CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1/2 STUDY OF OTO-313 GIVEN AS A SINGLE INTRATYMPANIC INJECTION IN SUBJECTS WITH SUBJECTIVE TINNITUS

Protocol Number: 313-201901

Sponsor Contact: 

Medical Monitor: 

Version: 3.0

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APPROVED BY:

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PROTOCOL AMENDMENT, VERSION 3.0

This protocol amendment serves to make the following changes.

Item No.	Change	Section
1	Revised exclusion criteria 15 to exclude the use of systemic steroids (including dexamethasone), within 6 weeks prior to the Screening visit. The use of intratympanic steroids had already been excluded for 6 weeks prior to the Screening visit, therefore the revision adds systemic steroids to the exclusion. Systemic steroids may be used for treating sensorineural hearing loss and the 6-week exclusionary period prior to Screening will allow for any residual effects of the systemic steroid, if any, to stabilize prior to randomization. The use of systemic steroids is also prohibited during the study and the prohibited therapies section has been revised accordingly.	Synopsis Section 4.3, Exclusion Criteria Section 7.1

SPONSOR CONTACT INFORMATION

Medical Monitor:

Name	[redacted]
Title	[redacted]
Office Phone Number	[redacted]
E-Mail	[redacted]

Other Appropriate Trial Contact Personnel:

Name	[redacted]
Title	[redacted]
Office Phone Number	[redacted]
E-Mail	[redacted]

Safety Email: [redacted]

If any Sponsor contact information needs to be changed during the course of the study, this will be done by the Sponsor, with written notification to the Investigator, and will not require a protocol amendment.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated and will abide by all applicable local and national regulatory obligations.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by Otonomy, Inc. (hereafter, "the Sponsor") or its representative and approved by the Institutional Review Board (IRB) responsible for this study and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study. I will assure that each subject enrolled into the study, or legally authorized representative, reads, understands, and signs the appropriate version of the informed consent. I agree that the Sponsor or its representatives shall have access to any original source documents to verify data captured for this clinical study.

I further agree not to originate or use the name of the Sponsor and/or OTO-313, or any of its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of the Sponsor.

Investigator's Signature	Date

Name of Investigator *(typed or printed)*

ABBREVIATIONS

AE	Adverse Event
ASHA	American Speech and Language Hearing Association
CRO	Clinical Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2B6	Cytochrome P450 Isoform 2B6
dB	Decibel
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
Hz	Hertz
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N	Number
NMDA	N-Methyl-D-Aspartic Acid
NRS	Numeric Rating Scale
OTO-311	Otonomy Investigational Product in poloxamer, Gacyclidine (Active Ingredient)
OTO-313	Otonomy Investigational Product in medium-chain triglyceride, Gacyclidine (Active Ingredient)
PK	Pharmacokinetics
PGIC	Patient Global Impression of Change
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFI	Tinnitus Functional Index
TSCHQ	Tinnitus Sample Case History Questionnaire

SYNOPSIS

NAME OF SPONSOR/COMPANY:	Otonomy, Inc.
NAME OF FINISHED PRODUCT:	OTO-313
NAME OF ACTIVE INGREDIENT(S):	Gacyclidine

Protocol No.: 313-201901

Title of Study: A randomized, double-blind, placebo-controlled Phase 1/2 study of OTO-313 given as a single intratympanic injection in subjects with subjective tinnitus

Study Center(s): Part A of this study will be conducted at 1 site in the United States and Part B will be conducted at approximately 20 sites in the United States

Study Period: approximately 12 months	**Phase of Development:** 1/2

Study Design:

This is the first study of intratympanic OTO-313 in subjects with tinnitus and is composed of 2 parts. Part A is a randomized, double-blind, placebo-controlled Phase 1 cohort to evaluate the safety and plasma pharmacokinetics (PK) of one dose level (0.11 mg) of OTO-313 in subjects with unilateral or bilateral subjective tinnitus. Eight eligible subjects will be randomly assigned to either OTO-313 (6 subjects) or placebo (2 subjects) for intratympanic injection to a single (study) ear. Subjects in Part A will undergo blood sampling for plasma concentration testing of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites) on Days 1, 2, and 8 and will be observed for safety and exploratory efficacy for 28 days.

If acceptable safety and tolerability is observed in Part A (as determined by review of data through Day 8 for all subjects by the Safety Review Committee), Part B of the study will be initiated. Part B is a randomized, double-blind, placebo-controlled cohort of subjects with unilateral subjective tinnitus to evaluate the safety and preliminary efficacy of OTO-313. Fifty subjects will be randomly assigned, using a 1:1 allocation ratio, to intratympanic injection of either 0.32 mg OTO-313 or placebo to the affected (study) ear. If acceptable safety and tolerability is observed for the first 12 subjects dosed in Part B (as determined by review of data through Day 8 by the Safety Review Committee), the remaining subjects in Part B will be enrolled. In the event that adverse safety findings occur with 0.32 mg OTO-313 in the first 12 subjects, Part B subjects may be enrolled using the 0.11 mg dose level of OTO-313, and enrollment expanded so that 50 subjects are randomized to that dose level or to placebo. All subjects in Part B will be observed for safety and preliminary efficacy for 8 weeks following dosing. Blood samples for PK analysis will be obtained on Day 1 and on Day 8 in a subset of approximately 16 subjects at selected sites in Part B.

Study Objectives:

Part A

Primary:

- To evaluate the safety and tolerability of OTO-313 in subjects with unilateral or bilateral tinnitus.

Secondary:

- To assess the plasma PK of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites).

Part B

Primary:

- To evaluate the safety and tolerability of OTO-313 in subjects with unilateral tinnitus.

Secondary:

- To examine the preliminary efficacy of OTO-313 in subjects with unilateral tinnitus, as measured by the change from Baseline in the Tinnitus Functional Index (TFI).

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- To assess, in a subset of subjects, the plasma PK of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites).

Exploratory:

- To explore the preliminary efficacy of OTO-313 on tinnitus annoyance using a subject-reported Numeric Rating Scale (NRS).
- To explore the preliminary efficacy of OTO-313 on tinnitus loudness using a subject-reported NRS.
- To explore the preliminary efficacy of OTO-313 on tinnitus severity using the Patient Global Impression of Change (PGIC).

Methods:

Part A

Part A will be conducted at 1 site in the United States and will involve 1 overnight stay in the research unit. The duration of Part A for each subject will be approximately 4-6 weeks, including an up to 2-week Screening period and a 4-week follow-up period.

After informed consent and Screening, eligible subjects will be randomized to OTO-313 or placebo at the Baseline visit (Day 1). Eight subjects will receive either 0.11 mg OTO-313 (N=6) or placebo (N=2). Plasma samples for pharmacokinetic (PK) analysis will be obtained on Day 1 (pre-dose, 0.5, 1, 2, 4, 8, and 12 hours post-administration), Day 2 (24 hours post-administration), and Day 8. Subjects will remain overnight in the research unit on Day 1 and will be discharged on Day 2. Additional follow-up visits for safety and efficacy assessments will be conducted on Day 8, Day 15, and Day 29 (end of study) or upon early termination from the study.

If acceptable safety and tolerability is observed for 8 days post-administration in Part A in all subjects, Part B will be initiated with the 0.32 mg dose level of OTO-313 (see Safety Data Review).

Part B

Part B will be conducted at approximately 20 sites in the United States. The duration of Part B for each subject will be approximately 10-12 weeks, including an up to 2-week Screening period, a 2-week Lead-in assessment period, and an 8-week Follow-Up period. If acceptable safety and tolerability is observed for 8 days for the first 12 subjects dosed (see Safety Data Review), the remaining subjects in Part B will be enrolled. In the event that adverse safety findings occur with 0.32 mg OTO-313 in the first 12 subjects, Part B subjects may be enrolled using 0.11 mg OTO-313, and enrollment expanded so that 50 subjects are randomized to this (lower) dose level or to placebo in order to reach the target number of subjects for Part B.

After informed consent and Screening, potential subjects will begin a 2-week lead-in assessment period. During this time, subjects will enter daily tinnitus annoyance and tinnitus loudness severity into an electronic diary using the appropriate Numeric Rating Scales (NRS) for each symptom. Subjects must have completed the tinnitus electronic diary on 4 of the last 7 days of the Lead-in period for eligibility. Subjects will also complete the Tinnitus Functional Index (TFI) at both the Screening visit and the Baseline visit (Day 1). Subjects must have a score of ≥ 25 at each TFI assessment for eligibility. At the Baseline visit (Day 1), eligible subjects will be randomized to OTO-313 or placebo using a 1:1 allocation ratio.

After a single intratympanic injection with OTO-313 or placebo to the affected (study) ear on Day 1, subjects will continue to record their tinnitus annoyance and tinnitus loudness on a daily basis using the electronic diary during the 8-week follow-up period. Subjects will complete the TFI at study visits on Day 1 (Baseline), Day 15, Day 29, and Day 57 (end of study). Additional safety and/or exploratory assessments will also be completed at Day 1 (Baseline), Day 8, Day 15, Day 29, and Day 57 (end of study) or upon early termination from the study.

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In a subset of 16 subjects at selected sites, blood samples for PK analysis will be obtained on Day 1 (pre-dose and 1-hour post-administration) and on Day 8.

Safety Data Review

The decision to proceed with initiation of dosing in Part B, and subsequent dosing decisions, will be made by a Safety Review Committee. The Safety Review Committee will include at a minimum the Medical Monitor, the Investigator at the Phase 1 research unit, and the Clinical Representative of the Sponsor. Safety data, including adverse events, clinical safety laboratory measurements, audiometry, otoscopy, tympanometry, and C-SSRS data through Day 8, will be evaluated and the decision to proceed will be based on the clinical significance of any adverse events or suspected investigational product-related findings. Initially, all data will be reviewed in a blinded manner with regard to treatment assignment. The treatment assignment for an individual subject may be unblinded, if deemed necessary to enable medical care or study decision-making by the Safety Review Committee.

Number of Subjects:

The planned sample size for this study is 58 to 70 subjects (8 subjects in Part A and 50 to 62 subjects in Part B).

Diagnosis and Main Criteria for Inclusion:

To be eligible for this study, each of the following criteria must be satisfied with a "YES" answer (unless not applicable):

Part A only

1. Subject has subjective unilateral or bilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.

Part B only

2. Subject has subjective unilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.
3. Subject's self-reported duration of tinnitus is between 1 month and 6 months (30 to 180 days) prior to signing informed consent.
4. Subject has an overall score of ≥ 25 on the TFI at Screening and Baseline (Day 1) visits.
5. Subject is able to use the electronic diary to complete their daily tinnitus ratings and has completed at least 4 of the last 7 days of diary entries during the 2-week Lead-in period.

Part A and B

6. Subject is a male or female aged 18 to 75 years, inclusive.
7. Subject's tinnitus is likely of cochlear origin, e.g., associated with sensorineural hearing loss; acute hearing loss from noise trauma, barotrauma, or traumatic cochlear injury (acute acoustic trauma, blast trauma, middle ear surgery, inner ear barotrauma); age-related hearing loss; resolved otitis media; ototoxic drug exposure.
8. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal ($\geq$12 months since last menstrual period and 45 years of age or older)] must have a negative urine pregnancy test at Baseline (Day 1). Women of childbearing potential who are not abstinent from sex with male partners must use effective methods of contraception for the duration of the study including: established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; or "double barrier" methods including a combination of male condom with either diaphragm or cervical cap with spermicide. Female subjects of childbearing potential must also refrain from egg donation or retrieval for the duration of the study.

9. Male subjects (unless surgically sterile) who are not abstinent from sex with female partners of childbearing potential must agree to use an effective contraceptive method (as detailed for Inclusion Criteria 8) for the duration of the study. Male subjects must refrain from sperm donation for the duration of the study.
10. Subject is willing to comply with the protocol and attend all study visits.
11. Subject is able to provide written informed consent after the scope and nature of the investigation have been explained, and before the initiation of any study-related procedures.

Diagnosis and Main Criteria for Exclusion:

To be eligible for this study, each of the following criteria must be satisfied with a "NO" answer (unless not applicable):

Part A and B

1. Subject has pulsatile tinnitus, tinnitus resulting from traumatic head or neck injury, or tinnitus resulting from a tumor or stroke.
2. Subject has active middle ear disease (including but not limited to: chronic otitis media, acute otitis media, middle ear effusions, middle ear atelectasis, or cholesteatoma), Meniere's disease as outlined by the American Academy of Otolaryngology-Head and Neck Surgery Equilibrium Committee in 2015 (Goebel 2016), or vestibular schwannoma.
3. Subject has recently (< 1 month of Screening) initiated new treatment for tinnitus (e.g. noise or sound generators, hearing aids, behavioral therapy; medications or over-the-counter supplements); only stable tinnitus treatments are allowed during the study and no new treatments should be introduced.
4. Subject is not able to accurately identify and report their tinnitus per Investigator's opinion.
5. Subject has an abnormality of the tympanic membrane in the affected (study) ear that would increase the risk associated with intratympanic injection, including but not limited to monomeric tympanic membrane.
6. Subject has evidence of perforation or lack of closure of the tympanic membrane at Screening or Baseline (Day 1) visits.
7. Subject is receiving any ongoing therapy known as potentially tinnitus-inducing (e.g. aminoglycosides, ototoxic chemotherapeutic drugs, loop diuretics, quinine, high doses of aspirin or other nonsteroidal anti-inflammatory drugs). Usage of low doses of aspirin or other non-steroidal anti-inflammatory drugs may be permitted at the Investigator's discretion.
8. Subject answered "Yes" to Question 4 or 5 regarding active suicidal ideation on the C-SSRS administered at Screening or Baseline (Day 1) visits. In addition, subjects deemed by the Investigator to be at significant risk of suicidal behavior should be excluded.
9. Subject has severe or untreated depression or anxiety that, in the Investigator's opinion, would likely reduce the safety of study participation or compliance with study procedures. Only stable doses (taken for ≥ 1 month prior to Screening) of antidepressant and anti-anxiety medications are allowed during the study.
10. Subject is pregnant or lactating.
11. Subject has a history of immunodeficiency disease.
12. Subject has a history of substance or alcohol abuse within the preceding 6 months prior to Screening.
13. Subject is receiving concomitant treatment with any other NMDA receptor antagonist (e.g. memantine, dextromethorphan).

