specified in Section 1.1: Eyes, ears, nose, head, oropharynx, respiratory system, cardiovascular system, abdomen, skin, musculoskeletal reflexes, and extremities. Clinically significant changes from the Screening and/or Baseline physical examinations will be recorded as adverse events. For abnormal findings, the investigator will comment on clinical significance; clinically significant or not clinically significant.

7.14 Pregnancy Tests

A urine pregnancy test must be performed at the times designated in Section 1.1. Results must be available prior to dosing. Subjects with a positive pregnancy test at screening or prior to the first dose will not be allowed to enter into the study (screen failure). Subjects with a positive pregnancy test any time after first dose will be discontinued from the study.

Positive results will be recorded on the Adverse Event section of the CRF. The pregnancy will be reported and monitored according to Section 10.3, Reporting Serious Adverse Events.

7.15 SPI-1005 Treatment

SPI-1005 and matching placebo are capsules for oral administration. Refer to Section 8 for Treatments to be administered. The time of dose administration should be documented in source and recorded in CRF for each onsite dose administration associated with PK sampling.

7.16 Aminoglycoside Treatment

Dosing with IV antibiotics may include tobramycin and additional antibiotics. For this trial, a minimum of 10-days of planned IV tobramycin treatment is required.

7.17 Tinnitus Functional Index

The Tinnitus Functional Index (TFI) will be administered according to the schedule of assessments in Section 1.1. The TFI is a validated self-report questionnaire that scales tinnitus severity and negative impact at baseline and post treatment change across multiple domains (Meikle 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. Patients should complete the TFI prior to audiologic and laboratory assessments. Data from the TFI will be captured from patients completing the assessment and all values captured in the CRF. See APPENDIX II Tinnitus Functional Index for the TFI and instructions.

7.18 Vertigo Symptoms Scale

The Vertigo Symptom Scale (VSS) 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 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 1.1. Patients should complete the VSS prior to audiological and laboratory assessments. Data from the VSS will be captured from patients completing the assessment and all values captured in the CRF. See APPENDIX III Vertigo Symptoms Scale for the VSS and instructions.

7.19 Otoscopy

The examination of the ear canal and tympanic membrane via an otoscope will be performed according to the schedule of assessments in Section 1.1. 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 source, and abnormalities will be captured in the Physical Examination or Adverse Event portions of the CRF.

7.20 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 1.1. Tympanometry will be performed with equipment provided or approved by Sound Pharmaceuticals. Measurements will not be captured in the CRF. Results will be assessed by the investigator as normal or abnormal and documented in source. See the SPI-3005-501 procedure manual for additional information. Testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

7.21 Distortion Product Otoacoustics Emission

Distortion Product Otoacoustic Emissions (DPOAE) are responses generated when the cochlea is stimulated by two pure tones. DPOAEs are a measure of outer hair cell function and may permit the early detection of ototoxicity. DPOAEs will be obtained with equipment provided by or approved by Sound Pharmaceuticals according to the schedule of assessments in Section 1.1. Results will be captured in the CRF for the DPOAE amplitude (dB) and corresponding test frequencies (Hz). See the SPI-3005-501 procedure manual for additional information. Audiometric testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

7.22 Pure-tone Audiometry Conventional Frequency (0.25 to 8 kHz)

Pure tone audiometry 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 dB HL at 250, 500, 1000, 2000, or 4000 Hz. Bone conduction testing will only be performed at screening and in the affected ear (>15 dB HL). Results will be documented in source and captured in the CRF for sound level and frequency. Audiometric testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

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 or circumaural earphones calibrated to meet ANSI 3.6-2004 specifications for clinical audiometers (provided or approved by Sound Pharmaceuticals). Patients 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. See the SPI-3005-501 procedure manual for additional information.

