CLINICAL STUDY PROTOCOL

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

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Sponsor Contact: 

Medical Monitor: 

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

APPROVED BY:

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PROTOCOL AMENDMENT, VERSION 3.0

This protocol amendment serves to make the following change:

Item No.	Change	Section
1	Added ongoing independent Safety Data Reviews to ensure appropriate safety and tolerability of OTO-313 and placebo.	Synopsis Section 3 Section 14.6.1

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If any contact information needs to be changed during 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) or Ethics Committee (EC) responsible for this study and will fulfill all responsibilities for submitting pertinent information to the IRB or EC 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
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
Hz	Hertz
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
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 triglycerides, Gacyclidine (Active Ingredient)
PGIC	Patient Global Impression of Change
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-12	Short Form 12 Health Survey
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.: OTO-313-201

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

Study Center(s): Study will be conducted at approximately 55 sites globally

Study Period: Approximately 20 months | **Phase of Development:** 2

Study Design:

This is a randomized, double-blind, placebo-controlled Phase 2 study to evaluate the efficacy and safety of intratympanic OTO-313. Approximately 140 eligible subjects with unilateral tinnitus will be randomly assigned 1:1 to either 0.32 mg OTO-313 or placebo for intratympanic injection to the affected (study) ear. Randomization is stratified by study site, duration of tinnitus (≥2 to ≤6 months and >6 to ≤ 12 months since onset) and by the average of the Tinnitus Functional Index (TFI) score at Screening and Baseline (≥32 to ≤53 points, ≥54 to ≤100 points). Subjects will be observed for efficacy and safety for 16 weeks following dosing. An independent Safety Review Committee will review accumulated individual subject safety data to ensure appropriate safety and tolerability of OTO-313 and placebo.

Study Objectives:

Primary:

- To determine the efficacy of OTO-313 in subjects with unilateral tinnitus by comparing the proportion of subjects achieving response using the TFI relative to placebo.

Secondary:

- To determine the effect of OTO-313 across additional secondary measures of efficacy (tinnitus loudness and annoyance NRS, PGIC, SF-12) relative to placebo.
- To determine the safety and tolerability of OTO-313 in subjects with unilateral tinnitus.

Methods:

This study will be conducted at approximately 55 sites globally.

The duration for each subject will be approximately 18-22 weeks, including an up-to 4-week Screening period, a 2-week Lead-in assessment period, and a 16-week Follow-up period.

After signing informed consent, subjects will complete the TFI at the Screening visit. Subjects must have an overall TFI score of ≥ 32 at both Screening and Baseline visits for eligibility. After 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 a diary using the appropriate Numeric Rating Scales (NRS) for each symptom. Subjects must have completed the tinnitus diary on 5 of the last 7 days of the 14-day Lead-in period for eligibility.

At the Baseline (Day 1) visit, approximately 140 eligible subjects will be randomized to OTO-313 or placebo using a 1:1 allocation ratio. Randomization is stratified by study site, duration of tinnitus (≥2 to ≤6 months and >6 to ≤ 12 months since onset) and by the average of the TFI score at Screening and Baseline (≥32 to ≤53 points, ≥54 to ≤100 points).

After a single intratympanic injection with 0.32 mg 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 diary during the 16-week Follow-up period. Subjects will complete the TFI at study visits at Week 4, Week 8, Week

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12, and Week 16. Additional efficacy and/or safety assessments will also be completed at Baseline (Day 1), Week 4, Week 8, Week 12, and Week 16 or upon early termination from the study.

Safety Data Review

An independent Safety Review Committee will review accumulated individual safety data for the first 25% (35 subjects), 50% (70 subjects), and 75% (105 subjects) of subjects randomized and who have post-administration safety data. Blinded safety data including adverse events, concomitant medications, medical history, clinical safety laboratory measurements, audiometry, otoscopy, tympanometry, and C-SSRS data will be reviewed. 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. The decision to continue with the study will be based on recommendations from the Safety Review Committee on the clinical significance of any adverse events or suspected investigational product-related or procedure-related findings. Additional information on the Safety Data Review and composition of the independent Safety Review Committee is provided in the Safety Review Committee Charter.

Number of Subjects:

The planned sample size for this study is approximately 140 subjects.

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):

1. Subject is a male or female aged 18 to 75 years, inclusive.
2. Subject has subjective unilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.
3. 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.
4. Subject's self-reported duration of tinnitus is between 2 months and 12 months (≥60 to ≤365 days) prior to signing informed consent.
5. Subject has an overall score of ≥ 32 on the TFI at both Screening and Baseline visits.
6. Subject has audiometrically-defined normal hearing or up to moderately severe hearing impairment in the affected ear (study ear) as characterized by pure tone average of ≤ 70 dB at 1000, 2000, and 4000 Hz at Screening.
7. Subject is able to use the diary to complete their daily tinnitus ratings and has completed at least 5 of the last 7 days of diary entries during the 14-day Lead-in period.
8. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal (≥12 months since last menstrual period without an alternative medical cause)] must have a negative urine pregnancy test at Baseline. Women of childbearing potential who are not abstinent from sex with male partners must use highly effective methods of contraception for the duration of the study including: established use of oral, injected, or implanted hormonal methods of contraception; or placement of an intrauterine device or intrauterine system. 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

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duration of the study.
Note: Abstinence (male or female subjects) is acceptable if this is the usual lifestyle and preferred contraception for the subject. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable.

10. Subject is willing to comply with the protocol and attend all study visits.
11. Subject is able to provide written informed consent, including agreement to privacy language compliant with country and/or local requirements, 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):

1. Subject has pulsatile tinnitus, temporomandibular joint disease associated with tinnitus perception, 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, otosclerosis, Eustachian tube dysfunction, or cholesteatoma), Meniere's disease as outlined by the American Academy of Otolaryngology-Head and Neck Surgery Equilibrium Committee in 2015 (Goebel 2016), concurrent vestibular pathology, 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, non-conventional therapy, medications or over-the-counter supplements, transcranial magnetic stimulation); only stable tinnitus treatments (i.e., initiated at least 1 month prior to Screening) are allowed during the study and no new treatments should be introduced during the course of the Study.
4. Subject is not able to accurately localize, 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, or a myringotomy tube in affected ear at Screening or Baseline visits.
7. Subject is receiving any ongoing therapy known as potentially tinnitus-inducing (e.g., aminoglycosides, ototoxic chemotherapeutic drugs, high doses of intravenous loop diuretics, quinine, high doses of aspirin or other nonsteroidal anti-inflammatory drugs). Usage of low doses of aspirin (e.g., daily doses of 81 mg) or low doses of other non-steroidal anti-inflammatory drugs for intermittent pain relief may be permitted at the Investigator's discretion (see Section 7.1).
8. Subject answered "Yes" to Question 4 or 5 regarding active suicidal ideation on the C-SSRS administered at Screening or Baseline 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. Antidepressant and anti-anxiety medications are allowed only if administered at stable doses and frequency for ≥ 1 month prior to Screening with the expectation that the stable daily dose will continue for the duration of the study.
10. Subject is pregnant, lactating, or undergoing fertility treatment.