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14. Subject has a history of previous use of intratympanic gentamicin in the affected ear.
15. Subject has received systemic or intratympanic steroids (including dexamethasone) within 6 weeks prior to the Screening visit.
16. Subject has a known hypersensitivity to gacyclidine or any of the excipients in OTO-313.
17. Subject has used moderate or strong inducers of CYP2B6 (e.g. carbamazepine, efavirenz, rifampin, or ritonavir) within 30 days prior to Screening.
18. Subject has other clinically significant illness, medical condition or medical history at Screening or Baseline (Day 1) that, in the Investigator's opinion, would likely reduce the safety of study participation or compliance with study procedures.

Test Product, Dose, and Mode of Administration:

0.11 mg OTO-313 or 0.32 mg OTO-313 (solution of gacyclidine in medium-chain triglycerides), single (0.2 mL volume) intratympanic injection to the affected (study) ear

Reference Product, Dose, and Mode of Administration:

Placebo (100% medium-chain triglycerides solution), single (0.2 mL volume) intratympanic injection to the affected (study) ear

Duration of Treatment:

Single (0.2 mL volume) intratympanic injection to the affected (study) ear

Endpoints for Evaluation:

Part A

Safety Endpoints:

- Assessment of treatment-emergent adverse events (TEAEs).
- Clinically significant adverse change from Baseline in audiometry assessments, tympanometry, and otoscopic examinations.
- Clinically significant adverse change from Baseline in clinical laboratory measurements (hematology, serum chemistry, and urinalysis) or vital signs measurements (systolic and diastolic blood pressure, pulse rate).
- Assessment of suicidality via Columbia-Suicide Severity Rating Scale (C-SSRS).

PK Endpoints:

- Plasma concentrations of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites).

Exploratory Efficacy Endpoints:

- Change in TFI overall score from Baseline at Day 8, 15, and 29.
- PGIC scores at Days 8, 15, and 29.

Part B

Safety Endpoints:

- Assessment of TEAEs.
- Clinically significant adverse change from Baseline in audiometry assessments, tympanometry, and otoscopic examinations.

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- Clinically significant adverse change from Baseline in clinical laboratory measurements (hematology, serum chemistry, and urinalysis) or vital signs measurements (systolic and diastolic blood pressure, pulse rate).
- Assessment of suicidality via C-SSRS.

PK Endpoints:

- Plasma concentrations of gacyclidine including (+) and (-) enantiomers of gacyclidine and (possibly its metabolites).

Primary Efficacy Endpoint:

- Change in TFI overall score from Baseline at Day 57.

Exploratory Efficacy Endpoints:

- Change from Baseline in the 7-day average NRS ratings of tinnitus annoyance at Weeks 2, 4, and 8.
- Change from Baseline in the 7-day average NRS ratings of tinnitus loudness at Weeks 2, 4, and 8.
- Change from Baseline in TFI overall score from Baseline at Days 15 and 29.
- The occurrence of at least a 13-point reduction in the overall TFI score from Baseline at Days 15, 29, and 57.
- Change in TFI subscale (Intrusiveness, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, Emotional) scores from Baseline at Days 15, 29, and 57.
- PGIC scores at Day 8, 15, 29, and 57.

Statistical Methods:

Sample Size Justification:

The sample size for Part A (8 subjects) was selected based on clinical judgment and is not based on statistical considerations. For Part B, the assumed true standard deviation (SD) of the change from Baseline to Day 57 in the TFI overall score is 17 points. Based on the use of a one-sided two-sample t test at the α=0.05 level of significance, a sample size of 50 subjects (25 subjects per arm) will provide 80% power to detect a mean difference between groups of 12 points.

Part A analyses:

Safety and PK data will be summarized descriptively. The analyses of the PK data will be conducted by an independent vendor with experience in PK analyses.

Part B analyses:

For Part B, the key secondary endpoint (change from Baseline to Day 57 in the TFI overall score) and all exploratory endpoints that are defined in terms of the change from baseline will be analyzed using analysis of covariance (ANCOVA) models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate. All proportion endpoints will be analyzed using Pearson's chi-square test, provided that the minimum expected cell count is at least 5. Otherwise, Fisher's exact test will be used. Correlations between endpoints will be assessed using the Pearson and Spearman correlation coefficients. All statistical analyses will be conducted using one-sided tests at the α=0.05 level of significance, with no adjustments for multiplicity.

Safety and PK data will be summarized descriptively.

Table 1: Time and Events Schedule Part A

Procedure	Screening	Check-in/ Baseline[1]/ IP Administration	Discharge	Follow Up		
	Visit 1	Visit 2 [overnight stay]		Visit 3	Visit 4	Visit 5 /ET[2]
	Up to 14 days prior to start of Baseline	Day 1	Day 2	Day 8 (±2 days)	Day 15 (±2 days)	Day 29 (±2 days)
Informed consent (including privacy language/documents)	X					
Eligibility criteria	X	X				
Medical history[3]	X	X				
Concomitant medications	X	X	X	X	X	X
Vital sign measurements[4]	X	X	X	X	X	X
Height and weight measurements	X					X[5]
Pregnancy test[6]	X	X				X
Clinical laboratory tests[7]	X	X		X		X
Subject video[8]	X					
Tympanometry	X			X	X	X
Audiometry	X			X	X	X
Otoscopy	X	X		X	X	X
TFI	X	X		X	X	X
PGIC				X	X	X
C-SSRS assessment[9]	X	X		X	X	X
Randomization[10]		X				
Administer investigational product[11]		X				
Adverse event monitoring		X	X	X	X	X
Plasma PK Sampling[12]		X	X	X		

[1] Baseline assessments on Day 1 are to be performed before administration of investigational product. Results from the concomitant medications review, urine pregnancy test (for females of childbearing potential), and C-SSRS ("Since Last Visit" version) must be available and reviewed by the Investigator to confirm the subject's eligibility before randomization.

[2] End-of-study procedures will be performed at Visit 5 (Day 29 ± 2 days) or upon early termination (ET) from the study.

[3] Medical history to include information on demographics. Medical history also includes completion of the modified Tinnitus Sample Case History Questionnaire (TSCHQ) to capture tinnitus and related medical history information. Only changes in medical history since the Screening visit will be recorded at the Baseline (Day 1) visit.

[4] Vital signs measurements include systolic and diastolic blood pressure and pulse rate.

[5] Only weight is to be measured at Day 29.

[6] Female subjects of childbearing potential will have a serum pregnancy test at Screening, a urine pregnancy test at Baseline (prior to randomization), and a urine pregnancy test at Day 29. If the Screening or Baseline pregnancy test result is positive, the subject is not eligible for enrollment into the study. If a subject is found to be pregnant after dosing with investigational product, they will complete the 4-week Follow-Up period. Serum pregnancy test results from Screening as well as the urine pregnancy test at Baseline prior to randomization must be included in eligibility assessment.

[7] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis. Subjects will be randomized using laboratory results from Screening. Laboratory results from Baseline (Day 1) are not required for randomization.

[8] Subjects view a short educational video on clinical research participation entitled "What it Means to Take Part in Clinical Research Studies". Viewing of the video will be completed after informed consent but prior to any efficacy assessments (e.g. TFI) during the screening visit.

[9] Columbia-Suicide Severity Rating Scale: "Baseline" version will be used at the Screening visit and the "Since Last Visit" version will be used at all subsequent visits.

[10] Randomization must occur prior to administration of investigational product. The study site will execute each randomization after a subject has met all prerequisites for randomization.

[11] Investigational product (OTO-313 or placebo) is administered by intratympanic injection to the affected (study) ear.

[12] Plasma samples for PK analysis will be obtained pre-dose on Day 1 (any time prior to intratympanic injection), at 0.5, 1, 2, 4, 8, and 12 hours post-dose on Day 1 (±15 minutes at each post-dose timepoint on Day 1), 24 hours (± 1 hour) post-dose on Day 2, and on Day 8 (single sample obtained at any time during study visit on Day 8)

Table 2: Time and Events Schedule Part B

Procedure	Screening	Lead-In	Baseline[1]/ IP Administration	Follow Up			
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 /ET[2]
	Up to 14 days prior to start of Lead-In	Day -14 to Day -1 (+ 3 days)	Day 1	Day 8 (±2 days)	Day 15 (±2 days)	Day 29 (±2 days)	Day 57 (+3 days)
Informed consent (including privacy language/documents)	X						
Eligibility criteria	X		X				
Medical history[3]	X		X				
Concomitant medications	X		X	X	X	X	X
Vital sign measurements[4]	X		X	X	X	X	X
Height and weight measurements	X						X[5]
Pregnancy test[6]	X		X				X
Clinical laboratory tests[7]	X		X	X			X
Subject video[8]	X						
Tympanometry	X		X	X	X	X	X
Audiometry	X		X	X	X	X	X
Otoscopy	X		X	X	X	X	X
Daily NRS tinnitus electronic diary and compliance review[9]	X	X	X	X	X	X	X
TFI	X		X		X	X	X
PGIC				X	X	X	X
C-SSRS assessment[10]	X		X	X	X	X	X
Randomization[11]			X				
Administer investigational product[12]			X				
Adverse event monitoring			X	X	X	X	X
Plasma PK sampling[13]			X	X			

[1] Baseline assessments on Day 1 are to be performed before administration of investigational product. Results from the concomitant medications review, urine pregnancy test (for females of childbearing potential), and C-SSRS ("Since Last Visit" version) must be available and reviewed by the Investigator to confirm the subject's eligibility before randomization.

[2] End-of-study procedures will be performed at Visit 6 (Day 57 ± 2 days) or upon early termination (ET) from the study.

[3] Medical history to include information on demographics. Medical history also includes completion of the modified Tinnitus Sample Case History Questionnaire (TSCHQ) to capture tinnitus and related medical history information. Only changes in medical history since the Screening visit will be recorded at the Baseline (Day 1) visit.

[4] Vital signs measurements include systolic and diastolic blood pressure and pulse rate.

[5] Only weight is to be measured at Day 57.

[6] Female subjects of childbearing potential will have a serum pregnancy test at Screening, a urine pregnancy test at Baseline (prior to randomization), and a urine pregnancy test at Day 57. If the Screening or Baseline pregnancy test result is positive, the subject is not eligible for enrollment into the study. If a subject is found to be pregnant after dosing with investigational product, they will complete the 8-week Follow-Up period. All serum pregnancy tests will be analyzed by a central laboratory, while the urine pregnancy test is conducted locally. Serum pregnancy test results from Screening as well as the urine pregnancy test at Baseline prior to randomization must be included in eligibility assessment.

[7] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis and will be analyzed by a central laboratory. Subjects will be randomized using laboratory results from Screening. Laboratory results from the Baseline visit (Day 1) are not required for randomization.

[8] Subjects view a short educational video on clinical research participation entitled "What it Means to Take Part in Clinical Research Studies". Viewing of the video will be completed after informed consent but prior to any efficacy assessments (e.g. TFI) during the screening visit.

[9] Once the subject has met the inclusion/exclusion criteria at Screening, the subject will enter a 2-week lead-in assessment period. Subjects may be entered into the lead-in period before laboratory results from Screening are available. During this period, the subject will record their tinnitus annoyance and tinnitus loudness daily using the NRS electronic diary. Subjects must complete their tinnitus ratings for at least 4 of last 7 days of lead-in testing to be eligible for randomization. Reminder alerts to subjects and site staff will help to ensure compliance. After randomization, subjects will continue to record their daily tinnitus annoyance and tinnitus loudness for the 56-day follow-up period. Review of diary compliance will be conducted throughout the lead-in and follow-up periods and additional instructions and training will be provided to ensure compliance.

[10] Columbia-Suicide Severity Rating Scale "Baseline" version will be used at the Screening visit and the "Since Last Visit version" will be used at all subsequent visits.

[11] Randomization must occur prior to administration of investigational product. Study sites will execute each randomization after a subject has met all prerequisites for randomization.

[12] Investigational product (OTO-313 or placebo, respectively) is administered by intratympanic injection to the affected (study) ear.

[13] Plasma samples for PK analysis will be obtained in a subset of approximately 16 subjects at select sites on Day 1 (pre-dose any time prior to intratympanic injection and 1 hour ± 15 minutes post-administration) and on Day 8 (single sample obtained at any time during study visit on Day 8).

1. BACKGROUND

Tinnitus or "ringing in the ears", is defined as a perception of sounds without a correlated external auditory stimulus. Estimates indicate that approximately 10% of the US adult population, or 21.4 million people, suffer from tinnitus (Bhatt et al 2016). The prevalence of tinnitus increases with age, peaking between 60 to 69 years of age. Exposure to recreational, firearm, and occupational noise increases the odds of experiencing tinnitus (Shargorodsky et al 2010), and tinnitus is the leading service-related cause of disability among US military veterans (US Veterans Benefits Administration). Tinnitus is often a long-term condition. Based on a 2007 US National Health Interview survey, 56% of individuals with tinnitus had symptoms longer than 5 years and 36% had nearly constant symptoms (Bhatt et al 2016).

