CLINICAL RESEARCH PROTOCOL

DRUG:	SPI-1005
STUDY NUMBER(S):	SPI-1005-251
PROTOCOL(S) TITLE:	A PHASE 2b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN MENIERE'S DISEASE
IND NUMBER:	127540
SPONSOR:	Sound Pharmaceuticals, Inc. 4010 Stone Way N., Suite 220 Seattle WA, 98103 Phone: 206-634-2559 FAX: 206-691-8262
ORIGINAL PROTOCOL DATE:	21 August 2017
VERSION NUMBER:	1.00
VERSION DATE:	21 August 2017

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

SPI-1005-251: CLINICAL TRIAL SYNOPSIS	
Title	A PHASE 2b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN MENIERE'S DISEASE
Study Objective(s)	The primary objective of this Phase 2 study is to determine the: • Safety of SPI-1005 treatment in adults with Meniere's disease. • Efficacy of SPI-1005 will be determined by the following clinically significant methods and measures (responder analysis): ➢ Pure tone audiometry (≥30 dBHL at 250, 500 or 1000 Hz) ≥10 dB improvement from baseline ➢ Words in Noise Test (0-35) ≥10 % increase from baseline ➢ Tinnitus Functional Index (TFI) (0-100) ≥10 pt. reduction from baseline ➢ Tinnitus Loudness: Q#2 of TFI (0-10) ≥2 pt. reduction from baseline ➢ Vertigo Symptom Scale (0-60) ≥6 pt. reduction from baseline The responder analysis from each method and measure will be compared between treatment groups for significance. • Efficacy of SPI-1005 treatment in adults with Meniere's disease based on o Improvement in sensorineural hearing loss using pure tone audiometry at 250, 500, or 1000 Hz; or o Word recognition score using WIN testing at 24, 20, 16, 12, 8, 4 and 0 SNR; or o Improvement in the Tinnitus Functional Index (TFI); or o Improvement in Tinnitus Loudness (TL); or o Improvement in the Vertigo Symptoms Scale (VSS). The secondary objectives of this study are to determine the: • Pharmacokinetics of SPI-1005.
Study Design	Randomized Double Blind Placebo Controlled Study of SPI-1005 in adult volunteers with Meniere's Disease (probable or definitive

SPI-1005-251: CLINICAL TRIAL SYNOPSIS	
	diagnosis) with active symptoms in the months preceding study enrollment. All subjects will undergo baseline audiometric testing and have their severity of sensorineural hearing loss, tinnitus and vertigo determined before initiating treatment. Subjects will be randomized to treatment, either placebo or two different doses of SPI-1005 (1:1:1) and treated for 28 days. Subjects will return to clinic 2 weeks after the start of study drug to have safety assessments and to receive additional study drug. Subjects will return to clinic at week 4 to have their hearing loss, tinnitus and vertigo re-assessed, and again 4 weeks after the end of study drug treatment. Therefore, 4 scheduled clinic visits will be performed over an 8 week period. Audiometry will be performed at baseline, at the end of the 4 week treatment period, and 4 weeks after treatment has stopped. The TFI and VSS will be performed at all scheduled clinic visits. Subjects are allowed to continue with their existing maintenance therapies (i.e. low salt diet, thiazide diuretic, or other PRN medications) except for the use of oral or locally injected steroids. New treatments should be avoided while on study.
Study Centers	Approximately 12 U.S. sites will participate in this study
Subjects	120 male and female adults with probable or definitive Meniere's disease.
Inclusion Criteria	• Adult male and female patients, 18-75 years of age at the time of enrollment. • Diagnosis of probable or definitive Meniere's disease by AAO-HNS 1995 criteria (Section 12.1, APPENDIX I). • Two of three active symptoms including vertigo or disequilibrium, fluctuating hearing loss, or tinnitus within the 3 months prior to study enrollment. • Hearing loss of ≥30 dBHL at either 250, 500 or 1000 Hz. • Voluntary consent to participate in the study. • Male subjects that are willing to use condoms throughout the study period and 90-days following study completion even if not fertile. • Females of childbearing potential should either be sexually inactive (abstinent) for 14 days prior to screening and throughout the study or be using one of the following acceptable birth control methods: o IUD in place for at least 3 months prior to study; or o Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or o Stable hormonal contraceptive for at least 3 months prior