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11. Subject has a history of serious substance abuse (e.g., cocaine, heroin) within 6 months prior to Screening.
12. Subject has received or is receiving concomitant treatment with any other NMDA receptor antagonist (e.g., memantine, dextromethorphan) within 30 days prior to the Baseline visit. Note, occasional use of dextromethorphan for cough suppression is allowed except between 7 days prior to Baseline and 7 days after injection of the investigational product.
13. Subject has a history of any use of intratympanic gentamicin in the affected ear.
14. Subject has received systemic or intratympanic steroids (including dexamethasone) within 6 weeks prior to the Screening visit.
15. Subject has previously participated in a clinical study with OTO-313 or OTO-311.
16. Subject has used moderate or strong inducers of CYP2B6 (e.g., carbamazepine, efavirenz, rifampin, or ritonavir) within 30 days prior to Baseline visit.
17. Subject has used an investigational drug or device within 30 days prior to Screening.
18. Subject has other clinically significant illness, medical condition or medical history at Screening or Baseline 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:

0.32 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), 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:

Primary Efficacy Endpoint:

- Percentage of responders with response defined as a ≥13-point reduction from baseline on the TFI total score at both Weeks 4 and 8

Secondary Efficacy Endpoints:

- Change from Baseline in the NRS ratings of tinnitus annoyance
- Change from Baseline in the NRS ratings of tinnitus loudness
- Change from Baseline in TFI total score
- Change from Baseline in TFI subscale scores (Intrusiveness, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, Emotional)
- PGIC score
- Change from Baseline in SF-12 scores

Safety Endpoints:

- Incidence of treatment-emergent adverse events
- Change from Baseline in tympanometry

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- Change from Baseline in otoscopy
- Change from Baseline in audiometry
- Change from Baseline in suicidal ideation or behavior
- Incidence of concomitant medications
- Change from baseline in vital signs and weight

Statistical Methods:

Sample Size Justification:

The primary endpoint is the percentage of responders, where response is defined as achieving at least a 13-point reduction from baseline in the TFI total score at both Weeks 4 and 8. It was observed from the previous study that the response rate for OTO-313 (0.32 mg) was 43%, and 13% for placebo. Based on these results, the assumed rate of response for OTO-313 is 43% and 18% for placebo, which is the 13% observed response rate in previous study plus 5% inflation for potential placebo response.

Assuming a 2-sided test and level of significance of 0.05, 60 subjects in the placebo group and 60 subjects in the OTO-313 group will provide approximately 85% power to detect a treatment difference in favor of OTO-313. It is also assumed that an observed discontinuation rate of 15% will be observed, hence the total sample size for this 2-arm study is planned to be 140 subjects, 70 subjects per arm. These sample size calculations were conducted using EASTv6.5 software with a test for a difference in proportions between two groups.

Analyses:

The primary endpoint, analyzed using the common risk difference between treatment groups, will be tested using a Mantel-Haenszel test controlling for duration of tinnitus and baseline TFI score at Week 8. The 95% confidence intervals (CI) around the common risk difference will be provided. The risk difference in responses rates will also be compared between treatment groups at Weeks 12 and 16 as secondary analyses.

The change from baseline in NRS Loudness, NRS Annoyance, TFI total score, each TFI subscale score, and SF-12 will each be analyzed using a linear mixed-effects model with treatment, study day, treatment-by-study day interaction, gender, and tinnitus duration as fixed effects. The unstructured covariance model will be used. Least-square adjusted means, the estimated difference in adjusted means between treatment groups and associated 95% CIs will be provided. Comparisons between treatment groups will be conducted at each post-baseline visit as secondary analyses.

The results of the PGIC will be analyzed using a Cochrane-Mantel-Haenszel mean score test controlling for baseline TFI score and duration of tinnitus. This will be done to compare OTO-313 with placebo.

Adverse events, audiometry, tympanometry, otoscopic, and C-SSRS safety endpoints will be summarized descriptively. Changes in vital signs and laboratory parameters will be summarized descriptively.

Table 1. Time and Events Schedule

Procedure	Screening	Lead-In	Baseline[1] / IP Dose	Follow Up Period			
	Visit 1	-	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 / ET[2]
	-	-	-	Week 4	Week 8	Week 12	Week 16
	Up to 28 days prior to Lead-In	Day -14 to Day -1 (+5 days)[3]	Day 1[1]	Day 29 (±2 days)	Day 57 (± 3 days)	Day 85 (± 4 days)	Day 113 (± 4 days)
Informed consent	X						
Clinical study participation video[4]	X						
Eligibility criteria	X		X				
Medical history[5]	X		X				
Prior/concomitant medications	X		←	→	→	→	→
Adverse event monitoring			←	→	→	→	→
Vital signs measurements[6]	X		X	X	X	X	X
Height and weight[7]	X						X
Pregnancy test[8]	X		X				X
Clinical laboratory tests[9]	X		X		X		
TFI	X		X	X	X	X	X
PGIC				X	X	X	X
SF-12			X		X		X
Otoscopy	X		X	X	X	X	X
Tympanometry	X		X	X	X	X	X
Audiometry	X		X	X	X	X	X
C-SSRS assessment[10]	X		X	X	X	X	X
NRS compliance review[11]		X	X	X	X	X	X
Randomization[12]			X				
Administer investigational product[13]			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 (Week 16) or upon early termination (ET) from the study. If a subject terminates early prior to Week 8, a clinical laboratory test should be performed.

[3] The +5 days window is allowed for purposes of scheduling the Baseline visit and is not included in determination of NRS diary compliance.

[4] 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.

[5] Medical history to include information on demographics and completion of the modified Tinnitus Sample Case History Questionnaire (TSCHQ) to capture tinnitus and related medical history information. Changes in medical history since the Screening visit will be recorded at the Baseline visit. In addition, if subject has any untoward medical occurrences that would meet the definition of a serious event (see Section 9.1 Serious Adverse Event) prior to investigational product administration, this information is to be recorded in medical history and immediately discussed with the Medical Monitor to evaluate whether the subject should be excluded from randomization/treatment. Serious medical events that occur prior to investigational product administration should be recorded on the Pre-Dose Serious Medical Occurrences report form. Medical history, conditions, and procedures that occurred prior to Screening, including COVID-19 infection, may be added throughout the study (if identified later).