Tinnitus can be distressful, negatively impacting quality of life (Nondahl et al 2007) as affected patients report associated symptoms of insomnia, anxiety, depression, and cognitive difficulties (Schecklmann et al 2015; Zeman et al 2014; Bhatt et al 2017; Tegg-Quinn et al 2016). While some habituate to the sound, approximately 1 in 4 people with tinnitus believe it to be a moderate to severe problem and nearly half will seek medical treatment (Bhatt et al 2016). At present, however, there is no cure or approved medication. Current management of tinnitus largely focuses on modulation of the patient's attention and responses to the sensation. Approaches include education and counseling, sound therapy, use of hearing aids, and cognitive behavioral therapy (Tunkel et al 2014).

Causes and conditions associated with tinnitus include sensorineural hearing loss, acute hearing loss from noise trauma, barotrauma, or traumatic cochlear injury (acute acoustic trauma, blast trauma, middle ear surgery, inner ear barotrauma), age-related hearing loss, Meniere's disease, otitis media, ototoxic drug use, and head and neck injuries (Langguth et al 2013). In many cases, tinnitus arises as a consequence of cochlear insults and therefore one pharmacotherapy approach to the treatment of tinnitus is directed at normalizing altered neural activity within the cochlea. Excessive activation of NMDA receptors at the level of the inner hair cell synapses with subsequent deafferentation may be a key mechanism of abnormal sensory signaling in tinnitus (Bing et al. 2015).

A number of systemically administered agents have been tested in clinical studies in tinnitus, aimed at influencing the putative imbalance in auditory firing rates produced by cochlear insults (Savage and Waddell 2013; Hoare et al 2011). However, efficacy of systemic pharmacotherapies and other interventions for tinnitus has yet to be proven. Intratympanic delivery of drugs permits deposition of drugs over the round window membrane. This enables access to the inner ear for more localized delivery to the cochlea and less systemic drug exposure (Bird et al. 2007). Esketamine (AM-101), a noncompetitive NMDA-receptor antagonist, has been administered as 3 separate intratympanic injections over a period of a few days. In a Phase 2 study, esketamine reduced tinnitus severity among some subjects (van de Heyning et al. 2014), although efficacy was not demonstrated in two Phase 3 studies (unpublished results).

1.1. Rationale

Gacyclidine, the active agent in OTO-313, is a noncompetitive NMDA-receptor antagonist that is considered to have greater potency, faster on-rate, and slower off-receptor rate than other

NMDA-receptor antagonists, including esketamine (Mitha and Maynard 2001; Piu et al 2018). Gacyclidine was originally formulated as OTO-311, a solution of gacyclidine in a liquid thermoreversible hydrogel polymer, to provide sustained exposure of gacyclidine to cochlear tissues following a single intratympanic administration. Additional preclinical studies showed that gacyclidine formulated in a lipid-based, medium-chain triglycerides solution (OTO-313) provided greater and longer lasting inner ear exposures of gacyclidine compared to OTO-311 and esketamine when injected intratympanically.

The pharmacology, safety, and toxicity of gacyclidine, OTO-311, and OTO-313 have been evaluated preclinically and provide sufficient rationale for advancing OTO-313 into clinical testing. Gacyclidine was originally studied using intravenous administration in clinical studies in spinal cord and brain trauma patients and no concerning safety issues were identified. Gacyclidine has also been administered to the otic compartment in an open label case-series in patients with chronic tinnitus. The drug was generally safe and well-tolerated and reduced subjective tinnitus ratings in 4 of the 6 subjects evaluated (Wenzel, et al. 2010). In a recently completed Phase 1 study in healthy subjects (Study 311-201501), OTO-311, placebo or sham was administered as a single intratympanic injection. All OTO-311 dose levels tested (0.15 mg, 0.3 mg, and 0.6 mg) were well-tolerated and no safety concerns were identified. The preclinical and clinical data obtained to date are described in more detail in the Investigator's Brochure.

The current study (313-201901) is the first clinical study of intratympanic OTO-313 in subjects with tinnitus and is composed of 2 parts. Part A is a randomized, double-blind, placebo-controlled cohort to evaluate the safety, tolerability, and plasma pharmacokinetics (PK) of 0.11 mg OTO-313, following intratympanic administration, in subjects with subjective unilateral or bilateral tinnitus. If acceptable safety and tolerability is observed for 8 days in Part A, as determined by the Safety Review Committee, Part B will be initiated. Part B is a randomized, double-blind, placebo-controlled study to investigate the safety, plasma PK, and preliminary efficacy of 0.32 mg OTO-313 in subjects with subjective unilateral tinnitus. If acceptable safety and tolerability is observed for 8 days in the first 12 subjects in Part B, as determined by the Safety Review Committee, the remaining subjects in Part B will be enrolled. The 0.11 mg and 0.32 mg doses of OTO-313 to be tested in this study are expected to be safe and well-tolerated based on preclinical studies and on the clinical Study 311-201501 conducted with OTO-311 in healthy subjects. Preclinical data suggest that the two dose levels of OTO-313 will produce sufficient inner ear exposures of gacyclidine in humans. In addition, the lipid formulation of OTO-313 is expected to maintain sustained exposures to the cochlea over time (at least 7 to 14 days in preclinical testing). Taken together, the preclinical and clinical data support the evaluation of the two dose levels of OTO-313 in this Phase 1/2 study in subjects with tinnitus.

2. OBJECTIVES

2.1. Part A

2.1.1. Primary Objective

- To evaluate the safety and tolerability of OTO-313 in subjects with unilateral or bilateral tinnitus.

2.1.2. Secondary Objective

- To assess the plasma PK of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites).

2.2. Part B

2.2.1. Primary objective

- To evaluate the safety and tolerability of OTO-313 in subjects with unilateral tinnitus.

2.2.2. Secondary Objectives

- To examine the preliminary efficacy of OTO-313 in subjects with unilateral tinnitus, as measured by the change from Baseline in the Tinnitus Functional Index (TFI).
- To assess the plasma PK of gacyclidine including (+) and (-) enantiomers of gacyclidine (and possibly its metabolites).

2.2.3. Exploratory Objectives

- To evaluate the exploratory efficacy of OTO-313 on tinnitus annoyance using subject-reported Numeric Rating Scales (NRS).
- To evaluate the exploratory efficacy of OTO-313 on tinnitus loudness using subject-reported NRS.
- To determine the exploratory efficacy of OTO-313 on the Patient Global Impression of Change (PGIC) with respect to tinnitus severity.

3. OVERVIEW OF STUDY DESIGN

3.1. Part A

Part A will be conducted at 1 site in the United States and will involve 1 overnight stay in the research unit. The duration of Part A for each of the 8 subjects will be approximately 4-6 weeks, including an up to 2-week Screening period and a 4-week follow-up period.

After informed consent and Screening, eligible subjects will be randomized to OTO-313 or placebo at the Baseline visit (Day 1). Eight subjects will receive either 0.11 mg OTO-313 (N=6) or placebo (N=2). Plasma samples for PK analysis will be obtained on Day 1 (pre-dose, 0.5, 1, 2, 4, 8, and 12 hours post-administration), Day 2 (24 hours post-administration), and Day 8. Subjects will remain overnight in the research unit on Day 1 and will be discharged on Day 2. Additional follow-up visits for safety and efficacy assessments will be conducted on Day 8, Day 15, and Day 29 (end of study) or upon early termination from the study.

If acceptable safety and tolerability is observed for 8 days post-administration in Part A, Part B will be initiated with the 0.32 mg dose level of OTO-313 (see Safety Data Review in Section 14.6.1).

3.2. Part B

Part B will be conducted at approximately 20 sites in the United States. The duration of Part B for each subject will be approximately 10-12 weeks, including an up to 2-week Screening period, a 2-week Lead-In assessment period, and an 8-week Follow-Up period. If acceptable safety and tolerability is observed for 8 days for the first 12 subjects dosed (see Safety Data Review in Section 14.6.1), the remaining subjects in Part B will be enrolled. In the event that adverse safety findings occur with 0.32 mg OTO-313 in the first 12 subjects, Part B subjects may be enrolled using 0.11 mg OTO-313, and enrollment expanded so that 50 subjects are randomized to this (lower) dose level or placebo to reach the target number of subjects for Part B.

After informed consent and Screening, potential subjects will begin a 2-week Lead-in assessment period. During this time, subjects will enter daily tinnitus annoyance and tinnitus loudness into an electronic diary using a Numeric Rating Scale (NRS). Subjects must have completed the tinnitus electronic diary on 4 of the last 7 days of the Lead-in period for eligibility. Subjects will also complete the Tinnitus Functional Index (TFI) at both the Screening visit and the Baseline visit (Day 1). Subjects must have a score of ≥ 25 at each TFI assessment for eligibility. At the Baseline visit (Day 1), eligible subjects will be randomized to OTO-313 or placebo using a 1:1 allocation ratio.

After a single intratympanic injection with OTO-313 or placebo to the affected (study) ear on Day 1, subjects will continue to record their tinnitus annoyance and tinnitus loudness on a daily basis using the electronic diary during the 8-week follow-up period. Subjects will complete the TFI at study visits on Day 1 (Baseline), Day 15, Day 29, and Day 57 (end of study). Additional safety and/or exploratory assessments will also be completed at Day 1 (Baseline), Day 8, Day 15, Day 29, and Day 57 (end of study) or upon early termination from the study. In a subset of approximately 16 subjects in Part B, blood samples for PK analysis will be obtained on Day 1 (pre-dose and 1-hour post-administration) and on Day 8.

Figure 1. Study Design Schematic – Part A

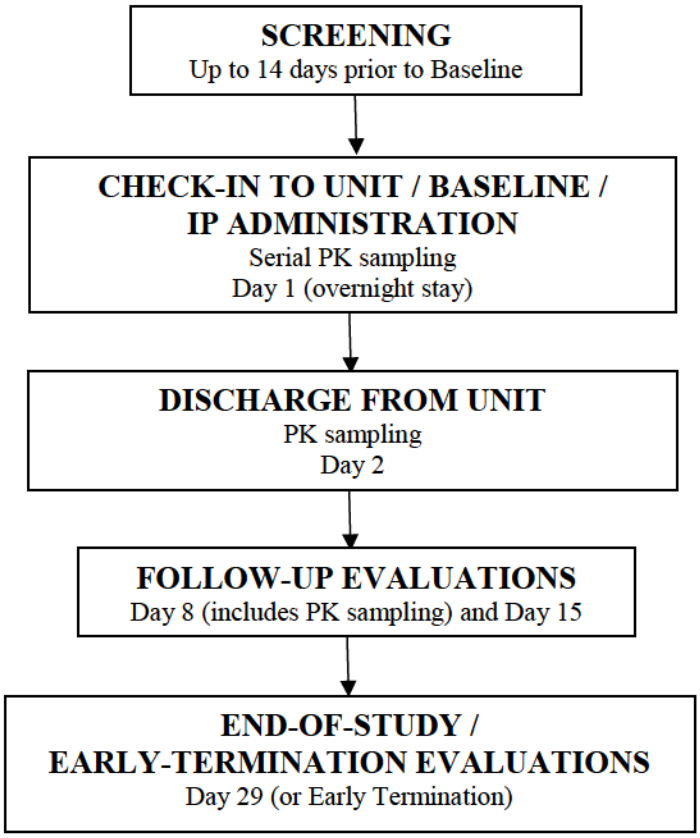
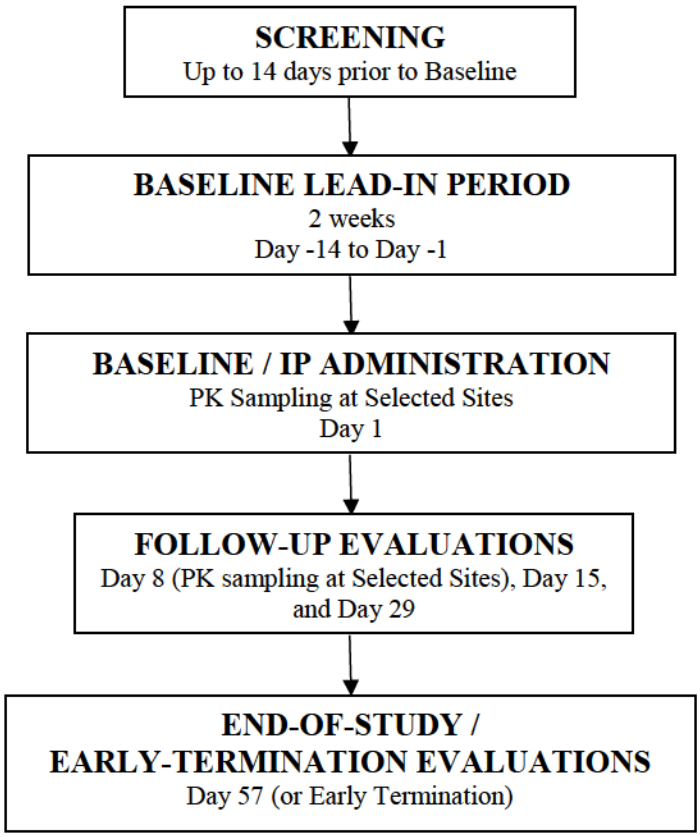


Figure 2. Study Design Schematic – Part B



4. STUDY POPULATION

4.1. General Considerations

Approximately 58 to 70 subjects (8 subjects in Part A and 50 to 62 subjects in Part B) will be enrolled at approximately 20 study sites in the United States. Subjects will be eligible if they meet all of the following inclusion criteria and none of the exclusion criteria.