7.23 Pure-tone Audiometry Extended High Frequency (9 up to 20 kHz)

Extended high-frequency (EHF) testing will be conducted by identifying the highest frequency heard (at 100 dB SPL) and in 1/6-octave increments below this highest frequency (S.A. Fausti & Frey, 1993; S. A. Fausti et al., 1993; S. A. Fausti, Henry, et al., 1992; S. A. Fausti et al., 1994). EHF testing will be performed according to the same standards in Section 7.22 for conventional frequency testing. Collapsing ear canals from supra-aural earphone pressure and poorly placed supra-aural earphone cushions can cause significant test-retest variability, especially in EHF testing (Schmuziger et al., 2004) and should not be used here. See the SPI-3005-501 procedure manual for additional information. Results will be documented in source and captured in the CRF for sound level and frequency. Audiometric testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

7.24 SRO Determination

A test protocol for determining this one-octave sensitive range for ototoxicity (SRO) sampled in 1/6-octave increments, has proven to be a sensitive, reliable and time-efficient behavioral measure of ototoxicity due to acute cisplatin, carboplatin, and aminoglycoside treatment. The SRO technique includes early ototoxicity detection and monitoring regardless of whether the SRO falls above or below 8 kHz. Use of the SRO sampling protocol is less demanding for the patient and has been shown to be more sensitive than conventional or limited EHF testing alone. See the SPI-3005-501 procedure manual for additional information. Results will be documented in source and captured in the CRF. Audiometric testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

7.25 Words-in-Noise Testing (WINT)

A word recognition test will be employed to evaluate ototoxicity. The WINT 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 patients' baseline hearing sensitivity. The WINT 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 WINT will be performed in alignment with US Department of Defense standard criteria (Wilson & Burks, 2005). See the SPI-3005-501 procedure manual for additional information. Results will be documented in source and captured in the CRF. Audiometric testing will be conducted by trained personnel, including state-licensed audiologists and supervised graduate students seeking a clinical doctorate in Audiology.

7.26 Spirometry

Pulmonary function test (PFT) will be performed at screening according to the schedule in Section 1.1. Forced expiratory volume in one second percent predicted (FEV_1) will be used for inclusion/exclusion criteria. FEV_1 percent predicted will be determined from commercially available spirometry using the GLI calculation or equivalent formula. The standard for completing the spirometry assessments and interpretation will be in accordance with American Thoracic Society/European Respiratory Society Standardization of Spirometry (Miller et al., 2005).

CF patients enrolled in the study will have a diagnosis of acute pulmonary exacerbation. As pulmonary function will be a key area of clinical assessments related to underlying care, additional systems monitoring is allowed and anticipated. This may include unscheduled PFTs, pulse oximetry, imaging, pulmonary hygiene techniques and/or other methods. Data reporting for this study is limited to elements of the PFT components, but other monitoring methodology may be relevant for adverse event reporting.

7.27 Pharmacodynamic and Pharmacogenomics (PGx) Sample

Informed consent specific for PGx sampling must be obtained prior to collection. To obtain sufficient DNA/RNA for pharmacogenetic studies, 5 mL blood sample (2.5 ml each) will be drawn at the specified time point indicated in Section 1.1, into the appropriate tube provided by the sponsor. Participation in PGx in assessment is optional; patients may participate in the trial and decline consent and providing PGx samples

Pharmacodynamic (PD) and pharmacogenetic (PGx) samples will be collected according to the schedule of assessments in Section 1.1. Exploratory PD analysis will include Nrf2 (nuclear translocation from cytosol), Glutathione (GSH (reduced) and GSSG (oxidized)), cysteine and cystine. PGx analysis will explore SPI-1005 as an inducer of gene expression for Nrf2, glutathione peroxidase-1, hemeoxygenase-1, and thioredoxin class of redox proteins. See SPI-3005-501 Laboratory Manual for details on sample collection, processing and analysis.

7.28 SPI-1005 Pharmacokinetics

Three (3) mL of blood will be collected at the specified time points indicated in Section 1.1 into the appropriate tubes (see SPI-3005-501 Laboratory Manual for sample acquisition, shipping and labeling instructions).