[6] Vital signs measurements include systolic and diastolic blood pressure, body temperature, respiratory rate, and pulse rate.

[7] Only weight is to be measured at Week 16.

[8] 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 Week 16. 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 based on urine test after dosing with investigational product, a confirmatory serum pregnancy test will be performed locally, and the subject should complete the 16-week follow-up period (See Section 9.2.3). Only the Screening serum pregnancy tests will be analyzed by a central laboratory. Urine pregnancy tests and confirmatory serum pregnancy test during follow up, is to be 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.

[9] 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 are not required for randomization.

[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] 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 each day using the NRS diary. Subjects must complete their tinnitus ratings for at least 5 of the last 7 days of the 14-day Lead-in testing to be eligible for randomization. Subjects will be able to record missed diary entries for 1 day after a missed entry. Reminder alerts to subjects and site staff will help to ensure compliance. After randomization, subjects will continue to record their tinnitus annoyance and tinnitus loudness for the 16-week 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.

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

[13] Investigational product (OTO-313 or placebo) is administered by intratympanic injection to the affected (study) ear. The subject should remain recumbent for at least 15 minutes after the injection.

1. BACKGROUND

Tinnitus or "ringing in the ears", is defined as a perception of sounds without a correlated external auditory stimulus. Tinnitus is a common disorder with prevalence estimates ranging from 11.9% to 30.3% across various countries with prevalence generally increasing with age (McCormack et al 2016). 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 and persistent condition with recent survey results finding that 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). Intratympanic administration of NMDA receptor antagonists in animal models of acute tinnitus was shown to reduce deafferentation and the decline of auditory brainstem response Wave I amplitude (Bing et al. 2015) and to reduce "tinnitus-like" behavior (Guitton et al. 2003). These findings suggest that activation of cochlear NMDA receptors may be an important mechanism for generating tinnitus and that intratympanic NMDA receptor antagonists may have potential as a local cochlear treatment for tinnitus.

1.1. Intratympanic formulation of gacyclidine (OTO-313)

Intratympanic administration 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). 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 (Mitha and Maynard 2001; Piu et al 2018). Gacyclidine was originally formulated as OTO-311, [redacted] to provide sustained exposure of

gacyclidine to cochlear tissues following a single intratympanic administration. Additional preclinical studies showed that gacyclidine formulated [redacted] (OTO-313) provided greater and longer lasting inner ear exposures of gacyclidine compared to OTO-311 when injected intratympanically.

1.2. Clinical studies with OTO-313

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 study 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 completed Phase 1 study in healthy subjects (Study 311-201501), OTO-311 (the earlier formulation of gacyclidine), 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.

Study 313-201901 was a randomized, double-blind, placebo-controlled Phase 1/2 study which evaluated the safety and exploratory efficacy of a single intratympanic administration of OTO-313 in subjects with subjective tinnitus. An initial safety and plasma PK cohort of 8 subjects dosed with 0.11 mg OTO-313 or placebo (3:1) demonstrated that this dose level was well-tolerated with no safety concerns. An exploratory efficacy cohort of 35 subjects with unilateral tinnitus of moderate to severe intensity (score of ≥ 25 on the Tinnitus Functional Index [TFI]) and a duration of tinnitus of 1 to 6 months received a single intratympanic injection of 0.32 mg OTO-313 or placebo (1:1). 0.32 mg OTO-313 was well-tolerated with a lower incidence of adverse events than placebo.

In the exploratory efficacy cohort, the mean TFI reduction from baseline trended in favor of OTO-313 at each timepoint (Day 15: -9.3 points OTO-313 vs -4.1 points Placebo; Day 29: -9.4 points OTO-313 vs -6.6 points Placebo; Day 57: -12.9 points OTO-313 vs -4.3 points Placebo). A clinically meaningful, 13-point improvement on the TFI was observed in 43% (6/14) of OTO-313 subjects at both Day 29 (Week 4) and Day 57 (Week 8) versus 13% (2/16) of Placebo subjects (*ad hoc* 1-sided p-value < 0.05). The higher responder rate for OTO-313 versus Placebo was maintained for all TFI improvement levels of 15, 20, 25 and 30 points. Treatment with OTO-313 also led to reduction in the daily ratings of tinnitus loudness and annoyance, as well as improved PGIC scores. Among responders, strong correlation was observed between the various endpoints in favor of OTO-313. As anticipated, plasma concentrations of gacyclidine were below the limit of assay quantitation (≤ 0.1 ng/mL) confirming limited systemic exposure. These results suggest that a single intratympanic injection of 0.32 mg OTO-313 was well-tolerated and exhibited preliminary efficacy in subjects with unilateral tinnitus.

1.3. Rationale for current study

The purpose of this Phase 2 study, Study OTO-313-201, is to investigate the efficacy and safety of 0.32 mg OTO-313 administered by intratympanic injection in subjects with unilateral tinnitus.

The 0.32 mg OTO-313 dose level is expected to be safe and well-tolerated, based on Study 313-201901 in subjects with unilateral tinnitus. In addition, preclinical data suggest that this dose level of OTO-313 will produce sufficient inner ear exposures of gacyclidine in humans. 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 0.32 mg OTO-313 in this Phase 2 study in subjects with unilateral tinnitus.

The preclinical and clinical data obtained to date are described in more detail in the Investigator's Brochure.

2. OBJECTIVES

2.1. Primary objective

- To determine the efficacy of OTO-313 in subjects with unilateral tinnitus by comparing the proportion of subjects achieving response using the TFI relative to placebo.

2.2. Secondary objectives

- To determine the effect of OTO-313 across additional secondary measures of efficacy (tinnitus loudness and annoyance NRS, PGIC, SF-12) relative to placebo.
- To determine the safety and tolerability of OTO-313 in subjects with unilateral tinnitus.

3. OVERVIEW OF STUDY DESIGN

This study will be conducted at approximately 55 sites globally.

The duration for each subject will be approximately 18-22 weeks, including an up-to 4-week Screening period, a 2-week Lead-in assessment period, and a 16-week Follow-up period.