4.2. Inclusion Criteria

To be eligible for this study, each of the following criteria must be satisfied with a "YES" answer (unless not applicable):

Part A only

1. Subject has subjective unilateral or bilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.

Part B only

2. Subject has subjective unilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.
3. Subject's self-reported duration of tinnitus is between 1 month and 6 months (30 to 180 days) prior to signing informed consent.

4. Subject has an overall score of ≥ 25 on the TFI at Screening and Baseline (Day 1) visits.
5. Subject is able to use the electronic diary to complete their daily tinnitus ratings and has completed at least 4 of the last 7 days of diary entries during the 2-week Lead-in period.

Part A and B

6. Subject is a male or female aged 18 to 75 years, inclusive.
7. Subject's tinnitus is likely of cochlear origin, e.g., associated with sensorineural hearing loss; acute hearing loss from noise trauma, barotrauma, or traumatic cochlear injury (acute acoustic trauma, blast trauma, middle ear surgery, inner ear barotrauma); age-related hearing loss; resolved otitis media; ototoxic drug exposure.
8. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal (≥12 months since last menstrual period and 45 years of age or older)] must have a negative urine pregnancy test at Baseline (Day 1). Women of childbearing potential who are not abstinent from sex with male partners must use effective methods of contraception for the duration of the study including: established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; or "double barrier" methods including a combination of male condom with either diaphragm or cervical cap with spermicide. Female subjects of childbearing potential must also refrain from egg donation or retrieval for the duration of the study.
9. Male subjects (unless surgically sterile) who are not abstinent from sex with female partners of childbearing potential must agree to use an effective contraceptive method (as detailed for Inclusion Criteria 8) for the duration of the study. Male subjects must refrain from sperm donation for the duration of the study.
10. Subject is willing to comply with the protocol and attend all study visits.
11. Subject is able to provide written informed consent after the scope and nature of the investigation have been explained, and before the initiation of any study-related procedures.

4.3. Exclusion Criteria

To be eligible for this study, each of the following criteria must be satisfied with a "NO" answer: (unless not applicable):

Part A and B

1. Subject has pulsatile tinnitus, tinnitus resulting from traumatic head or neck injury, or tinnitus resulting from a tumor or stroke.
2. Subject has active middle ear disease (including but not limited to: chronic otitis media, acute otitis media, middle ear effusions, middle ear atelectasis, or cholesteatoma), Meniere's disease as outlined by the American Academy of Otolaryngology-Head and Neck Surgery Equilibrium Committee in 2015 (Goebel 2016), or vestibular schwannoma.
3. Subject has recently (< 1 month of Screening) initiated new treatment for tinnitus (e.g. noise or sound generators, hearing aids, behavioral therapy; medications or over-the-counter supplements); only stable tinnitus treatments are allowed during the study and no new treatments should be introduced.

4. Subject is not able to accurately identify and report their tinnitus per Investigator's opinion.
5. Subject has an abnormality of the tympanic membrane in the affected (study) ear that would increase the risk associated with intratympanic injection, including but not limited to monomeric tympanic membrane.
6. Subject has evidence of perforation or lack of closure of the tympanic membrane at Screening or Baseline (Day 1) visits.
7. Subject is receiving any ongoing therapy known as potentially tinnitus-inducing (e.g. aminoglycosides, ototoxic chemotherapeutic drugs, loop diuretics, quinine, high doses of aspirin or other nonsteroidal anti-inflammatory drugs). Usage of low doses of aspirin or other non-steroidal anti-inflammatory drugs may be permitted at the Investigator's discretion.
8. Subject answered "Yes" to Question 4 or 5 regarding active suicidal ideation on the C-SSRS administered at Screening or Baseline (Day 1) visits. In addition, subjects deemed by the Investigator to be at significant risk of suicidal behavior should be excluded.
9. Subject has severe or untreated depression or anxiety that, in the Investigator's opinion, would likely reduce the safety of study participation or compliance with study procedures. Only stable doses (taken for $\geq$ 1 month prior to Screening) of antidepressant and anti-anxiety medications are allowed during the study.
10. Subject is pregnant or lactating.
11. Subject has a history of immunodeficiency disease.
12. Subject has a history of substance or alcohol abuse within the preceding 6 months prior to Screening.
13. Subject is receiving concomitant treatment with any other NMDA receptor antagonist (e.g. memantine, dextromethorphan).
14. Subject has a history of previous use of intratympanic gentamicin in the affected ear.
15. Subject has received systemic or intratympanic steroids (including dexamethasone) within 6 weeks prior to the Screening visit.
16. Subject has a known hypersensitivity to gacyclidine or any of the excipients in OTO-313.
17. Subject has used moderate or strong inducers of CYP2B6 (e.g. carbamazepine, efavirenz, rifampin, or ritonavir) within 30 days prior to Screening.
18. Subject has other clinically significant illness, medical condition or medical history at Screening or Baseline (Day 1) that, in the Investigator's opinion, would likely reduce the safety of study participation or compliance with study procedures.

5. RANDOMIZATION AND BLINDING

5.1. Overview

In Part A, 8 enrolled subjects will be assigned randomly to 0.11 mg OTO-313 or placebo using a 6:2 allocation ratio, based on a computer-generated randomization schedule.

- 0.11 mg OTO-313; single (0.2 mL volume) intratympanic injection to the affected (study) ear
- Placebo (vehicle); single (0.2 mL volume) intratympanic injection to the affected (study) ear

In Part B, 50 enrolled subjects will be assigned randomly to 0.32 mg OTO-313 (or 0.11 mg OTO-313 after Safety Data Review; see Section 14.6.1) or placebo using a 1:1 allocation ratio, based on a computer-generated randomization schedule.

- 0.32 mg OTO-313; single (0.2 mL volume) intratympanic injection to a single, affected (study) ear
- Placebo (vehicle); single (0.2 mL volume) intratympanic injection to a single, affected (study) ear

In the event that adverse safety findings occur with 0.32 mg OTO-313 in the first 12 subjects, Part B subjects may be enrolled using 0.11 mg OTO-313, and enrollment expanded so that 50 subjects are randomized to this (lower) dose level or placebo to reach the target number of subjects for Part B.

A subset of approximately 16 subjects will undergo PK testing at select study sites in Part B.

5.2. Enrollment Procedures

5.2.1. Assignment of Subject Identification Numbers

At the Screening visit (Visit 1), subjects signing the informed consent will be assigned a sequential subject identification number by the site. Once assigned, the subject identification number will not be re-assigned and should not be changed. This number will be used to identify the subject throughout the study, including the Screening and Lead-in periods. Subjects will be considered enrolled into the study once they are randomized.

5.2.2. Treatment Assignment

After a subject has met all prerequisites for randomization on Day 1 (Baseline/Visit 2), study sites will execute each randomization via the interactive web randomization system (WebEZ). Study site personnel, who are blinded to treatment assignment, will receive a randomization notification indicating the kit number (packaged investigational product), and the date and time of randomization for each subject. Once assigned, kit numbers cannot be re-assigned. Subjects will be considered enrolled into the study once they are randomized.

Study sites will provide the information contained in the WebEZ randomization notification to the person responsible for preparation of the syringe containing investigational product (OTO-313 or placebo). The unique kit number provided by WebEZ will correspond to a kit of

packaged investigational product labeled with the identical kit number. The syringe will be prepared from the contents of the investigational product package corresponding to the WebEZ kit number according to the instructions in the study Pharmacy Manual. The subject identification number and kit number both must be recorded in the subject's record.

5.2.3. Randomization Algorithm

In Part A, subjects will be randomized in a 6:2 ratio (OTO-313:placebo) of treatment groups using a permuted block randomization algorithm. In Part B, subjects will be randomized in a 1:1 ratio (OTO-313:placebo) of treatment groups using a permuted block randomization algorithm.

The randomization process will be deployed via WebEZ which is accessible 24 hours a day to authorized users. The subject's randomization number will determine the randomized treatment assignment. Investigational product kits will be labeled with a unique kit number using a separate and independent randomization algorithm. Numbered kits will be dispensed based on the treatment assignment.

5.3. Blinding

The study will be double-blinded. Each treatment syringe will be prepared according to the detailed instructions in the Pharmacy Manual.

The blind should be broken for site personnel only if knowing the subject's treatment allocation would facilitate specific medical treatment. In all cases, the Investigator should consult with the medical monitor prior to unblinding, if possible, and must contact the medical monitor as soon as it is practical after unblinding has occurred and treatment initiated.

If the blind is broken, the subject will continue to be followed and evaluated per-protocol. The date, time, and reason for the unblinding must be documented on the appropriate page of the eCRF.

The randomization schedule or blocking factor(s) will not be revealed to study subjects, Investigators, clinical staff, site managers or the Sponsor until all subjects have completed the study and the database has been finalized by the Sponsor.

6. DOSAGE AND ADMINISTRATION

6.1. Investigational Product Administration

OTO-313 or placebo is provided in individual Investigational Product kits. All kits must be stored at 2-8°C until use.

Syringes containing OTO-313 or placebo are prepared in a clean location at room temperature. Refer to the Pharmacy Manual for instructions on OTO-313 and placebo preparation instructions.

OTO-313 or placebo will be administered as a single (0.2 mL volume) intratympanic injection to an affected (study) ear. Only a physician may perform the intratympanic injection.

OTO-313 or placebo should be prepared with a 1 mL luer-lock sterile syringe only. Luer slip tip syringes are not acceptable for use due to the viscosity of OTO-313. Needles can be 25, 26, or 27 gauge and typically range from 1.5 to 3.5 inches in length.

The recommended injection procedure for intratympanic administration of OTO-313 or placebo in subjects is as follows. A ventilation hole in the tympanic membrane is not needed due to the small injection volume.

1. Place the subject in a recumbent position with the affected (study) ear upwards.
2. Prior to OTO-313 or placebo administration, confirm the ear to be treated is the affected (study) ear.
3. Anesthetize the tympanic membrane by covering the external surface of the inferior-posterior quadrant with topical lidocaine or lidocaine/prilocaine cream [redacted]) until the tympanic membrane is numb. If applicable, suction away the topical lidocaine or lidocaine/prilocaine cream. Phenol should not be used to anesthetize the tympanic membrane.
4. Using the prepared syringe, insert the needle into the inferior-posterior quadrant of the tympanic membrane at the level of the round window, taking care not to insert the needle further than necessary.
5. With the needle bevel facing in the inferior-posterior direction, inject 0.2 mL of OTO-313 or placebo towards the round window.
6. Have the subject remain recumbent for 15 minutes following the injection.

6.2. Compliance

OTO-313 or placebo will be administered by a physician as a single, intratympanic injection at Day 1. Any deviations in administration will be documented in the source documents and the eCRF.

The site will maintain a log of all investigational product dispensed and returned. Investigational product supplies for each subject will be inventoried and accounted for in the study.

7. PRIOR, CONCOMITANT AND SUBSEQUENT THERAPY

Use of all concomitant medications will be recorded in the subject's eCRF. This will include all symptomatic relief medications for tinnitus symptoms, prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 30 days before randomization, which will be considered prior therapy. Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the Investigator except for those medications listed in Section 7.1. Any changes in concomitant medications will be recorded in the subject's eCRF.

7.1. Prohibited Therapy During the Study Period

The following therapies are prohibited during the study:

- Phenol for use in anesthetizing the tympanic membrane.

- Intratympanic injection other than that outlined in the current study.
- Systemic corticosteroids
- Other investigational drug(s) or device(s).
- Other NMDA receptor antagonists (e.g. memantine, dextromethorphan).
- Medications known as potentially tinnitus-inducing (e.g. aminoglycosides, ototoxic chemotherapeutic drugs, loop diuretics, quinine, high doses of aspirin or other non-steroidal anti-inflammatory drugs). Usage of low doses of aspirin or other non-steroidal anti-inflammatory drugs may be permitted at the Investigator's discretion.
- Medications that are considered moderate or strong inducers of CYP2B6 (e.g. carbamazepine, efavirenz, rifampin, and ritonavir).

Use of any of these prohibited therapies will be considered a protocol deviation.

7.2. Symptomatic Relief Medications and Therapies

It is recognized that subjects may at times use certain medications for relief of symptoms related to tinnitus during the study. Stable doses (taken for ≥ 1 month prior to Screening) of antidepressant and anti-anxiety medications are allowed during the study. Stable prior use (≥ 1 month prior to Screening) of over-the-counter supplements or medications for tinnitus (e.g. Gingko biloba, melatonin) may also be used. No new medications or over-the-counter supplements for tinnitus may be introduced during the study. Any changes reported by the subjects in concomitant medications should be recorded in the subject's eCRF.

Stable prior use (≥ 1 month prior to Screening) of hearing aids, noise generators, and/or sound therapy devices is allowed and, if utilized, these devices should be used consistently throughout the duration of study. Similarly, any behavioral therapy for tinnitus should also be stable (≥ 1 month prior to Screening) and continue throughout the duration of the study. No new hearing aids, sound/noise therapy devices, or behavioral therapy for tinnitus may be introduced during the study.

8. STUDY EVALUATIONS

8.1. Study Procedures by Visit – Part A

8.1.1. Screening Period: Up to 14 days prior to Baseline – Part A

The following assessments, as listed in the Time and Events Schedule for Part A (Table 1), will be performed during the screening period: informed consent, review and confirm eligibility criteria, medical history, demographics, concomitant medications, vital signs, height and weight measurements, serum pregnancy test (for female subjects of childbearing potential only), clinical laboratory tests, tympanometry, audiometry, otoscopy, TFI assessment, and C-SSRS assessment: Baseline version. The modified Tinnitus Sample Case History Questionnaire (TSCHQ) will be completed at Screening as part of medical history to capture tinnitus-specific medical history. Each subject will also view a short educational video on clinical research participation entitled

"What It Means to Take Part in Clinical Studies". Viewing of the video will be completed after informed consent but prior to any efficacy assessments (e.g. TFI) at the screening visit.