Sample collection times (actual clock time using 24:00) are to be recorded in source and captured in the CRF. PK samples should be taken 30-60 minutes prior to taking their morning dose of SPI-1005. Pharmacokinetics will evaluate repeated trough levels of total selenium, ebselen SPI-1005 and its major metabolite in the plasma.

7.29 Clinical Laboratory Tests

The following will be performed according to standard laboratory procedures at a Central Laboratory designated by the sponsor. Chemistry 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 should be obtained prior to study drug administration. Clinical laboratory results will be analyzed according to the SPI-3005-501 Laboratory Manual.

Table 3 SPI-3005-501 Clinical Laboratory Assessments

Hematology	Chemistry		Urinalysis
RBC	Sodium	Albumin	pH
Hematocrit	Potassium	AST (SGOT)	Specific gravity
Hemoglobin	Chloride	ALT (SGPT)	Protein
Platelets	Bicarbonate	GGT	Glucose
WBC	Glucose	Total bilirubin	Ketones
Neutrophils	Blood urea nitrogen (BUN) or Urea	Alkaline phosphatase	Blood
Lymphocytes	Creatinine	Uric acid	Microscopic exam only if indicated
Monocytes	Calcium	LDH	
Basophils	Magnesium	Cholesterol	Beta-Human Chorionic Gonadotropin (β-HCG) for women of childbearing potential
Eosinophils	Inorganic phosphorus	Triglycerides	
	Total protein		

If during the trial any laboratory result is outside the reference range and is considered to be clinically significant by the investigator, the test should be repeated at appropriate time intervals until it returns to baseline or becomes a clinically insignificant finding. Any adverse clinically significant change will be recorded on the CRF as an Adverse Event. All laboratory tests, including urinalysis results, will be recorded or captured in the study database. All laboratory tests will be collected according to the schedule in Section 1.1. The clinical laboratory values will be reviewed by the investigator for significance and consideration as an AE.

8 TREATMENT DESCRIPTION

8.1 Formulation

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

8.2 Storage

SPI-1005 should be stored in a secure, dry place at room temperature 20°C to 25°C (68-77°F), with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Temperature logs should be available for review at each monitor site visit. When a temperature within the storage location at the site is noted to be outside the excursion range for 24 hours or more, or exceeds 40°C, the Sponsor should be notified. Storage environmental conditions will be monitored and documented. Study drug supplies will be stored in a secure and limited-access location.

8.3 Packaging and Shipment

SPI will provide study medication packaged in blister packs with sufficient IMP for intra-visit intervals.

The labels will include the name of study drug and study code. Additional information such as batch number, lot number, expiration date, storage conditions, local country requirements, and other information may be added as required by the sponsor's Clinical Supplies representative/designee. The label should be produced in a language appropriate for the study site and contain at least.

- Study No.: SPI-3005-501
- Administer as directed per protocol

8.4 Dose and Administration

SPI-1005 (200, 400 or 600 mg or placebo) is administered orally with approximately 240 ml of water, with or without food. SPI-1005 should be taken twice daily, as close to 12 hours apart as possible.

8.5 Method of Treatment Assignment, Randomization, and/or Stratification

This protocol is a randomized, double-blind, placebo-controlled, study design. The Sound Pharmaceuticals Staff, Principal Investigator(s), all sub-investigators including Medical Doctor (MD), Physician's Assistant (PA), Registered Nurse (RN), Medical Assistant (MA), Audiologist (AuD), Study Coordinator (SC), Clinical Research Associate (CRA), Clinical Research Coordinator (CRC), and laboratory personnel will be blinded to the treatment received by each patient. Bioanalytical staff will be un-blinded for PK analysis.

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 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.