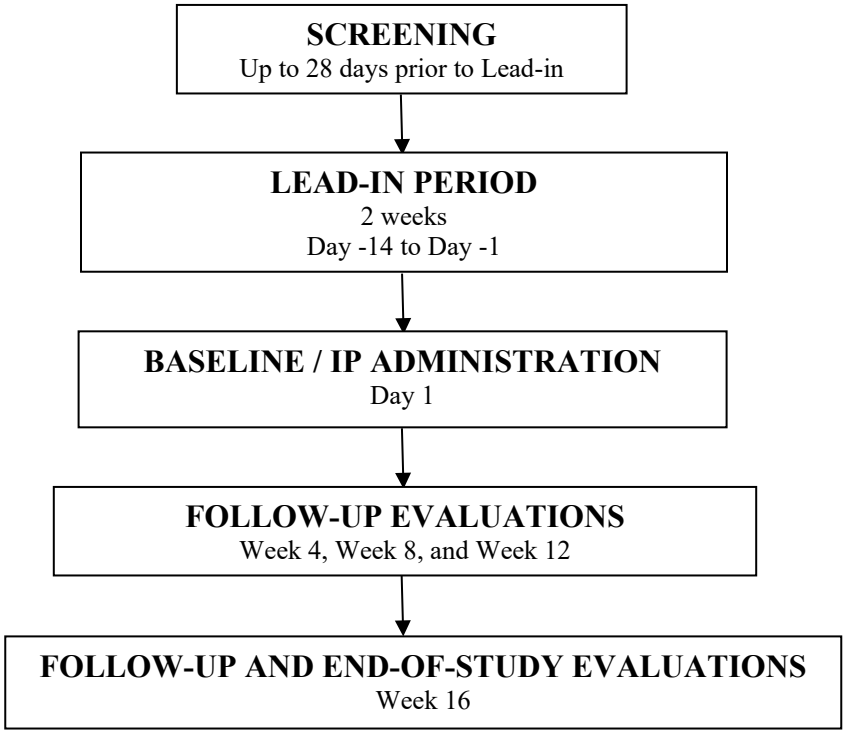
After signing informed consent, subjects will complete the TFI at the Screening visit. Subjects must have an overall score of ≥ 32 on the TFI at both Screening and Baseline. After Screening, potential subjects will begin a 2-week Lead-in assessment period. During this time, subjects will enter daily tinnitus annoyance and tinnitus loudness severity into a diary using the appropriate Numeric Rating Scales (NRS) for each symptom. Subjects must have completed the tinnitus diary on at least 5 of the last 7 days of the 14-day Lead-in period for eligibility. The additional +5 days of the Lead-in period will not be used for eligibility.

At the Baseline (Day 1) visit, approximately 140 eligible subjects will be randomized to OTO-313 or placebo using a 1:1 allocation ratio. Randomization is stratified by study site, duration of tinnitus (≥2 to ≤6 months and >6 to ≤ 12 months since onset) and by the average of the TFI score at Screening and Baseline (≥32 to ≤53 points, ≥54 to ≤100 points).

After a single intratympanic injection with 0.32 mg 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 diary during the 16-week Follow-up period. Subjects will complete the TFI at study visits at Week 4, Week 8, Week 12, and Week 16. Additional efficacy and/or safety assessments will also be completed at Baseline (Day 1), Week 4, Week 8, Week 12, and Week

16 or upon early termination from the study. An independent Safety Review Committee will review accumulated individual subject safety data to ensure appropriate safety and tolerability of OTO-313 or placebo.

Figure 1. Study Design Schematic



4. STUDY POPULATION

4.1. General Considerations

Approximately 140 subjects will be enrolled at approximately 55 sites globally. 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):

1. Subject is a male or female aged 18 to 75 years, inclusive.
2. Subject has subjective unilateral tinnitus and is consistently aware of their tinnitus throughout much of the waking day.
3. 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.

4. Subject's self-reported duration of tinnitus is between 2 months and 12 months (≥60 to ≤365 days) prior to signing informed consent.
5. Subject has an overall score of ≥ 32 on the TFI at both Screening and Baseline visits.
6. Subject has audiometrically-defined normal hearing or up to moderately severe hearing impairment in the affected ear (study ear) as characterized by pure tone average of ≤ 70 dB at 1000, 2000, and 4000 Hz at Screening.
7. Subject is able to use the diary to complete their daily tinnitus ratings and has completed at least 5 of the last 7 days of diary entries during the 14-day Lead-in period.
8. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal (≥12 months since last menstrual period without an alternative medical cause)] must have a negative urine pregnancy test at Baseline. Women of childbearing potential who are not abstinent from sex with male partners must use highly effective methods of contraception for the duration of the study including: established use of oral, injected, or implanted hormonal methods of contraception; or placement of an intrauterine device or intrauterine system. 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.
   Note: Abstinence (male or female subjects) is acceptable if this is the usual lifestyle and preferred contraception for the subject. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable.
10. Subject is willing to comply with the protocol and attend all study visits.
11. Subject is able to provide written informed consent, including agreement to privacy language compliant with country and/or local requirements, 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):

1. Subject has pulsatile tinnitus, temporomandibular joint disease associated with tinnitus perception, 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, otosclerosis, Eustachian tube dysfunction, or cholesteatoma), Meniere's disease as outlined by the American Academy of Otolaryngology-Head and Neck Surgery Equilibrium Committee in 2015 (Goebel 2016), concurrent vestibular pathology, 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, non-conventional therapy, medications or over-the-counter supplements, transcranial magnetic stimulation); only stable tinnitus treatments (i.e., initiated at least 1 month prior to Screening) are allowed

during the study and no new treatments should be introduced during the course of the Study.

4. Subject is not able to accurately localize, 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, or a myringotomy tube in affected ear at Screening or Baseline visits.
7. Subject is receiving any ongoing therapy known as potentially tinnitus-inducing (e.g., aminoglycosides, ototoxic chemotherapeutic drugs, high doses of intravenous loop diuretics, quinine, high doses of aspirin or other nonsteroidal anti-inflammatory drugs). Usage of low doses of aspirin (e.g., daily doses of 81 mg) or low doses of other non-steroidal anti-inflammatory drugs for intermittent pain relief may be permitted at the Investigator's discretion (see Section 7.1).
8. Subject answered "Yes" to Question 4 or 5 regarding active suicidal ideation on the C-SSRS administered at Screening or Baseline 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. Antidepressant and anti-anxiety medications are allowed only if administered at stable doses and frequency for ≥ 1 month prior to Screening with the expectation that the stable daily dose will continue for the duration of the study.
10. Subject is pregnant, lactating, or undergoing fertility treatment.
11. Subject has a history of serious substance abuse (e.g., cocaine, heroin) within 6 months prior to Screening.
12. Subject has received or is receiving concomitant treatment with any other NMDA receptor antagonist (e.g., memantine, dextromethorphan) within 30 days prior to the Baseline visit. Note, occasional use of dextromethorphan for cough suppression is allowed except between 7 days prior to Baseline and 7 days after injection of the investigational product.
13. Subject has a history of any use of intratympanic gentamicin in the affected ear.
14. Subject has received systemic or intratympanic steroids (including dexamethasone) within 6 weeks prior to the Screening visit.
15. Subject has previously participated in a clinical study with OTO-313 or OTO-311.
16. Subject has used moderate or strong inducers of CYP2B6 (e.g., carbamazepine, efavirenz, rifampin, or ritonavir) within 30 days prior to Baseline visit.
17. Subject has used an investigational drug or device within 30 days prior to Screening.
18. Subject has other clinically significant illness, medical condition or medical history at Screening or Baseline 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

Approximately 140 eligible subjects will be assigned randomly to 0.32 mg OTO-313 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 the affected (study) ear
- Placebo (vehicle); single (0.2 mL volume) intratympanic injection to the affected (study) ear

OTO-313 and placebo solutions are identical in appearance.