8.1.2. Check-in to Research Unit/Baseline/Investigational Product Administration: Day 1 – Part A

Once a subject has signed consent, completed the Screening assessments, and met all study eligibility criteria, the subject will check into the Research Unit for an overnight stay. Results from the concomitant medications review, urine pregnancy test (for female subjects of childbearing potential), and C-SSRS ("Since Last Visit" version) must be available and reviewed by the Investigator to confirm the subject's eligibility before randomization. In addition, the following assessments are to be performed on all subjects prior to dosing to establish Baseline status: medical history, vital signs, clinical laboratory tests, otoscopy, TFI, and pre-dose PK sample.

If the subject is no longer eligible, the subject will not be randomized and should be recorded as a screen failure. Information related to specific inclusion/exclusion criteria will be documented. Once eligibility status is confirmed and the subject is randomized, the investigational product is administered and the remaining Day 1 assessments (e.g. PK sampling at 0.5, 1, 2, 4, 8, and 12 hours [± 15 minutes at each timepoint] post-dose, AE monitoring) are completed.

All assessments as listed in the Time and Events Schedule for Part A (Table 1) are to be performed at this visit.

8.1.3. Discharge from Research Unit: Day 2 – Part A

Prior to discharge from the research unit on Day 2, the following assessments are to be performed: concomitant medications, vital signs, AE collection, and the plasma PK sample at 24 hours.

All assessments as listed in the Time and Events Schedule for Part A (Table 1) are to be performed at this visit.

8.1.4. Day 8 (± 2 days): Follow Up and Safety Review – Part A

The primary purpose of Day 8 visit is to capture safety and PK data. Safety assessments include concomitant medications, vital signs, clinical laboratory tests, tympanometry, audiometry, otoscopy, C-SSRS, and AE collection. A final PK sample will be obtained at this visit (at any time during the visit). Exploratory efficacy assessments include the TFI and PGIC.

All Day 8 safety, efficacy, and PK assessments as listed in the Time and Events Schedule for Part A (Table 1) are to be performed.

8.1.5. Day 15 (± 2 days): Follow Up – Part A

The primary purpose of Day 15 visit is to capture safety data. Safety assessments include concomitant medications, vital signs, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. Exploratory efficacy assessments include the TFI and PGIC.

All Day 15 safety and efficacy assessments as listed in the Time and Events Schedule for Part A (Table 1) are to be performed.

8.1.6. Day 29 (± 2 days): End of Study/ Early Termination – Part A

The primary purpose of Day 29 visit is to capture final safety data for Part A. Safety assessments include concomitant medications, weight, vital signs, urine pregnancy test for women of childbearing potential, clinical laboratory tests, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. Exploratory efficacy assessments include the TFI and PGIC.

All Day 29 safety and efficacy assessments as listed in the Time and Events Schedule for Part A (Table 1) are to be performed.

If a subject terminates from the study prior to Day 29 (Early-Termination), every attempt should be made to perform all assessments as listed for Day 29.

8.2. Study Procedures by Visit – Part B

8.2.1. Screening Period: Up to 14 days prior to Baseline – Part B

The following assessments, as listed in the Time and Events Schedule for Part B (Table 2), will be performed during the screening period: informed consent, review and confirm eligibility criteria, medical history, demographics, concomitant medications, vital signs, height and weight measurements, serum pregnancy test (for female subjects of childbearing potential only), clinical laboratory tests, tympanometry, audiometry, otoscopy, TFI assessment, C-SSRS assessment: "Baseline" version, and review of daily NRS electronic diary instructions with the subject. The modified Tinnitus Sample Case History Questionnaire (TSCHQ) will also be completed at Screening as part of medical history to capture tinnitus-specific medical history. Each subject will also view a short educational video on clinical research participation entitled "What It Means to Take Part in Clinical Studies". Viewing of the video will be completed after informed consent but prior to any efficacy assessments (e.g. TFI) at the screening visit.

8.2.2. Lead-In Period: Day -14 to Day -1 (+ 3 days) – Part B

The subject will record their tinnitus loudness and tinnitus annoyance daily, using the NRS for each symptom, in an electronic diary during the 14-day Lead-In assessment period.

8.2.3. Baseline/Investigational Product Administration: Day 1 – Part B

Once a subject has signed consent, completed the Screening assessments, met all study eligibility criteria, and completed the Lead-In period, the Day 1 baseline assessments and investigational product administration are performed. Results from the concomitant medications review, urine pregnancy test (for female subjects of childbearing potential), and C-SSRS ("Since Last Visit" version) must be available and reviewed by the Investigator to confirm the subject's eligibility before randomization. In addition, the following assessments are to be performed on all subjects prior to dosing to establish Baseline status: medical history, vital signs, clinical laboratory tests, tympanometry, audiometry, otoscopy, and TFI. For subjects undergoing Part B PK evaluations, a pre-dose plasma PK sample will be obtained on Day 1 at any time prior to investigational product administration.

If the subject is no longer eligible, the subject will not be randomized and should be recorded as a screen failure. Information related to specific inclusion/exclusion criteria will be documented. Once eligibility status is confirmed and the subject is randomized, the investigational product is

administered and the remaining Day 1 assessments (e.g. PK sampling at 1 hours [± 15 minutes] in select subjects, AE monitoring) are completed.

All assessments as listed in the Time and Events Schedule for Part B (Table 2) are to be performed at this visit.

8.2.4. Day 8 (± 2 days): Follow Up and Safety Review – Part B

The primary purpose of Day 8 visit is to capture safety, PK, and preliminary efficacy data. Safety assessments include concomitant medications, vital signs, clinical laboratory tests, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. A final PK sample will be obtained at this visit (at any time during the visit). Efficacy assessment includes the PGIC. Compliance for completing the daily NRS electronic diary will be reviewed with the subject.

All Day 8 safety, efficacy, and PK assessments as listed in the Time and Events Schedule for Part B (Table 2) are to be performed.

8.2.5. Day 15 (± 2 days): Follow Up – Part B

The primary purpose of Day 15 visit is to capture safety and preliminary efficacy data. Safety assessments include concomitant medications, vital signs, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. Efficacy assessments include the TFI and PGIC. Compliance for completing the daily NRS electronic diary will be reviewed with the subject.

All Day 15 safety and efficacy assessments as listed in the Time and Events Schedule for Part B (Table 2) are to be performed.

8.2.6. Day 29 (± 2 days): Follow Up – Part B

The primary purpose of Day 29 visit is to capture safety and preliminary efficacy data. Safety assessments include concomitant medications, vital signs, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. Efficacy assessments include the TFI and PGIC. Compliance for completing the daily NRS electronic diary will be reviewed with the subject.

All Day 15 safety and efficacy assessments as listed in the Time and Events Schedule for Part B (Table 2) are to be performed.

8.2.7. Day 57 (+ 3 days): End-of-Study/Early Termination – Part B

The primary purpose of Day 57 visit is to capture final safety and preliminary efficacy data. Safety assessments include concomitant medications, weight, vital signs, urine pregnancy test for women of childbearing potential, clinical laboratory tests, tympanometry, audiometry, otoscopy, C-SSRS, and AE monitoring. Efficacy assessments include the TFI and PGIC.

All Day 57 safety and exploratory efficacy assessments as listed in the Time and Events Schedule for Part B (Table 2) are to be performed.

If a subject terminates from the study prior to Day 57 (Early-Termination), every attempt should be made to perform all assessments as listed for Day 57.

8.2.8. Unscheduled Visit

Unscheduled Visits may occur in the event of safety-related issues. Appropriate safety assessments (e.g. otoscopy, vital signs, clinical laboratory tests) may be conducted at the Investigator's discretion at Unscheduled Visits.

8.3. Medical History and Demographics

The medical history will be obtained from medical records and/or via subject interview at the Screening visit, and includes general medical history, medication history, and reproductive history. Tinnitus-specific medical history information is also obtained by having potential subjects complete the modified TSCHQ at Screening.

Demographic information will also be obtained at the Screening visit and will include: age; sex; race; height, without shoes (cm); body weight, without shoes (kg); and highest level of education completed.

8.4. Video for Subjects on Clinical Research Participation

Subjects will view an educational video on clinical research participation entitled "What It Means to Take Part in Clinical Studies". This 7-minute video provides general information, in lay terms, on the purpose of blinded, controlled clinical research studies and the roles and responsibilities of a subject in a clinical research study. Viewing of the video will be completed after informed consent but prior to any efficacy assessments (e.g. TFI) at the screening visit.

8.5. Efficacy Evaluations

Efficacy assessments include:

- Tinnitus Functional Index (TFI)
- Daily Tinnitus Annoyance NRS
- Daily Tinnitus Loudness NRS
- Patient Global Impression of Change (PGIC)

Subjects who use hearing aids, noise generators, and/or sound therapy devices should continue to do so during the study and should complete the tinnitus assessments and ratings (i.e. TFI, daily tinnitus annoyance NRS, daily tinnitus loudness NRS, and PGIC) based on their tinnitus experience with the devices in use.

The recommended order in which study questionnaire assessments are conducted is: TFI, PGIC, and C-SSRS.

8.5.1. Tinnitus Functional Index (TFI)

The TFI is a validated, 25-item questionnaire that can be used to scale overall severity of tinnitus and to assess treatment-related change in tinnitus (Meikle et al., 2012; Henry et al., 2015). The 25 items of the TFI represent 8 subscales covering multiple domains of tinnitus severity: 1) Intrusive, 2) Sense of Control, 3) Cognitive, 4) Sleep, 5) Auditory, 6) Relaxation, 7) Quality of Life, and 8) Emotional. Subjects answer each TFI question by rating their experience over the past week.

Completing the TFI provides an index score from 0 to 100, with higher scores representing a greater problem with tinnitus. A reduction in the TFI index score of 13 points or more is considered clinically meaningful improvement in tinnitus (Meikle et al., 2012).

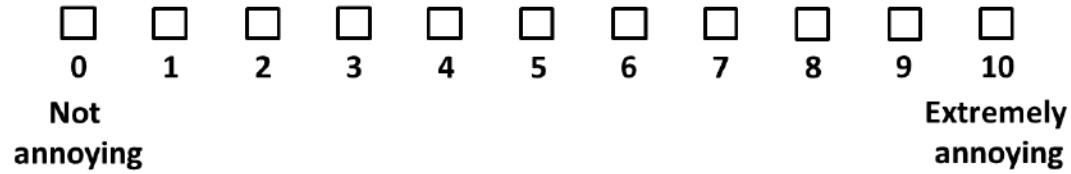
In Part A, subjects will complete the TFI at Screening, Day 1 (pre-dose), and Days 8, 15, and 29.

In Part B, subjects will complete the TFI at Screening, Day 1 (pre-dose), and Days 15, 29, and 57.

8.5.2. Daily Tinnitus Annoyance NRS

In Part B, subjects will record their daily tinnitus annoyance using a tinnitus NRS electronic diary. Numeric rating scales have been widely used to assess tinnitus severity and have demonstrated good test-retest reliability and concordance with other subjective measures of tinnitus (Meikle et al. 2008). Subjects rate their tinnitus annoyance over the past 24 hours. Subjects respond to the following question by checking the box on the NRS scale corresponding to their degree of tinnitus annoyance on a scale of 0 (Not annoying) to 10 (Extremely annoying):

In the past 24 hours, how annoying was your tinnitus?



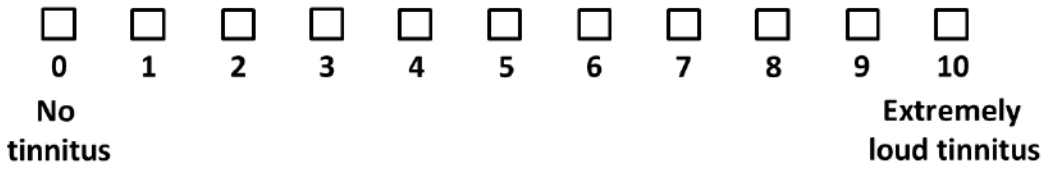
Subjects eligible at screening in Part B will begin using the tinnitus NRS diary at the start of the Lead-in period to record daily tinnitus annoyance and will continue to record their tinnitus annoyance once per day through the 56-day Follow Up period. Subjects will be able to record missed diary entries for 1 day after a missed entry. Compliance with the tinnitus NRS diary will be monitored throughout the study with re-training as necessary.

8.5.3. Daily Tinnitus Loudness NRS

In Part B, subjects will record their daily tinnitus loudness using a tinnitus NRS electronic diary.

Subjects rate their tinnitus loudness over the past 24 hours. Subjects respond to the following question by checking the box on the NRS scale corresponding to the degree of tinnitus loudness on a scale of 0 (No tinnitus) to 10 (Extremely loud tinnitus):

In the past 24 hours, how would you rate the loudness of your tinnitus at its worst?



Subjects in Part B will begin using the tinnitus NRS diary at the start of the Lead-in period to record daily tinnitus loudness and will continue to record their tinnitus loudness once per day through the 56-day Follow Up period. Subjects will be able to record missed diary entries for 1 day after a missed entry. Compliance with the tinnitus NRS diary will be monitored throughout the study with re-training as necessary.