Study participants who are eligible for enrollment will receive medication labelled with a Subject Identification Code (SIC). Randomization codes were pre-randomized with study parameters entered into a randomization software tool. These codes were provided to the Contract Research Organization (CRO) that printed these (material ID) codes onto each patient supply (contains 3 blister cards, each with 42 capsules containing either SPI-1005 or placebo).

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 Study Visits. The PI should contact the Medical Monitor in the case of an adverse event that requires unblinding of IMP.

8.6 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.

8.7 Accountability

Receipt and dispensing of study medication must be recorded by an authorized person at the investigator's site. The investigator agrees neither to dispense the study drug from, nor store it at any site(s) other than those listed on the Form FDA 1572 or Investigator's Agreement. The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Form FDA 1572 or Investigator's Agreement, or their qualified designees. The investigator, sub-investigator, or qualified designees also agree that the study drug(s) will be dispensed only to study patients who have provided written informed consent and have met all entry criteria. Clinical supplies may not be used for any purpose other than that stated in the protocol. An adequate quantity of study drug will be provided to replace units damaged in shipment/handling, to replace patients meeting the entry criteria or to enroll additional subjects.

Accurate and current accounting of the dispensing and return of investigational product will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product dispensed to the site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor);

- Investigational medicinal product dispensed to each patient will be recorded in the trial-specific Patient IMP Accountability Log (or equivalent document approved by the sponsor).

- The Site IMP Accountability Log and Patient IMP Accountability Log will be verified by the sponsor's trial monitor. The original Site IMP Accountability Log and Patient IMP Accountability Log will be approved by the investigator

and retained at the trial site and a copy supplied to the sponsor when the trial is complete.

A final inventory of the total number of investigational products received at the trial site against the amount used and destroyed must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

8.8 Compliance

Compliance with dosing will be assessed according to the schedule in Section 1.1. Any patient not completing dosing according to schedule should be discontinued from the study. Compliance with dosing is consumption of 80% of doses within a 7-day cycle; i.e., missing no more than 3 doses in a 7-day period. The following data will be captured at each dispensing visit in the CRF:

- Capsules dispensed
- Capsules taken
- Capsules returned
- Capsules missed

All drug packaging (used and unused) remaining capsules will remain on site until prior written authorization from the Sponsor to destroy material or return to the Sponsor or designee.

8.9 Product Quality Complaint

A product quality complaint (PQC) is any written, electronic or oral communication that alleges a product defect. A Product Quality Complaint includes suspected product counterfeit, diversion or tampering. A Product Quality Complaint does not include Product Complaints alleging an Adverse Event.

Any occurrence of a product quality complaint by a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor or designee using the Investigational Medicinal Product Quality Complaint Form provided by the sponsor/designee within 1 working day of becoming aware of the event.

9 ADVERSE EVENTS

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this 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.

Subjects will be monitored for the occurrence of AEs - including SAEs - immediately after the subject has signed the informed consent form until the last study visit. The results of the physical examinations at Screening and/or Baseline will be listed in the medical history listing. Post-baseline findings of the physical examinations that meet the criteria of an AE will be listed in the relevant AE listings. Adverse events persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilization has occurred. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since the first dose/yesterday/your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

9.1 Documenting Adverse Events

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the Case Report Forms, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

9.2 Assessment of Intensity/Severity

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The severity of AEs will be graded according to the following definitions:

- Mild: awareness of sign, symptom, or event, but easily tolerated;
- Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;
- Severe: incapacitating with inability to do normal daily living activities, or significantly affects clinical status, and warrants intervention;

9.3 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as reasonably possibility or not reasonably possibility based on available information, using the guidelines listed below:

- Reasonable Possibility: There is evidence to suggest a causal relationship between the drug and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure) (please see below for more information)
- No Reasonable Possibility: There is no evidence to suggest a causal relationship between the drug and the AE.