5.2. Enrollment Procedures

5.2.1. Assignment of Subject Identification Numbers

At the Screening visit (Visit 1), subjects who have signed 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. Any subject that is re-screened will be assigned a new subject identification number. Subjects will be considered enrolled into the study once they complete the informed consent process.

The subject identification number will consist of 9 digits separated by 2 hyphens (e.g., 201-XXX-YYY). The first 3 digits are the study number (201) followed by a hyphen. The second 3 digits are the site number followed by a hyphen. The final 3 digits are the subject number.

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 Response Technology (IRT) randomization system. All study site personnel are blinded to treatment assignment. Study sites 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.

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

Subjects will be randomized in a 1:1 ratio (OTO-313:placebo) of treatment groups using a permuted block randomization algorithm. Randomization is stratified by study site, duration of

tinnitus (≥2 to ≤6 months and >6 to ≤ 12 months since onset) and by the average of the TFI score at Screening and Baseline (≥32 to ≤53 points, ≥54 to ≤100 points).

The randomization process will be deployed via IRT 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.

In case of emergency, 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, and if not possible 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. Recommended needles are 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 (e.g., [redacted] or lidocaine spray or solution) until the tympanic membrane is numb. If applicable, suction away any excess topical preparation. Use of phenol is prohibited for anesthetizing the tympanic membrane (Section 7.1).
4. Using the prepared syringe, insert the needle (bevel facing) 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.

The site will maintain a log of all investigational product received, 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 Screening, which will be considered prior therapy. COVID-19 vaccination at any time prior to Screening or during the study will also be recorded.

At the discretion of the Investigator, any medication deemed necessary for the welfare of the subject may be continued at stable doses during the study, 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 (inhaled and nasal steroids are permitted)
- Other investigational drug(s) or device(s)
- Other NMDA receptor antagonists (e.g., memantine, dextromethorphan). Note, occasional use of dextromethorphan for cough suppression is allowed except during

the period 7 days prior to Baseline and 7 days after the injection of the investigational product.

- Medications known as potentially tinnitus-inducing (e.g., aminoglycosides, ototoxic chemotherapeutic drugs, high doses of intravenous loop diuretics, quinine, high doses of aspirin or other non-steroidal anti-inflammatory drugs). Usage of low doses of aspirin (e.g., daily doses of 81 mg) or low doses of other non-steroidal anti-inflammatory drugs for intermittent pain relief 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. Other Medications and Therapies

It is recognized that during the study subjects may require use of certain medications for relief of symptoms related to tinnitus or other disease (e.g., worsening depression). Use of the following medication and therapies are permitted during the study:

- Stable doses (taken for ≥ 1 month prior to Screening) of antidepressant and anti-anxiety medications are allowed during the study, and
- Stable prior use (≥ 1 month prior to Screening) of over-the-counter supplements, medications for tinnitus (e.g., Gingko biloba, melatonin), nonconventional therapy, and transcranial magnetic stimulation for tinnitus.

No new medications, over-the-counter supplements, or other therapies for tinnitus may be introduced during the study.

Any changes reported by the subjects in concomitant medications, including changes in dose or frequency of dosing, while not considered a protocol deviation, should be recorded in the subject's eCRF.

No new hearing aids, sound/noise therapy devices, or behavioral therapy for tinnitus may be introduced during the study. However, patients using devices or behavioral therapy pre-study are permitted to continue stable use.

- 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.

Any changes in the concurrent use of these devices or behavioral therapy for tinnitus, while not considered a protocol deviation, should be recorded in the subject's eCRF.

8. STUDY EVALUATIONS

8.1. Study Procedures by Visit

8.1.1. Screening Period: Up to 28 days prior to Lead-In

The following assessments, as listed in the Time and Events Schedule (Table 1), will be performed during the screening period: obtain documented informed consent, review and confirm eligibility criteria, medical history, demographics, prior and concomitant medications, vital signs, height and weight measurements, serum pregnancy test (for female subjects of childbearing potential only), clinical laboratory tests, TFI assessment, otoscopy, tympanometry, audiometry, 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 Research Studies". Viewing of the video will be completed after informed consent but prior to the TFI at the screening visit.

8.1.2. Lead-In Period: Day -14 to Day -1 (+ 5 days)

The subject will record their tinnitus loudness and tinnitus annoyance each day, using the NRS for each symptom, in a diary during the 14-day Lead-In assessment period. Subjects must have completed the tinnitus diary on at least 5 of the last 7 days of the 14-day Lead-in period for eligibility. The additional +5 days of the Lead-in period will not be used for eligibility.

8.1.3. Baseline/Investigational Product Administration: Day 1

The purpose of the Day 1 Baseline visit is to confirm subject eligibility, capture baseline efficacy and safety data, and administer the investigational product.

Once the Lead-in period is complete and the subject has met the eligibility criteria for tinnitus diary compliance, the Day 1 Baseline assessments are performed. Results from the prior and 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 (with particular attention to any untoward medical occurrences that would meet the definition of a serious outcome – See Section 9.1 Serious Adverse Event), vital signs, clinical laboratory tests, TFI (overall score of ≥ 32 on the TFI at Screening and Baseline visits is required for eligibility), SF-12, otoscopy, tympanometry, and audiometry. Once eligibility status is confirmed and the subject is randomized, the investigational product is administered and the remaining Day 1 assessments (i.e., AE monitoring) are completed.

If the subject is no longer eligible, the subject will not be randomized and should be recorded as a screen failure (documentation for screen failures will be limited specifically to end of study reason, demographic information, TSCHQ, reason for screen failure, and inclusion/exclusion criteria). Re-screening of subjects may be permitted after discussion with the medical monitor and sponsor.

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

8.1.4. Week 4 (Day 29 ± 2 days): Follow Up

The primary purpose of the Week 4 visit is to capture efficacy and safety data. Efficacy assessments include the TFI and PGIC. Safety assessments include concomitant medications, vital signs, otoscopy, tympanometry, audiometry, C-SSRS, and AE monitoring. Compliance for completing the daily NRS diary will be reviewed with the subject.