8.5.4. Patient Global Impression of Change (PGIC)

The PGIC is a patient-reported outcome that evaluates the change in overall "global" tinnitus status as perceived by the subject (Adamchic et al. 2012; van de Heyning et al. 2014). The subject is asked: "Since the beginning of the clinical study, how would you rate your tinnitus?". The beginning of the clinical study in this context is the time prior to investigational product administration. The 7 response categories (and point scores) for the PGIC are:

- Very much improved = 3
- Much improved = 2
- Minimally improved = 1
- Unchanged = 0
- Minimally worse = -1
- Much worse = -2
- Very much worse = -3

In Part A, subjects will complete the PGIC at Days 8, 15, and 29.

In Part B, subjects will complete the PGIC at Days 8, 15, 29, and 57.

8.6. Blood Sampling for Plasma PK Evaluations

Blood samples for plasma gacyclidine (including (+) and (-) enantiomers of gacyclidine and possibly its metabolites) will be collected from all subjects in Part A and from a subset of approximately 16 subjects in Part B. Only select sites in Part B will conduct PK sampling. Conducting PK in 16 subjects will ensure that approximately 8 subjects will be exposed to OTO-313, providing a sufficient number for the analysis.

In Part A, on Day 1 (Baseline), a pre-dose sample will be collected at any time prior to the intratympanic administration and post-dose samples will be collected at 0.5, 1, 2, 4, 8, and 12 hours (±15 minutes at each timepoint) after intratympanic administration. On Day 2, a 24-hour PK sample will be obtained. On Day 8, a final PK sample will be obtained at any time during the study visit.

In Part B, on Day 1 (Baseline), a pre-dose sample will be collected at any time prior to the intratympanic administration and a post-dose sample will be collected at 1 hour (± 15 minutes) after intratympanic administration. On Day 8, a third and final blood sample will be collected at any time during the study visit.

Collection, storage, and shipping of plasma PK samples for gacyclidine will be performed as outlined in the Laboratory Manual. Every attempt should be made to collect samples at the protocol-specified times.

Plasma samples will be evaluated for gacyclidine including (+) and (-) enantiomers of gacyclidine and (possibly its metabolites) using validated analytical procedures by a bioanalytical laboratory.

8.7. Safety Evaluations

Safety assessments include:

- Vital Signs and Weight Measurements
- Clinical Laboratory Tests (Hematology, Serum Chemistry, and Urinalysis)
- Tympanometry
- Audiometry
- Otoscopy
- C-SSRS Assessment
- Concomitant Medications
- Adverse events (see Section 9)

8.7.1. Vital Signs and Weight Measurements

In Part A, vital signs measurements (including systolic and diastolic blood pressure and pulse rate) will be collected at Screening, Day 1 (pre-dose), Day 2, Day 8, Day 15, and Day 29.

In Part B, vital signs will be collected at Screening, Day 1 (pre-dose), Day 8, Day 15, Day 29, and Day 57.

Vital signs will be measured after subjects have been seated for 5 minutes and while subjects are in a sitting position.

Weight will only be measured at Screening (Part A and B) and at Day 29 (Part A) or Day 57 (Part B).

8.7.2. Clinical Laboratory Tests

All clinical laboratory tests (except for urine pregnancy) will be processed by a Central Laboratory.

Blood and urine samples for hematology, serum chemistry, urinalysis, and pregnancy tests will be prepared using standard procedures.

For Part A, clinical laboratory testing will be completed at Screening, Day 1 (pre-dose), Day 8, and Day 29. In addition, female subjects of childbearing potential will have serum pregnancy test at Screening and a urine pregnancy test at Day 1 (pre-dose) and Day 29. The urine pregnancy tests will be performed locally at the site, so results are available that day.

For Part B, clinical laboratory testing will be completed at Screening, Day 1 (pre-dose), Day 8, and Day 57. In addition, female subjects of childbearing potential will have serum pregnancy test at Screening and a urine pregnancy test at Day 1 (pre-dose) and Day 57. The urine pregnancy tests will be performed locally at the site, so results are available that day.

The blood and urine samples will be used for the following tests:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and platelet count.

Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl-transpeptidase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, and total protein.

Urinalysis: appearance, color, pH, specific gravity, protein, glucose, ketones, nitrite, leukocyte esterase, urobilinogen, and microscopic sediment examination.

8.7.3. Tympanometry

Tympanometry assessments will be used to assess the mobility and compliance of the tympanic membrane, pressure and volume in the outer ear canal, and function of the tympanic membrane, ossicles and eustachian tube.

In Part A, tympanograms will be completed in both ears at Screening and in study ear only at Days 8, 15, and 29.

In Part B, tympanograms will be completed in both ears at Screening and in study ear only at Day 1 (pre-dose), Day 8, Day 15, Day 29, and Day 57.

8.7.4. Audiometry

Audiometric assessments must be conducted in accordance with American-Speech-Language-Hearing Association Guidelines (ASHA, 2005). Equipment calibration must be current and documented. The audiometric assessments must be conducted by a licensed or certified audiologist or a qualified assistant with appropriate training under the direct supervision of a licensed or certified audiologist.

Audiograms are conducted at 1000, 2000, 4000, 6000, and 8000 Hz for air conduction and at 1000, 2000, and 4000 Hz for bone conduction at all study visits. Both air and bone conduction thresholds will be assessed. Subjects wearing hearing aids should be instructed not to wear their hearing aids during the audiogram.

For Part A, audiometry will be used to assess hearing function in both ears at Screening and in study ear only at Days 8, 15, and 29.

For Part B, audiometry will be used to assess hearing function in both ears at Screening and in study ear only at Days 1 (pre-dose), 8, 15, 29, and 57.

8.7.5. Otoscopy

Otoscopic exams will be used to assess the auditory canal, the appearance of the tympanic membrane, and the healing of the intratympanic injection site. Presence and size of tympanic membrane perforations will be recorded. Perforations of the tympanic membrane will be captured as AEs if the perforation does not resolve by the end of the study or increases in size.

For Part A, otoscopic examinations will be performed by the physician in both ears at Screening and Day 1 (pre-dose) and in the study ear only at Days 8, 15, and 29.

For Part B, otoscopic examinations will be performed by the physician in both ears at Screening and Day 1 (pre-dose) and in the study ear only at Days 8, 15, 29, and 57.

8.7.6. C-SSRS Assessment

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner 2011). The U.S. Food and Drug Administration requires that a prospective assessment for suicidal ideation and behavior be included in clinical studies involving all drugs and biological products for neurological indications. This is true whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. The C-SSRS fulfills this requirement. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS must be administered by appropriately trained and certified personnel.

For Part A, the C-SSRS assessment will be administered at Screening, Day 1 (pre-dose) and Days 8, 15, and 29. The "Baseline" version of the C-SSRS will be used at Screening. For all other days, the "Since Last Visit" version will be used.

For Part B, the C-SSRS assessment will be administered at Screening, Day 1 (pre-dose), and Days 8, 15, 29, and 57. The "Baseline" version will be used at Screening. For all other days, the "Since Last Visit" version will be used.

Any subject who answered "Yes" to Question 4 or 5 regarding active suicidal ideation at Screening or Baseline (Day 1) visits will be excluded per exclusion criteria #8. In addition, subjects deemed by the Investigator to be at significant risk of suicidal behavior should be excluded. Any subject with a positive score on the "Baseline" version of the C-SSRS or report of new suicidal ideation or suicidal behavior on the "Since Last Visit" version must be evaluated by a clinician/mental health professional skilled in the evaluation of suicidal ideation and behavior (e.g. psychiatrist, licensed clinical psychologist) who will determine if it is safe for the subject to participate/continue in the study.

If a subject has any post-Day 1 C-SSRS score of 1-3 for Ideation (i.e., a "yes" answer to Questions 1, 2, or 3) or a "yes" response to the Non-Suicidal Self-Injurious Behavior question and the score is higher than the Day 1 C-SSRS score, then this assessment should be recorded as an AE. Similarly, during the screening period, if a subject has a post-Screening score of 1-3 for Ideation (i.e., a "yes" answer to Questions 1, 2, or 3) or a "yes" response to the Non-Suicidal Self-Injurious Behavior question and the score is higher than the Screening C-SSRS score, then this assessment should be recorded as an AE. This information is reported as indicated in Section 9 (Possible AE terms: Suicidal plans, Suicidal ideation, Suicidal tendency, Suicidal behavior, Suicidal intention, Suicidal depression, Active suicidal ideation, Passive suicidal ideation, Self-injurious behavior without suicidal intent).

If a subject has any post-Day 1 C-SSRS score of 4 or 5 for Ideation (i.e., a "yes" answer to question 4 or 5) and/or any questions answered yes for Suicidal Behavior (with the exception of a "yes" response to the Non-Suicidal Self-Injurious Behavior question), and this was not observed at Day 1 testing, then this assessment should be recorded as a Serious Adverse Event

(SAE). Similarly, during the screening period, if a subject has a post-Screening C-SSRS score of 4 or 5 for Ideation (i.e., a "yes" answer to question 4 or 5) and/or any questions answered yes for Suicidal Behavior (with the exception of a "yes" response to the Non-Suicidal Self-Injurious Behavior question), and this was not observed at Screening testing, then this assessment should be recorded as a Serious Adverse Event (SAE). This information is reported as indicated in Section 9.2.2.

9. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical trials will be conducted in accordance with Good Clinical Practice.

All AEs and serious adverse events (SAEs), with the exception of post-Screening AEs and SAEs related to the C-SSRS, that are reported or observed during or after dosing with the investigational product will be recorded on the AE page of the eCRF for all enrolled subjects. Any post-Screening AEs and SAEs related to the C-SSRS that occur prior to dosing will be captured as AEs (see Section 8.7.6). Information to be collected includes description of event, date of onset, Investigator-specified assessment of the severity and relationship to investigational product, relationship to the intratympanic injection, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Perforations of the tympanic membrane will be captured as AEs if the perforation does not resolve by the end of the study or increases in size.

If the existing medical condition worsens at any time after the injection, it should be recorded as an AE.

9.1. Adverse Event Classification Definitions

Adverse Event:

An AE is any unfavorable and unintended diagnosis, symptom, sign, syndrome or disease which occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, including abnormal results of diagnostic procedures and/or laboratory test abnormalities, which are considered AEs if they:

- result in discontinuation from the study
- require treatment or any other therapeutic intervention
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact

Serious Adverse Event (SAE):

An SAE is defined as any untoward medical occurrence that:

- results in death,
- is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event rather than to an event which hypothetically might have caused death if it were more severe.),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition. These events should be considered serious.

9.1.1. Assessment of Severity

The Investigator will assess the intensity of the AE and rate the AE as mild, moderate, or severe using the following criteria:

Grade 1 – Mild: These events are easily tolerated, require minimal or no treatment, and do not interfere with the subject's daily activities.

Grade 2 – Moderate: These events cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication, e.g., analgesics or anti-emetics.

Grade 3 – Severe: These events incapacitate and prevent usual activity or require complex medication/treatment or hospitalization.

Grade 4 – 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.

Grade 5 – Death: The event resulted in the death of the subject.

Changes in the severity of an AE should be documented to allow for an assessment of the duration of the event at each level of intensity to be performed.

9.1.2. Assessment of Causality

The Investigator will assess the relationship or association of the investigational product in causing or contributing to the AE, which will be characterized using the following classification and criteria:

Definite: AEs that, after careful medical evaluation, are considered definitely related to the investigational product; other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Probable: AEs that, after careful medical evaluation, are considered with a high degree of certainty to be related to the investigational product. The following characteristics will apply:

- a reasonable temporal relationship exists between the event and exposure to the investigational product, and
- the event is a known reaction to the investigational product that cannot be explained by an alternative cause commonly occurring in the population/individual, or
- the event is not a known reaction to the investigational product but cannot be reasonably explained by an alternative cause.

Possible: AEs that, after careful medical evaluation, do not meet the criteria for a definite or probable relationship to the investigational product, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- the event occurs after exposure to the investigational product, and
- there is a reasonable temporal relationship to the application, but the event is not a known reaction to the investigational product and could be explained by a commonly occurring alternative cause, or
- in the absence of a reasonable temporal relationship, the event cannot be explained by an alternative cause.

Not related: AEs in this category will have either of the following characteristics:

- the event does not have a reasonable temporal relationship to investigational product administration and/or can be explained by a commonly occurring alternative cause.

9.1.3. Follow up of Adverse Events

The Investigator will follow a non-serious AE until resolution, stabilization, or the End of Study Visit. The Investigator will follow an SAE (regardless of relationship to investigational product) until the event resolves, stabilizes, or becomes non-serious. All AEs identified on the last scheduled contact must be recorded on the AE page of the eCRF and current status (ongoing or resolved) will be noted. In addition, SAEs will be reported to Worldwide Clinical Trials Drug Safety (drugsafety@worldwide.com) according to the reporting guidelines identified in Section 9.2.2.

9.2. Monitoring of Adverse Events

9.2.1. All Adverse Events

All AEs will be analyzed for safety. Those meeting the definition of SAE must be reported using the SAE Form. Subjects should voluntarily report any AEs or report AEs in response to general, non-directed questioning (e.g., "How has your health been since the last visit?"). For each AE volunteered by the subject, the Investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it.

All AEs, regardless of seriousness, severity, or presumed relationship to investigational product, must be recorded using medical terminology in the source document and on the eCRF.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record on the eCRF their opinion concerning the relationship of the AE to investigational therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

Any non-serious AE that occurs after administration of investigational product must be reported in detail on the appropriate eCRF page and followed until resolution, stabilization, or the End of Study Visit. The description of the AE will include description of event, date of onset, date of resolution, Investigator assessment of severity and relationship to investigational product (with rationale), seriousness (with rationale), any required treatment or evaluations, and outcome.

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the Investigators all SAEs that are unlisted in the Investigator's Brochure and associated with the use of the investigational product. The Investigators must report these events to the appropriate Institutional Review Board (IRB) in accordance with local regulations.