9.4 Outcome of the Event

One of the following terms should be used to report the outcome of an event:

- Recovered/Resolved: The event has fully recovered. If the event was a worsening of an underlying medical condition, the event is considered recovered when the condition has returned to the initial level.
- Recovered with sequelae: The event has recovered, but the patient has developed chronic sequelae as a consequence of the event.
- Not recovered/Not resolved: The event was ongoing at the time of the report.
- Fatal: The patient died.
- Unknown
- Clinical Laboratory Changes

The clinical laboratory values will be reviewed by the investigator for significance and consideration as an AE.

9.5 Adverse Event Follow-up

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. AEs, actions taken as a result of AEs, and follow-up results must be recorded in the Case Report Forms, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

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

10.2 Definition of Terms

Life threatening: These events are those for which the subject was at risk of death at the time of the event rather than an event which hypothetically might have caused death if it were more severe.

Hospitalization: These events incapacitate and prevent usual activity or require complex medication/treatment or hospitalization.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

10.3 Reporting Serious Adverse Events

All SAEs occurring during clinical trials must be reported within 24 hours to the following:

Sound Pharmaceuticals, Inc. (SPI) contact information:
Jonathan Kil, MD
Sound Pharmaceuticals, Inc.
4010 Stone Way N. Suite 120
Seattle, WA
(206) 634-2559 (office)
(206) 769-4820 (cell)
safety.soundpharma@soundpharma.com

The cause of death of a subject in a clinical trial, whether the event is expected or associated with the investigational agent, is an SAE.

The initial report of an SAE may be made by telephone, e-mail or facsimile (fax). The investigator must provide the minimal information: i.e., protocol number, subject's initials and date of birth, subject number or medication code number, nature of the AE and investigator's attribution.

All oral reports of an SAE must be confirmed within 24 hours by a written, more detailed report and signed by the investigator. For this purpose, the sponsor will provide the investigator with the Serious Adverse Event Form for Clinical Trials.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until either:

- the event resolves,
- the event stabilizes, or
- the event becomes non-serious

The investigator should report any follow-up information as it becomes available.

10.4 Pregnancies

Pregnancies occurring after the first dose of SPI-1005 and during participation of the study are considered immediately reportable events. While not considered a SAE unless a serious criterion is met, pregnancies occurring in subjects enrolled on the study must be reported and followed to outcome. Following delivery or termination of pregnancy, the follow-up pregnancy report form should be completed. Spontaneous abortions should always be reported as SAEs. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11 STATISTICS

11.1 General Procedures

Prior to the database lock, a detailed, finalized Statistical Analysis Plan (SAP) will be completed and placed on file. The SAP will contain a more comprehensive explanation of the methodology used in the statistical analyses. The Statistical Analysis Plan will also contain the rules and data handling conventions used to perform the analyses and the procedure used for accounting for missing data.

11.2 Sample Size

The determination of sample size for this 4-arm study (N=80) is based upon on two prior completed studies including the recent observational Phase 1b study (N=20 enrolled) in an affected CF population. Here, the incidence of the clinically relevant hearing loss was determined using pure tone audiometry, the SRO protocol, and ASHA criteria in an adult CF population receiving IV tobramycin for 11-22 days. Approximately 80% of the completed subjects (N=14 of 18) showed clinically relevant hearing loss (ototoxicity) in at least one ear, at 2 and 4 weeks post-IV tobramycin treatment.(Kil et al., 2018) The hypothesis to be tested in this interventional Phase 2 study, is that concomitant SPI-1005

treatment will reduce the incidence of the ototoxicity induced by one course of IV tobramycin treatment by 50%, relative to placebo. Specifically, we hypothesize that one of the three SPI-1005 treatment arms will reduce the incidence of ototoxicity to 40% vs 80% in the placebo group. Therefore, a sample of N=20 per treatment arm is sufficient to reject the type-I error with 80% power.