All Week 4 efficacy and safety assessments as listed in the Time and Events Schedule (Table 1) are to be performed.

8.1.5. Week 8 (Day 57 ± 3 days): Follow Up

The primary purpose of the Week 8 visit is to capture efficacy and safety data. Efficacy assessments include the TFI, PGIC, and SF-12. Safety assessments include concomitant medications, vital signs, clinical laboratory tests, otoscopy, tympanometry, audiometry, C-SSRS, and AE monitoring. Compliance for completing the daily NRS diary will be reviewed with the subject.

All Week 8 efficacy and safety assessments as listed in the Time and Events Schedule (Table 1) are to be performed. In the event that a subject terminates early prior to Week 8, a clinical laboratory test should be conducted.

8.1.6. Week 12 (Day 85 ± 4 days): Follow Up

The primary purpose of the Week 12 visit is to capture efficacy and safety data. Efficacy assessments include the TFI and PGIC. Safety assessments include concomitant medications, vital signs, C-SSRS, and AE monitoring. Compliance for completing the daily NRS diary will be reviewed with the subject.

All Week 12 efficacy and safety assessments as listed in the Time and Events Schedule (Table 1) are to be performed.

8.1.7. Week 16 (Day 113 ± 4 days): End of Study/Early Termination

The primary purpose of the Week 16 visit is to capture final efficacy and safety data. Efficacy assessments include the TFI, PGIC, and SF-12. Safety assessments include concomitant medications, weight, vital signs, urine pregnancy test for women of childbearing potential, otoscopy, tympanometry, audiometry, C-SSRS, and AE monitoring.

All Week 16 efficacy and safety assessments as listed in the Time and Events Schedule (Table 1) are to be performed. In the event that a subject terminates prior to Week 8, a clinical laboratory test should be conducted.

8.1.8. 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.

8.2. 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, reproductive history, and history of COVID-19 infection. In addition, if subject has any untoward medical occurrences that would meet the definition of a serious event (see Section 9.1 Serious Adverse Event) prior to investigational product administration, this information is to be recorded in medical history and immediately discussed with the Medical Monitor to evaluate whether the subject should be excluded from randomization/treatment. Serious medical events that occur prior to investigational product administration should be recorded on the Pre-Dose Serious Medical Occurrences report form.

Tinnitus-specific medical history information is also obtained by having potential subjects complete the modified TSCHQ at Screening. Medical history, conditions, and procedures that occurred prior to Screening may be added throughout the study (if identified later).

Demographic information will also be obtained at the Screening visit and will include age; sex; race; ethnicity; height, without shoes; weight, without shoes. Weight will also be obtained at Week 16.

8.3. 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 Research 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.

8.4. Efficacy Evaluations

Efficacy assessments include:

- Tinnitus Functional Index (TFI)
- Daily Tinnitus Annoyance NRS
- Daily Tinnitus Loudness NRS
- Patient Global Impression of Change (PGIC)
- Short Form 12 (SF-12) Health Survey

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, PGIC, and SF-12) based on their tinnitus experience with the devices in use. Only stable tinnitus treatments (i.e., started at least 1 month prior to Screening) are allowed during the study and no new treatments should be introduced.

The TFI should be completed at the beginning of each visit prior to other study assessments. The recommended order in which study questionnaire assessments are conducted is: TFI, PGIC, SF-12, and C-SSRS (the C-SSRS is administered after all efficacy questionnaires have been

completed). The daily tinnitus loudness and annoyance NRS should be completed at home on the study visit days.

8.4.1. 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).

Subjects will complete the TFI at Screening, Baseline (pre-dose), and Weeks 4, 8, 12 and 16. The TFI should completed at the beginning of each study visit.

8.4.2. Daily Tinnitus Annoyance Numeric Rating Scale (NRS)

Subjects will record their tinnitus annoyance using a tinnitus NRS 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 selecting 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 will begin using the tinnitus NRS diary at the start of the 14-day Lead-in period to record their tinnitus annoyance every day and will continue to record their tinnitus annoyance once per day through the 16-week 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.

8.4.3. Daily Tinnitus Loudness Numeric Rating Scale (NRS)

Subjects will record their tinnitus loudness using a tinnitus NRS diary.

Subjects rate their tinnitus loudness over the past 24 hours. Subjects respond to the following question by selecting 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 eligible at screening will begin using the tinnitus NRS diary at the start of the 14-day Lead-in period to record their tinnitus loudness every day and will continue to record their tinnitus loudness once per day through the 16-week 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.

8.4.4. 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

Subjects will complete the PGIC at Weeks 4, 8, 12 and 16.

8.4.5. Short Form 12 (SF-12) Health Survey

The SF-12 is a validated, multipurpose short form survey of 12 questions, all selected from the SF-36 Health Survey (Ware et al. 1996). The questions are weighted and scored to create two subscales, physical and mental health composite scores, as well as an overall health-related quality of life score.

Subjects will complete the SF-12 at Baseline (pre-dose), Week 8, and Week 16.

8.5. Safety Evaluations

Safety assessments include:

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

8.5.1. Vital Signs and Height/Weight Measurements

Vital signs measurements (including systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate) will be collected at Screening, Baseline (pre-dose), Week 4, Week 8, Week 12, and Week 16.

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

8.5.2. Clinical Laboratory Tests

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

Non-fasting blood samples and urine samples for hematology, serum chemistry, urinalysis, and pregnancy tests will be prepared using standard procedures.

Clinical laboratory testing will be completed at Screening, Baseline (pre-dose) and Week 8. In addition, female subjects of childbearing potential will have serum pregnancy test for human chorionic gonadotropin (hCG) at Screening and a urine pregnancy test (hCG) at Baseline (pre-dose) and Week 16. 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.

8.5.3. 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.

Otoscopic examinations will be performed by the physician or qualified healthcare professional in both ears at Screening and Baseline (pre-dose) and in study ear only at Weeks 4, 8, 12 and 16.

8.5.4. 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.

Tympanograms will be completed in both ears at Screening and Baseline (pre-dose) and in study ear only at Weeks 4, 8, 12 and 16, unless the examiner determines there is a contraindication to performing the procedure.

8.5.5. 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 250, 500, 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.

Audiometry will be used to assess hearing function in both ears at Screening and Baseline (pre-dose) and in study ear only at Weeks 4, 8, 12 and 16.

8.5.6. C-SSRS Assessment

The rater-administered Columbia Suicide Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner 2011). Otologic conditions are sometimes associated with anxiety or depression, requiring prospective assessment of suicidal ideation to ensure patient safety. This is true whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and/or behavior.