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	to study and through study completion; or o Surgical sterilization (vasectomy) of partner at least 6 months prior to study enrollment. • Females of non-childbearing potential should be surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study enrollment, hysterectomy, or bilateral oophorectomy at least 2 months prior to study) or be at least 1 year since last menses.
Exclusion Criteria	• Current use of or within 60 days prior to study IV ototoxic medications such as chemotherapy including cisplatin, carboplatinum, or oxaliplatin; aminoglycoside antibiotics including gentamicin, amikacin, tobramycin, kanamycin, or streptomycin; or loop diuretics including furosemide. • History of otosclerosis or vestibular schwannoma. • History of significant middle ear or inner ear surgery. • Current conductive hearing loss, otitis media, or mixed hearing loss. • Significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, or psychiatric disease. • Current use or within 30 days prior to study enrollment systemic steroids or drugs known to be strong inhibitors or inducers of cytochrome P450 enzymes. • Hypersensitivity or idiosyncratic reaction to compounds related to ebselen or selenium. • Female patients who are pregnant or breastfeeding. • Participation in another interventional drug or device study within 30 days prior to study consent.
Study Duration	Estimated duration of 12 months
Participant Duration	Participation for each study participants will be approximately 8 to 12 weeks across 4 clinic visits.
Dose & Regimen	Subjects will receive either SPI-1005 or matching placebo for 28 days. Treatment will be taken orally BID. Doses include 200 mg or 400 mg of ebselen or matching placebo in capsule form. Two week supplies will be provided on Clinic Visit 1 and 2.

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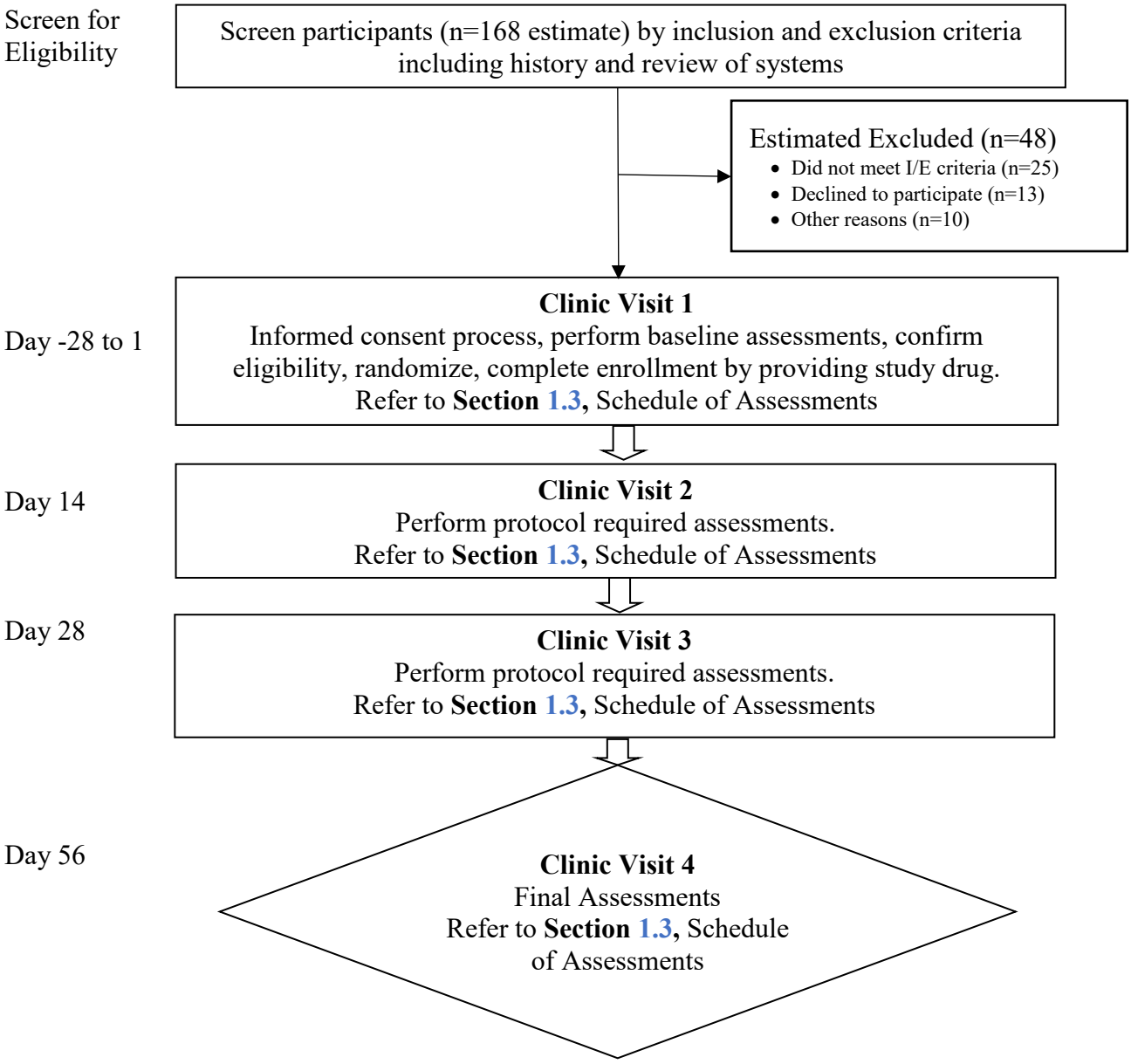
Safety & Tolerability Assessments	Physical examinations, vital signs, adverse events, hematology (CBC) and serum chemistries will encompass safety assessments. Adverse events will be coded using MedDRA (Version 18.1 or higher) and summarized by treatment group for the number of adverse events and compared. Vital signs and clinical laboratory results will be summarized for each treatment group and compared.
PK Assessments	The trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined using LC-MS/MS. The corresponding selenium plasma levels will be determined by ICP-MS. PK results will be summarized by treatment group.
Lead Investigator (s)	Paul R. Lambert, MD