9.2.2. Serious Adverse Events

All SAEs occurring during clinical studies must be reported within 24 hours to Worldwide Clinical Trials Drug Safety.

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

The initial report of an SAE may be made by email to: drugsafety@worldwide.com. 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 SAE and Investigator's attribution of causality.

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.

9.2.3. Pregnancies

Pregnancies occurring after the first dose of investigational product 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. The Investigator should complete the pregnancy report eCRF within

one (1) working day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the follow-up pregnancy report form should be completed on the pregnancy CRF. Spontaneous abortions should always be reported as SAEs. Follow-up information regarding the outcome of the pregnancy will be required.

9.3. Contacting Sponsor Regarding Safety

Any AE considered serious by the Investigator, or that meets the SAE criteria stated in this protocol, must be reported to Drug Safety within 24 hours from the time that study site personnel first learns of the event. The study site must enter the SAE into the EDC system.

- [redacted]

Source documents will be requested from the study sites for SAEs and should be provided to Drug Safety. If the subject is hospitalized during the study, a copy of the hospital discharge summary should be provided to Drug Safety as soon as it becomes available. If a subject deceases during the course of the study, autopsy results should be provided to Drug Safety as soon as they become available.

10. SUBJECT COMPLETION

10.1. Completion

For Part A, study subject participation is complete after Day 29 (Visit 5). Subjects who withdraw their consent to be followed or are lost-to-follow-up before completion of Day 29 will not be considered to have completed the study. For Part B, study subject participation is complete after Day 57 (Visit 6). Subjects who withdraw their consent to be followed or are lost-to-follow-up before completion of Day 57 will not be considered to have completed the study.

10.2. Withdrawal

All subjects have the right to withdraw from study evaluations at any time, for any reason, without prejudice; nonetheless, Investigators should attempt to encourage subjects to complete the protocol so that continued observation and follow-up measurements may be obtained.

Subjects must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The subject is unwilling or unable to comply with the protocol

Other reasons for withdrawal of subjects from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Decision by the Investigator or Sponsor

At any point, the Investigator may discontinue the subject's study participation at the discretion of the Investigator or at the request of the subject, and ensure the subject receives appropriate medical care; the Investigator may also consult the medical monitor to discuss out-of-range test results.

10.2.1. Handling of Withdrawals

Subjects will be free to withdraw from the study, including discontinuing investigational product administration, and further follow-up of the study at any time.

Should a request for early withdrawal from the study with no further follow-up be made, the subject should be encouraged to return to the study site for a last follow up visit and undergo all End-of-Study/Early-Termination assessments.

When a subject withdraws from the study prior to completing the End-of-Study Visit, the reason for withdrawal is to be documented on the eCRFs and in the source document.

10.2.2. Replacements

In order to meet the target for 50 evaluable subjects for Part B, subjects who discontinue participation in the study for non-safety related reasons will be replaced up to a maximum of 10 additional subjects.

11. STATISTICAL METHODS

11.1. Sample Size

The sample size for Part A (8 subjects) was selected based on clinical judgment and is not based on statistical considerations. For Part B, the assumed true standard deviation (SD) of the change from Baseline to Day 57 in the TFI overall score is 17 points. Based on the use of a one-sided two-sample t test at the α=0.05 level of significance, a sample size of 50 subjects (25 subjects per arm) will provide 80% power to detect a mean difference between groups of 12 points on the TFI.

11.2. Analysis Sets

The intent-to-treat analysis set includes all subjects from Part A and all subjects that are randomized in Part B. All efficacy analyses will be carried out in the intent-to-treat analysis set. Subjects will be included in the group to which they were randomized.

The safety analysis set includes all subjects who receive study treatment. The safety analysis set will be used for all summaries of safety. In safety analyses and summaries, subjects will be included in the treatment group based on the treatment that was received.

11.3. Subject Demographics, Baseline Disease Status, and Disposition

Descriptive statistics for subject demographics, baseline disease status, and subject disposition will be provided.

11.4. Study Endpoints

11.4.1. Safety Endpoints – Part A

The safety endpoints for Part A are:

- Assessment of treatment-emergent adverse events (TEAEs).
- Clinically significant adverse change from Baseline in audiometry assessments, tympanometry, and otoscopic examinations.
- Clinically significant adverse change from Baseline in clinical laboratory measurements (hematology, serum chemistry, and urinalysis) and vital signs measurements (systolic and diastolic blood pressure, pulse rate).
- Assessment of suicidality via the C-SSRS.

11.4.2. Plasma PK Endpoint – Part A

The PK endpoint for Part A is:

- Plasma concentrations of gacyclidine (including (+) and (-) enantiomers of gacyclidine and possibly its metabolites).

11.4.3. Exploratory Efficacy Endpoints – Part A

Exploratory efficacy endpoints for Part A are:

- Change in TFI overall score from Baseline at Day 8, 15, and 29.
- PGIC scores at Day 8, 15, and 29.

11.4.4. Safety Endpoints – Part B

The safety endpoints for Part B are:

- Type and incidence of treatment-emergent adverse events (TEAEs).
- Clinically significant adverse change from Baseline in audiometry assessments, tympanometry, and otoscopic examinations.
- Clinically significant adverse change from Baseline in clinical laboratory measurements (hematology, serum chemistry, and urinalysis) and vital signs measurements (systolic and diastolic blood pressure, pulse rate).
- Assessment of suicidality via the C-SSRS.

11.4.5. Plasma PK Endpoint – Part B

The PK endpoint for Part B is:

- Plasma concentrations of gacyclidine (including (+) and (-) enantiomers of gacyclidine and possibly its metabolites).

11.4.6. Efficacy Endpoints

The primary efficacy endpoint for Part B is:

- Change in TFI overall score from Baseline at Day 57.

11.4.7. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for Part B are:

- Change from Baseline in the 7-day average NRS ratings of tinnitus annoyance at Weeks 2, 4, and 8.
- Change from Baseline in the 7-day average NRS ratings of tinnitus loudness at Weeks 2, 4, and 8.
- Change from Baseline in TFI overall score from Baseline at Days 15 and 29.
- The occurrence of at least a 13-point reduction in the overall TFI score from Baseline at Days 15, 29, and 57.
- Change in TFI subscale (Intrusiveness, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, Emotional) scores from Baseline at Days 15, 29, and 57.
- PGIC scores at Days 8, 15, 29, and 57.

11.4.8. Analytic Methods for Efficacy

For Part B, the key primary endpoint (change from Baseline to Day 57 in the TFI overall score) and all exploratory endpoints that are defined in terms of the change from baseline will be analyzed using analysis of covariance (ANCOVA) models with treatment group as a factor and the baseline value of the corresponding endpoint as a covariate. All proportion endpoints will be analyzed using Pearson's chi-square test, provided that the minimum expected cell count is at least 5. Otherwise, Fisher's exact test will be used. Correlations between endpoints will be assessed using the Pearson and Spearman correlation coefficients. All statistical analyses will be conducted using one-sided tests at the α=0.05 level of significance, with no adjustments for multiplicity.

11.5. Safety Evaluations

Safety endpoints to be examined include:

- Vital Signs and Weight Measurements
- Clinical Laboratory Tests
- Tympanometry
- Audiometry
- Otoscopy
- C-SSRS Assessment
- Concomitant Medications
- Adverse events

Descriptive statistical tabulations will be presented for all subjects included in the Safety Analysis Set.

11.5.1. Adverse Events

The current version of Medical Dictionary for Regulatory Activities (MedDRA), as indicated in the Data Management Plan, will be used to code all AEs.

The primary analysis of AEs will consider only treatment-emergent adverse events (TEAEs), events occurring for the first time, or worsening during or after the first dose of investigational product. Subject incidence of TEAEs and SAEs will be tabulated by Preferred Terms (PTs) and System Organ Class (SOC). Severity and relationship to investigational product will also be presented. For summary tables, a subject who experiences the same coded event more than once is counted only one time for that coded event at the highest severity level. AEs will be presented by descending order of frequency in MedDRA SOC and PT.

Listings of all SAEs, AEs leading to study withdrawal, and deaths on-study will also be included. Duration and outcome of each AE will be reported in subject listings.

Adverse events for the C-SSRS occurring during the Lead-in period prior to exposure to investigational product will be reported in data listings. Further details will be provided in the SAP.

11.5.2. Vital Signs and Laboratory Parameters

The analysis of vital signs and laboratory parameters will include descriptive statistics for the change from Baseline to the endpoint visit, change from Baseline for each visit (vital signs only). Where appropriate, analyses will also include shifts from Baseline to the endpoint visit. For laboratory values, the normal ranges will be used to determine the classifications. Values below the normal range will be classified as low, values above the normal range will be classified as high, and values within the normal range will be classified as normal.

11.5.3. Otoscopic Examinations

Observations recorded during the conduct of otoscopic exams will be descriptive in nature. The number and percent of subjects presenting with each Otoscopic classification will be provided by treatment group and study visit. Where relevant, the number and proportion of subjects with changes in their otoscopic classification from Baseline to the endpoint visit will also be provided for each treatment group.

11.5.4. Audiometry Assessments

Descriptive summary statistics for audiometric assessments of air and bone conduction thresholds at each frequency will be provided by treatment group and study visit.

All audiometry assessments will be tabulated separately for the treated and untreated ear.

11.5.5. Tympanometry

Shift tables representing the proportion of subjects with changes in their tympanogram from Baseline to each post-Baseline study visit will be calculated for each treatment group. Tympanogram changes will include both the type of tympanogram (A, B-small volume and/or normal, B-large volume, or C), as well as, whether the tympanogram was judged to be normal or abnormal.

11.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be administered at each visit using the appropriate version i.e. "Baseline" or "Since Last Visit".

The "Baseline" version of the C-SSRS captures both suicidal ideation and suicide behavior (lifetime). There are 5 suicidal ideation questions, each captured as yes/no for the subject's lifetime. There are 4 suicidal behavior questions, each captured as yes/no for the subject's lifetime. An additional question asks if suicidal behavior is present during the visit. All suicidal ideation and behavioral variables as outlined here will be tabulated overall and by treatment group.

The C-SSRS version used at visits subsequent to the Baseline Visit will be a modified version of the "Baseline" C-SSRS. This "Since Last Visit" version uses the same individual variables for suicidal ideation and behavior assessed at Baseline to capture changes, if any, from previous assessments. In addition, overall suicidality (yes/no) will be defined as any suicidal ideation or behavior since the last visit. All suicidal ideation and behavior variables will be tabulated overall and by treatment group for each study visit. All C-SSRS data will be included in data listings.

11.6. Handling of Missing Data, Subject Withdrawals, and Treatment Failures

The SAP will include details regarding the handling of missing data as well as the instructions for scoring the TFI, including handling of missing TFI questionnaire items. Every reasonable effort will be made to encourage compliance with study measurement methods and study procedures to minimize missing data.

Every reasonable effort will be made to follow subjects who withdraw from the study for safety evaluation until the date they would have completed participation.

11.7. Interim Analyses

There are no formal interim analyses planned. Blinded reviews of safety data will be conducted as described in Section 14.6; however, the review of such data is not intended to impact the study conduct unless there are safety concerns. As such, it is expected that the study will continue to its scheduled completion barring any unexpected safety issues.

12. INVESTIGATIONAL PRODUCT INFORMATION

12.1. Physical Description of Investigational Product

The investigational product administered to subjects will be OTO-313 and placebo. OTO-313 is supplied as a 1 mL sterile solution (1.6 mg/mL [0.16%] gacyclidine in medium-chain triglycerides) in a vial. Placebo is provided as 1 mL of sterile 100% medium-chain triglycerides solution in a vial. The vials are provided as kits, and all kits must be stored at 2-8°C until use.

12.2. Directions for Use

OTO-313 and placebo syringes will be prepared in a clean, secure location at room temperature. Please refer to the Pharmacy Manual for detailed investigational product preparation instructions.

12.3. Packaging and Labeling

12.3.1. Packaging

All investigational product kits will be labeled with information that will meet the applicable regulatory requirements.

12.3.2. Labels and Labeling Instructions

A label will be affixed to each kit box indicating kit number and storage instructions. A label will be affixed to the OTO-313 and placebo vials indicating contents and storage instructions.

12.4. Management of Clinical Supplies

The clinical supplies will be managed by WebEZ randomization system. WebEZ will create shipment requests that will be generated based on inventory thresholds that are set for each site. A shipment request will be generated by WebEZ and sent to the clinical supply vendor (Almac). Upon shipment and receipt of the clinical study material, the site personnel will acknowledge the shipment and identify any damaged, missing, or unusable kits so they will not be dispensed.

12.4.1. Storage of Kits

All kits will be stored at 2-8°C, with allowable temperature excursions up to 25°C for up to 72 hours. All temperature excursions of the investigational product must be documented in the investigational product accountability log. Any excursions within the allowable temperature range and conditions should be documented, but the investigational product is still acceptable for use and dispensing to subjects. If any excursions are outside of these conditions, the investigational product should not be used to treat subjects. If this occurs, the individual preparing the investigational product should immediately quarantine the product and report the kit(s) as unacceptable for dispensing to WebEZ to remove it from inventory.

12.5. Investigational Product Accountability

It is the responsibility of the Investigator to ensure that all investigational product received at the site will be inventoried and accounted for throughout the study and the result recorded on the drug accountability form maintained in the Pharmacy Manual. The person responsible for preparing the syringe containing the investigational product will be instructed to return all original containers, whether empty or containing investigational product, when instructed by the study monitor to return. Investigational product returned by the clinical site staff will be stored and disposed of according to the Sponsor's instructions. Investigational product accountability will be verified by the study monitor during the study. Investigational product will be stored in a limited access area or in a locked refrigerator under appropriate environmental conditions.