The C-SSRS scale includes 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.

The C-SSRS assessment will be administered at Screening, Baseline (pre-dose) and Weeks 4, 8, 12, and 16.

- The “Baseline” version of the C-SSRS will be used at Screening.
- The “Since Last Visit” version will be used at Baseline (pre-dose), and Weeks 4, 8, 12 and 16 or premature termination.

At Screening or Baseline (Day 1) visits, subjects are to be excluded (per Exclusion Criterion 8) if:

- subject answered “Yes” to Question 4 or 5 regarding active suicidal ideation,
- subject was deemed by the Investigator to be at significant risk of suicidal behavior, or
- subject had a positive score or report of new suicidal ideation or suicidal behavior on the “Since Last Visit” version.

The Investigator should record medical history of suicidal ideation or non-suicidal self-injurious behavior at Screening or Baseline (Day 1) visits if:

- subject has a post-Screening score of 1-3 for Ideation (i.e., a "yes" answer to Questions 1, 2, or 3), or
- subject has responded "yes" to the Non-Suicidal Self-Injurious Behavior question and the score is higher than the Screening C-SSRS score.

At post-dose visits (Weeks 4, 8, 12, and 16), the Investigator is to record an AE and assess use and dose of concomitant antidepressant medication (Section 7.2) if:

- subject has a positive score or report of new suicidal ideation or suicidal behavior,
- subject has a C-SSRS score of 1-3 for Ideation (i.e., a "yes" answer to Questions 1, 2, or 3),
- subject has a "yes" response to the Non-Suicidal Self-Injurious Behavior question and the score is higher than the "Baseline" C-SSRS score.

At post-dose visits (Weeks 4, 8, 12, and 16) the Investigator is to record a Serious Adverse Event (SAE) and assess use and dose of concomitant antidepressant medication (Section 7.2) if:

- subject has any post-Baseline 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 pre-dose testing.

SAE information is reported as indicated in Section 9.2.2.

Subjects reporting new suicidal ideation or behavior can be managed by concomitant antidepressants and may continue in the study or may be discontinued, at the discretion of the Investigator. It is advised that subjects be referred to trained specialists for the treatment of depression, at the discretion of the Investigator.

Suicidality information is to be reported using the following 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.

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.

Adverse events will be monitored and documented starting during and after administration of investigational product until study participation is complete.

All AEs and serious adverse events (SAEs) 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.

Information to be collected includes description of event, affected ear (for ear-related events only), 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 (e.g., requires intervention or treatment), it should be recorded as an AE (e.g., worsening tinnitus [identify L, R, or both ears]).

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF using medical terminology. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs, symptoms or require medical intervention. Laboratory values considered to be clinically significant may be more extreme than values that are simply outside normal ranges. A clinically significant finding on an examination (e.g., vital signs) or laboratory abnormality (e.g. detected on clinical chemistry or hematology), present at screening and significantly worsens, and requires medical or surgical intervention, or leads to study drug interruption or discontinuation - should be reported as an AE. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

9.1. Adverse Event Classification Definitions

Adverse Event:

An AE is any unfavorable and unintended diagnosis, symptom, sign, syndrome, or disease which occurs after administration of investigational product, 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 and the study procedure (intratympanic injection) in causing or contributing to the AE, which will be characterized using the following classification and criteria:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

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 or study procedure) 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 Medpace Clinical Safety (email: medpace-safetynotification@medpace.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 within the electronic data capture system eCRF. 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 or to study procedure, 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 and to study procedure. 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 and to study procedure (with rationale), seriousness (with rationale), any required treatment or evaluations, and outcome (e.g., fatal, not resolved, resolved, resolved with sequelae, unknown).

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) or Ethics Committee (EC) in accordance with local regulations.

9.2.2. Serious Adverse Events

All SAEs occurring after administration of investigational product must be reported to Medpace Clinical Safety within 24 hours.

The initial report of an SAE should be made via the electronic data capture system SAE eCRF. The system will alert the Safety team and appropriate action will commence. If a SAE occurs and access to EDC is not practical within the 24-hour time frame, [redacted] can be notified via email or telephone.

The Investigator must provide the minimal information: i.e., protocol number, subject's initials and date of birth, subject number or medication code number, nature of the AE and Investigator's attribution.

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.

All oral reports of an SAE must be confirmed within 24 hours by a written, more detailed report and signed by the Investigator. Source documents will be requested from the study sites for the SAE. If the subject is hospitalized during the study, a copy of the hospital discharge summary should be provided as soon as it becomes available.

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary) to Medpace Clinical Safety via Fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

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.

9.2.3. Pregnancies

Pregnancies occurring after administration of the investigational product and during participation of the study are considered immediately reportable events. While not considered an 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 Exposure In Utero form within one (1) working day of knowledge of the pregnancy. The pregnancy will be followed until information of the final outcome becomes available and a follow-up Exposure in Utero form is completed. Spontaneous abortions should always be reported as SAEs.

10. SUBJECT COMPLETION

10.1. Completion

Study subject participation is complete after Week 16 (Visit 6). Subjects who discontinue the study before completion of Week 16 (Visit 6) will not be considered to have completed the study.

10.2. Study Discontinuation

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 may be discontinued from the study for any of the following:

- Withdrawal of consent
- Lost to Follow-up
- Adverse Event
- Principal Investigator decision
- Sponsor decision
- Protocol deviation
- Other

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

Subjects who discontinue participation in the study for any reason after dosing will not be replaced. The sample size was estimated to account for an assumed discontinuation rate of 15% by Week 8.

11. STATISTICAL METHODS

11.1. Introduction

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP may appropriately modify the analyses specified in the protocol, as necessary.

11.2. Analysis Sets

The all enrolled set will include all subjects who sign an informed consent form.

The full analysis set (FAS) includes all randomized subjects, and they will be included in the group to which they were randomized.

The per-protocol analysis set (PP) includes all subjects in the full analysis set that provide TFI data at Weeks 4 and 8, and do not have any protocol deviations that may impact the outcome of the TFI overall score.

The safety analysis set includes all subjects who receive study treatment, and they will be included in the treatment group based on the treatment received.

The FAS and PP sets will be used for efficacy analyses. The safety analysis set will be used for all safety analyses.

11.3. Study Endpoints

11.3.1. Efficacy Endpoints

The primary endpoint for this study is the percentage of subjects achieving response, where response is defined as achieving at least a 13-point reduction from baseline in the TFI overall score at both Weeks 4 and 8.