1.2 Schema


Screen for Eligibility
Screen participants (n=168 estimate) by inclusion and exclusion criteria including history and review of systems
Estimated Excluded (n=48)
Did not meet I/E criteria (n=25)
Declined to participate (n=13)
Other reasons (n=10)
Day -28 to 1
Clinic Visit 1
Informed consent process, perform baseline assessments, confirm eligibility, randomize, complete enrollment by providing study drug.
Refer to Section 1.3, Schedule of Assessments
Day 14
Clinic Visit 2
Perform protocol required assessments.
Refer to Section 1.3, Schedule of Assessments
Day 28
Clinic Visit 3
Perform protocol required assessments.
Refer to Section 1.3, Schedule of Assessments
Day 56
Clinic Visit 4
Final Assessments
Refer to Section 1.3, Schedule of Assessments

1.3 Schedule of Assessments

Clinic Visit	CV1 (Screening/Baseline)	CV2	CV3	CV4
Study Day	**-28 to 1**	**14 (+/- 3)**	**28 (+/- 3)**	**56 (+/-3)**
Informed Consent	X			
Demographics	X			
Medical History	X			
Physical Exam	X	X	X	X
Hight	X			
Weight	X	X	X	X
BMI	X			
Vital Signs	X	X	X	X
CBC	X	X	X	X
Serum Chemistry	X	X	X	X
Urine Pregnancy [(1)]	X			
Otoscopy	X		X	X
Tympanometry	X			
TFI	X	X	X	X
VSS	X	X	X	X
PTA	X		X	X
WINT	X		X	X
Concomitant Medication Review	X	X	X	X
Randomization	X			
SPI-1005 Treatment [(2)]	X	X	X	
Adverse Events	X	X	X	X
PK	X	X	X	X

[(1)] Urine pregnancy test on CV1 screening visit only.

[(2)] SPI-1005 treatment **begins** after safety labs (CBC, serum chemistry) are reviewed and all inclusion/exclusion criteria are met.