11.3 Statistical Methods

11.3.1 Primary Endpoint(s)

The efficacy endpoint for this interventional Phase 2 study is a clinically relevant reduction (50%) in the incidence of ototoxicity induced by one course of IV tobramycin treatment. Specifically, the incidence of ototoxicity in one or more SPI-1005 treatment arms will be compared to the incidence of ototoxicity in the placebo arm, using the aforementioned assessments and ASHA criteria, at 2 and 4 weeks post-IV tobramycin. In a separate completed Phase 2 study involving noise induced hearing loss, SPI-1005 treatment was shown to reduce the incidence of a significant threshold shift by 50% vs placebo (p=.027, Fisher's Exact test). (Kil et al., 2017) A more detailed description will be provided in the SAP.

11.3.2 Safety Parameters

All AEs noted during the study will be listed. The number of subjects reporting each AE (by dose group) and severity will also be presented. AEs will be tabulated by body system/organ class. Placebo should be pooled. Active treatments across different dose groups may also be pooled.

The results of hematology, serum chemistry and urinalysis will be listed for each subject. Laboratory values outside the normal ranges will be flagged. Baseline is defined by values prior to or at time 0 on Day 1. Placebo will be pooled.

Systolic and diastolic blood pressures, heart rate, and body temperature will be listed for each subject. If applicable, summary statistics (mean changes, % change from baseline, and absolute change from baseline) by dose group at each time point will be provided. Baseline is defined by values prior to or at time 0 on Day 1. Placebo will be pooled.

The results of the physical examinations at Screening and/or Baseline will be listed in the medical history listing. Post-baseline findings of the physical examinations that meet the criteria of an AE will be listed in the relevant AE listings.

11.3.3 Audiometric Data

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 test 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 0.05 level.

11.3.4 Pharmacokinetic Parameters

Descriptive statistics will be provided for the concentration data at each sampling time and the derived pharmacokinetic parameters. Descriptive statistics will comprise number of observations (n), arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum.

Concentration-versus-time (C-t) plots may be made for each subject in PK group. The mean concentrations by treatment will be depicted as C-t plots.

11.3.5 Pharmacodynamics

Exploratory pharmacodynamic relationships of dose and effect analyses may be conducted, if deemed appropriate.

11.3.6 Pharmacokinetic-Pharmacodynamic Analysis

Exploratory pharmacokinetic-pharmacodynamic relationships and analyses may be conducted, if deemed appropriate. PK-PD analyses if done will be reported separately.

11.3.7 Pharmacogenomic Analysis

The DNA/RNA sample(s) collected in the current trial will be used to study various genetic causes for how subjects may respond to a drug. The sample(s) will also be stored to provide a resource for future studies conducted by SPI focused on the study of genes responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. All samples will be used by SPI or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

11.3.8 Analysis of Safety

See Section 11.3.1.1 Primary Endpoints for analysis of safety.

11.3.9 Demographic and Baseline Characteristics

Demographic variables (e.g., sex, race, age, weight) will be listed and summarized using descriptive statistics for the entire study population and for each cohort.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

The study must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonization of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the study must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the study is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the study is conducted in the EU; and (iii) any specific local regulations if the study is conducted elsewhere.

12.2 Data and Safety Monitoring Committee

A Data Monitoring Committee (DMC) is planned for this study. Details are outlined in a separate DMC Charter.

12.3 Institutional Review Board/Independent Ethics Committee

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

12.4 Informed Consent

The details of the protocol must be provided in written format and discussed with each potential subject and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guide-lines E6 and local laws. In addition, the sponsor specifically requests that

the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s) are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

12.5 Records Management

The site will complete electronic Case Report Forms (eCRF). The investigator will provide subject data on the eCRFs, compliant with GCP practices. As agreed with the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to the study center. All databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidance's, laws, and regulations.

All data collection forms such as CRFs, diaries; EDC screens; electronic database entries, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on any trial documents transferred to the Sponsor. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

12.6 Source Documentation

All data entered in the CRF will be supported by source data at the study center. Source data is defined as the original record capturing the observation of description of events.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will attest in writing at the beginning of the trial that his/her electronic signature is the legally binding equivalent of a written signature and will acknowledge by entering his/her electronic signature that he/she has verified the accuracy of the recorded data.