The Investigator agrees not to supply the investigational product to any person other than sub-Investigators, designated staff and the subjects participating in the study. Investigational product

may not be relabeled or reassigned for use by other subjects except under special circumstances approved by the Sponsor.

The Investigator will retain and store all original containers returned by the clinical site staff until these containers are inventoried by the study monitor. Unless otherwise instructed by the Sponsor, the Investigator agrees at the end of the study to return all original containers, whether empty or containing investigational product, to the Sponsor as instructed by the study manager. The Investigator agrees to neither dispense the investigational product from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

The Sponsor will ensure proper disposal of original containers empty or full of returned or unused investigational product. Appropriate documentation will be maintained. Permission may be granted for local disposal, with supporting documentation.

13. ETHICAL ASPECTS

13.1. Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, as well as with the Note for Guidance on Good Clinical Practice (ICH/135/95), and applicable regulatory requirements. These documents set forth that the informed consent of the subjects is an essential precondition for participation in the clinical study.

13.2. Institutional Review Board (IRB)

This study will be undertaken only after full approval of the protocol and addenda has been obtained from a designated IRB and the Sponsor has received a copy of this approval.

The IRB must be informed of all subsequent protocol amendments issued by the Sponsor.

Reports on, and reviews of, the study and its progress will be submitted to the IRB by the Investigator at intervals stipulated in their guidelines.

13.3. Informed Consent

Each subject must give written consent and sign other locally required documents after the nature of the study has been fully explained. The consent form is typically signed at the Screening Visit (Visit 1) and must be completed prior to performance of any study-related activity. The consent form that is used must be approved both by the Sponsor and by the reviewing IRB. The informed consent is in accordance with the Declaration of Helsinki, current International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and Sponsor policy.

The Investigator must explain to potential subjects the aims and methods of the study. The Investigator must also explain potential discomfort, benefits, and risks of study participation. Subjects will be informed that they are free not to participate in the study and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they decline to participate in the study. Subjects will also be told that declining to

participate in the study will not prejudice future treatment. Finally, they will be told that their records may be examined by competent authorities and authorized persons, but that personal information will be treated as strictly confidential and will not be publicly available. Subjects must be given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's dated signature of the informed consent form. If a subject is unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness on the informed consent form will certify the subject's consent. The subject should receive a signed and dated copy of the informed consent form.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Protocol Modifications

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor, change of telephone number). Responsibilities for reporting protocol amendments to any Regulatory Authority (if applicable) and/or IRB are further described in the Ethical Aspects section of the protocol.

In situations requiring a departure from procedures defined in the protocol, the Investigator or other physician in attendance will contact the site manager, Medical Monitor, or other appropriate Sponsor representative by email or telephone (see Sponsor Contact Information page). If possible, this contact will be made before implementing any departure from protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The eCRF and source document will describe any deviations from procedures defined in the protocol and the circumstances requiring such deviations.

14.2. Regulatory Documentation

There are essential documents that must be provided to the Sponsor at the beginning of the study that will enable the site to be initiated and to receive investigational product. In some cases, there may be new documents required or the initial essential documents will be updated during the course of the study.

Essential documents include, but are not limited to: curriculum vitae for each Investigator and sub-Investigator, documentation of IRB protocol approval and associated subject consent documents, signed clinical trial agreement, and signed protocol. The Sponsor or its representatives will work with the sites to identify, collect, review, and approve the appropriate documentation package.

14.3. Record Retention

In compliance with the ICH/GCP guidelines, the Investigator or institution will maintain all eCRFs and all source documents that support the data collected from each subject. All study documents specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6) and the

applicable regulatory requirement(s) will also be collected from each subject. The Investigator or institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two (2) years after the last approval of a marketing application in an ICH region or after at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a qualified person who will accept the responsibility. The Sponsor must be notified in writing of the name, address, and qualifications of the new custodian.

14.4. Electronic Case Report Form (eCRF)

eCRFs will be completed by site staff for each subject. Access for data entry will be provided to designated site staff. All data must be entered into the eCRFs in English and signed and dated electronically by the Investigator.

The eCRFs should be completed by Investigator site staff at the time of the subject's visit, with the exception of results of tests performed outside the Investigator's office, so that the eCRFs always reflect the latest observations on the subjects participating in the study.

As the site staff enters data, discrepancies will be automatically generated within the Electronic Data Capture (EDC) system for the site staff to resolve immediately. In addition, as a result of data review by the Sponsor or designee, manual queries will be raised electronically in the EDC system. Queries may also be raised as a result of source data verification by the clinical monitor. All corrections will be made within the EDC system by the Investigator or other authorized study site personnel. The clinical monitor and data management teams will ensure appropriate resolution of queries. The Investigator must authorize changes to the safety and efficacy data recorded in the EDC system.

14.5. Termination

Closure of a center or study termination can be initiated at any time either by the Sponsor or by the Investigator, provided that reasonable cause and sufficient notice are given in advance of the intended termination. Reasons for such action taken by the Sponsor include, but are not limited to:

- Successful completion of the study at the center
- The maximum number of eligible subjects for the study has been enrolled
- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the Investigator
- Business reasons

14.6. Data and Safety Monitoring Plan

The Sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from this clinical study and any other clinical study conducted with OTO-313.

The medical personnel of the Sponsor and clinical research organization (CRO) will have the ability to review blinded safety information as it is entered and verified in the EDC system (Section 14.4). All AEs coded to the System Organ Class of ear and labyrinth disorders in the Medical Dictionary for Regulatory Activities (MedDRA) will be reviewed for significant safety trends at least every other month. Reasons for study discontinuation will be reviewed to determine if any trends in study discontinuation, such as the occurrence of specific SAEs or worsening of symptoms, are identified.

Investigators are instructed to contact Drug Safety within 24 hours following the identification of a SAE (Section 9.2.2). All SAEs will be reviewed by the Sponsor and CRO medical personnel within 1-2 days after receipt whether or not the event was considered associated with investigational product. The Sponsor assumes responsibility for appropriate reporting to the regulatory authorities. The Investigator assumes responsibility for reporting events to the IRB in accordance with the IRB requirements, respectively. All SAEs and non-serious AEs will be reviewed by the medical personnel of the CRO and Sponsor during the conduct of the study.

If, during ongoing data review, the Sponsor determines that OTO-313 presents a significant risk to subjects, the Sponsor shall take appropriate steps to suspend or discontinue the study and notify regulatory authorities, Investigators and IRBs as appropriate.

14.6.1. Safety Review Committee

The decision to proceed with initiation of dosing in Part B will be made by a Safety Review Committee. The Safety Review Committee will include at a minimum the Medical Monitor, the Investigator at the Phase 1 research unit, and the Clinical Representative of the Sponsor. Safety data, including adverse events, clinical safety laboratory measurements, audiometry, otoscopy, tympanometry, and C-SSRS data through Day 8, will be evaluated and the decision to proceed will be based on the clinical significance of any adverse events or suspected investigational product-related findings. Initially, all data will be reviewed in a blinded manner with regard to treatment assignment. The treatment assignment for an individual subject may be unblinded, if deemed necessary to enable medical care or study decision-making by the Safety Review Committee.

14.7. 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 study center visit log to be kept at the site. Monitoring visits will be made according to the Clinical Monitoring Plan. At all 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 investigational product 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.

14.8. Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to study initiation, and periodic monitoring visits by the Sponsor or its representatives. eCRFs will be reviewed for accuracy and completeness in the EDC system database by the Sponsor or its representatives during and after on-site monitoring visits, and any discrepancies will be resolved with the Investigator or designees, as appropriate, and documented in the EDC system.

14.9. On-Site Audits

Representatives of the Sponsor's Quality Assurance department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

14.10. Publication Policy

Publication of study results is addressed in the clinical trial agreement.

15. REFERENCES

Adamchic I, PA Tass, B Langguth, C Hauptmann, M Koller, M Schecklmann, F Zeman, and M Landgrebe. “Linking the Tinnitus Questionnaire and the Subjective Clinical Global Impression: Which Differences are Clinically Important.” Health and Quality of Life Outcomes 10 (2012): 79.

American Speech Language Hearing Association. "Guidelines for Manual Pure-Tone Threshold Audiometry." asha.org. 2005. http://www.asha.org/policy/GL2005-00014.htm.

Bhatt, JM, HW Lin, and N Bhattacharyya. “Tinnitus Epidemiology: Prevalence, Severity, Exposures and Treatment Patterns in the United States”. JAMA Otolaryngology Head and Neck Surgery 142 (2016): 959-965.

Bhatt JM, N Bhattacharyya, and HW Lin. “Relationships Between Tinnitus and the Prevalence of Anxiety and Depression”. Laryngoscope 127 (2017): 466-469.

Bing, D, SC Lee, D Campanelli, H Xiong, M Matsumoto, R Panford-Walsh, S Wolpert, M Praetorius, U Zimmermann, H Chu, M Knipper, L Ruttiger, and W Singer. “Cochlear NMDA Receptors as a Therapeutic Target of Noise-Induced Tinnitus.” Cellular Physiology and Biochemistry 35 (2015): 1905-1923.

Bird, PA, EJ Begg, M Zhang, AT Keast, DP Murray, and TJ Balkany. “Intratympanic Versus Intravenous Delivery of Methylprednisolone to Cochlear Perilymph.” Otology & Neurootology 28 (2007): 1124-1130.

Goebel, JA. “2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Meniere’s Disease”. Otolaryngology-Head and Neck Surgery (2016):1-2.

Henry, JA, S Griest, E Thielman, G McMillan, C Kaelin, and KF Carlson. "Tinnitus Functional Index: Development, Validation, Outcomes Research, and Clinical Application." Hearing Research (2015): 1-7.

Hoare DJ, VL Kowalkowski, S Kang, and DA Hall. “Systematic Review and Meta-Analyses of Randomized Controlled Trials Examining Tinnitus Management”. The Laryngoscope 121 (2011): 1555-1564.

Langguth B, PM Kreuzer, T Kleinjung, and D DE Ridder. “Tinnitus: Causes and Clinical Management”. Lancet Neurology 12 (2013): 920-930.

Meikle, MB, BJ Stewart, SE Griest, and JA Henry. “Tinnitus Outcomes Assessment”. Trends in Amplification 12, no. 3, (2008): 223-235.

Meikle, MB, et al. "The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus." Ear & Hearing 33 (2012): 152-176.

Mitha APA and KI Maynard. “Gacyclidine (Beafour-Ipsen)”. Current Opinion in Investigational Drugs 2, no. 6 (2001): 814-819.

Nondahl, DM, KJ Cruickshanks, DS Dalton, BE Klein, R Klein, CR Schubert CR, TS Tweed, and TL Wiley. “The Impact of Tinnitus on Quality of Life in Older Adults”. Journal of the American Academy of Audiology 18 (2007): 257-266.

Piu F, N Tsivkovskaia, R Fernandez, X Wang, S Szobota, and J Anderson. "Preclinical and Clinical Development of OTO-311, a Sustained-Exposure Formulation of the NMDA Receptor Antagonist Gacyclidine, for the Treatment of Tinnitus". Society for Neuroscience Annual Meeting (2018).

Posner K, GK Brown, B Stanley, DA Brent, KV Yershov, MA Oquendo, GW Currier, GA Melvin, L Greenhill, S Shen, and JJ Mann. "The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults." American Journal of Psychiatry, 168 (2011): 1266-1277.

Savage J and A Waddell. "Tinnitus". Clinical Evidence 10 (2014): 506.

Schecklmann M, M Pregler, PM Kreuzer, TB Poeppl, A Lehner, T Cronlein, TC Wetter, E Frank, M Landgrebe, and B Langguth. "Psychological Associations between Chronic Tinnitus and Sleep: A Cross Validation of Tinnitus and Insomnia Questionnaires". Biomed Research International (2015): 461090.

Shargorodsky J, GC Curhan, and WR Farwell. "Prevalence and Characteristics of Tinnitus Among US Adults". American Journal of Medicine 123 (2010): 711-718.

Tegg-Quinn S, RJ Bennett, RH Eikelboom, and DM Baguley. "The Impact of Tinnitus upon Cognition in Adults: A Systematic Review". International Journal of Audiology 55 (2016): 533-540.

Tunkel DE, CA Bauer, GH Sun, et al. "Clinical Practice Guideline: Tinnitus". Otolaryngology Head and Neck Surgery 151 (2014): S1-S40.

US Veterans Benefits Administration, US Department of Veterans Affairs. Annual Benefits Report for Fiscal Year 2013. http://www.benefits.va.gov/REPORTS/abr/ABR_FY2013_Compensation_07172014.pdf. Published July 17, 2014.

Van de Heyning P, G Muehlmeier, T Cox, G Lisowska, H Maier, K Morawski, and T Meyer. "Efficacy and Safety of AM-101 in the Treatment of Acute Inner Ear Tinnitus – A Double-Blind, Randomized, Placebo-Controlled Phase II Study." Otology & Neuro-otology 35 (2014): 598-597.

Wenzel GI, A Warnecke, T Stover, and T Lenarz. "Effects of Extracochlear Gacyclidine Perfusion on Tinnitus in Humans: A Case Series". European Archives of Otorhinolaryngology 267 (2010): 691-699.

Zeman F, M Koller, B Langguth, Landgrebe M, and Tinnitus Research Initiative Database Study Group. "Which Tinnitus-Related Aspects are Relevant for Quality of Life and Depression: Results from a Large International Multicentre Sample". Health and Quality of Life Outcomes 12 (2014): 7-16.