12.7 Study Files and Record Retention

During the trial and after termination of the trial, including after early termination of the trial, the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines or the EU Good Clinical Practices Directive, whichever is longer:

- The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is dis-continued.
- The EU GCP Directive specifies that trial records must be retained for 5 years after the completion of the trial.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

12.8 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Clinical Investigator Financial Certification Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (e.g., sub-investigators) read and answer the Clinical Investigator Financial Certification Form as a condition of their participation in the trial.

If the financial interests reported on the Clinical Investigator Financial Certification Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

13 AUDITING AND MONITORING

13.1 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, patient charts and study source documents, and other records relative to study conduct.

13.2 Study Monitoring

The sponsor or its representatives will perform on-site monitoring visits as frequently as necessary based on site activity to review protocol compliance, compare eCRFs with individual subject's medical records and clinic charts, and ensure that the study is being conducted according to pertinent regulatory requirements. The dates of the visits will be recorded by the monitor in a trial center visit log to be kept at the site. The first post-initiation visit will usually be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered onto the eCRFs with the hospital or clinic records (source documents). The review of medical records will be performed in a manner that ensures subject confidentiality is maintained. At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant medication, drug receipt/dispensing/return records, and study drug administration information. Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate, the study coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

14 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Sound Pharmaceuticals. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Sound Pharmaceuticals will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Sound Pharmaceuticals, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

15 STUDY REPORT AND PUBLICATIONS

15.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with Section 15.3 of this protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 90 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, e.g., any computer access system such as the Internet, World Wide Web, etc.) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. proprietary information that is protected by the provisions contained in Section15.2;
2. the accuracy of the information contained in the publication; and
3. to ensure that the presentation is fairly balanced and in compliance with FDA and other national regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

15.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

15.3 Use of Trial Information in a Publication

Investigator is granted the right to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

15.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

- Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
- Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
- Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

16 STUDY DISCONTINUATION

Both Sound Pharmaceuticals and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Sound Pharmaceuticals and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17 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.

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19 APPENDICES

19.1 APPENDIX I – Names of Study Personnel

Sponsor:	Sound Pharmaceuticals, Inc. 4010 Stone Way N., Suite 220 Seattle WA, 98103 Phone: 206-634-2559 FAX: 206-691-8262
Medical Monitor:	Jonathan Kil, MD President & CEO (206) 634-2559 (office) (206) 769-4820 (cell) jkil@soundpharma.com

19.2 APPENDIX II Tinnitus Functional Index

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*
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*
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*
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?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

E **Over the PAST WEEK...**

23. How **ANXIOUS** or **WORRIED** has your tinnitus made you feel?

Not at all anxious or worried ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely anxious or worried*

24. How **BOTHERED** or **UPSET** have you been because of your tinnitus?

Not at all bothered or upset ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely bothered or upset*

25. How **DEPRESSED** were you because of your tinnitus?

Not at all depressed ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely depressed*

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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)
I: INTRUSIVE (unpleasantness, intrusiveness, persistence)
SC: SENSE OF CONTROL (reduced sense of control)
C: COGNITIVE (cognitive interference)
SL: SLEEP (sleep disturbance)
A: AUDITORY (auditory difficulties attributed to tinnitus)
R: RELAXATION (interference with relaxation)
Q: QUALITY OF LIFE (QOL) (quality of life reduced)
E: EMOTIONAL (emotional distress)

ITEMS IN SUBSCALE
#1, #2, #3
#4, #5, #6
#7, #8, #9
#10, #11, #12
#13, #14, #15
#16, #17, #18
#19, #20, #21, #22
#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.

19.3 APPENDIX III Vertigo Symptoms Scale

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

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	