Secondary endpoints include the following:

- Change from Baseline in the NRS ratings of tinnitus annoyance
- Change from Baseline in the NRS ratings of tinnitus loudness
- Change from Baseline in TFI total score
- Change from baseline in TFI subscale scores (Intrusiveness, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, Quality of Life, Emotional)
- PGIC score

- Change from Baseline in SF-12 scores

11.3.2. Safety Endpoints

The safety endpoints include:

- Incidence of treatment-emergent adverse events
- Change from Baseline in tympanometry
- Change from Baseline in otoscopy
- Change from Baseline in audiometry
- Change from Baseline in suicidal ideation or behavior
- Incidence of concomitant medications
- Change from Baseline in vital signs and weight

11.4. Statistical Analyses

11.4.1. General

There will be two sets of analyses. The Primary analyses will be conducted after all subjects complete Week 8 of the study, with all planned analyses to be conducted with all data collected in the database at time of database freeze. There will be a final analysis conducted once all subjects complete Week 16 of the study, to include all data collected from all subjects across all time points.

All data collected will be summarized descriptively. Descriptive statistics for continuous data are number of subjects, mean, standard deviation, median, minimum, and maximum values. Descriptive statistics for categorical variables will include number of observations and percentages.

11.4.2. Efficacy Analyses

All efficacy endpoints will be summarized descriptively and analyzed using FAS. The primary endpoint will also be summarized descriptively and analyzed using PP.

11.4.2.1. Primary Analyses

The primary endpoint is the percent of responders at Week 8, where subjects will be classified as responders if they achieve at least a 13-point reduction from baseline in the TFI overall score at both Weeks 4 and 8. The primary endpoint will be summarized descriptively by treatment group. The percentage of responders will be analyzed using the common risk difference between treatment groups and will be tested using a Mantel-Haenszel test controlling for study site, duration of tinnitus, and baseline TFI overall score. Specifically, comparison between OTO-313 and placebo will be made by testing the following hypothesis:

H_0: $P_{OTO\text{-}313} = P_{Placebo}$ vs H_A: $P_{OTO\text{-}313} \neq P_{Placebo}$

The primary analysis will be conducted for the comparison of OTO-313 and placebo, using a 2-sided test and an alpha level of 5%. The 95% confidence intervals (CI) around the common risk difference will also be provided.

Missing data for the primary endpoint will be imputed using a multiple imputation technique that will be described in detail in the SAP.

11.4.2.2. Secondary Analyses

Secondary endpoints of the change from baseline in NRS Annoyance score, NRS Loudness score, TFI overall score, TFI subscale scores, PGIC, and SF-12 will be summarized descriptively by treatment group and visit.

There will be no adjustment of multiplicity across secondary endpoints.

11.4.2.2.1. Additional Responder Analyses

The following additional responder definitions will also be derived for Weeks 12 and 16:

- Week 12 responder #1: achieving at least a 13-point reduction from baseline in the TFI overall score at Weeks 8 and 12
- Week 12 responder #2: achieving at least a 13-point reduction from baseline in the TFI overall score at Weeks 4, 8, and 12
- Week 16 responder #1: achieving at least a 13-point reduction from baseline in the TFI overall score at Weeks 12 and 16
- Week 16 responder #2: achieving at least a 13-point reduction from baseline in the TFI overall score at Weeks 8, 12, and 16
- Week 16 responder #3: achieving at least a 13-point reduction from baseline in the TFI overall score at Weeks 4, 8, 12 and 16

These additional responder secondary endpoints will be analyzed in the same manner as the primary analysis as described in Section 11.4.2.1.

11.4.2.2.2. Continuous Endpoint Analyses

The change from baseline in NRS Loudness, NRS Annoyance, TFI Total score, each TFI subscale score, and SF-12 will each be analyzed using a linear mixed-effects model with treatment, study day, treatment-by-study day interaction, study site, baseline TFI overall score, and duration of tinnitus as fixed effects. The unstructured covariance model will be used. Least-square adjusted means, the estimated difference in adjusted means between treatment groups and associated 95% CIs will be provided.

11.4.2.2.3. Categorical Endpoint Analyses

The results of the PGIC will be analyzed using a Cochrane-Mantel-Haenszel mean score test controlling for study site, baseline TFI score, and duration of tinnitus. This will be done to compare OTO-313 with placebo.

11.4.3. Safety Analyses

All safety endpoints will be summarized descriptively using the safety analysis set. If descriptive summaries warrant further exploration of comparisons between treatment groups, then additional safety analyses may be conducted in an *ad hoc* manner.

11.4.3.1. Adverse Events

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.

11.4.3.2. Tympanometry, Otoscopic, and Audiometry

The tympanometry category (A, B-small volume and/or normal, B-large volume, or C) will be summarized by treatment group and study visit.

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. Presence and absence of tympanic membrane perforations will be summarized by treatment group and study visit; the size of any tympanic membrane perforation will be classified as follows: pinhole; ≤25% of tympanic membrane; 25% to ≤50% of tympanic membrane; >50% of tympanic membrane.

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.

11.4.3.3. 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 using a shift table for interpretation of changes in C-SSRS results between baseline and post-baseline assessments. All C-SSRS data will be included in data listings.

11.4.4. Concomitant Medications

Incidence of concomitant medications of interest will be provided for each treatment group. The list of concomitant medications of interest will be provided in the SAP.

11.4.5. Laboratory Parameters, Vital Signs and Weight

The analysis of laboratory parameters and vital signs 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. Sample Size

The primary endpoint is the percentage of responders, where response is defined as achieving at least a 13-point reduction from baseline in the TFI total score at both Weeks 4 and 8. It was observed from the previous study (Study 313-201901) that the response rate for OTO-313 (0.32 mg) was 43% and 13% for placebo. Based on these results, the assumed rate of response for OTO-313 is 43% and 18% for placebo, which is the 13% observed response rate in previous study plus 5% inflation for potential placebo response.

Assuming a 2-sided test and level of significance of 0.05, 60 subjects in the placebo arm and 60 subjects in each of the OTO-313 arms will provide approximately 85% power to detect a treatment difference in favor of OTO-313. It is also assumed that an observed discontinuation rate of 15% will be observed, hence the total sample size is planned to be 140 subjects, 70 subjects per arm. These sample size calculations were conducted using EASTv6.5 software with a test for a difference in proportions between two groups.

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 a 1 mL sterile solution of 100% medium-chain triglycerides 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 the IRT system; instructions will be provided to all sites. The IRT 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 IRT and sent to the clinical supply vendor. 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 in accordance with instructions on the investigational product label. 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 IRT 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. 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. Activities assigned to the Investigator may be delegated by the Investigator to staff qualified by education, training, and experience. Delegation should be documented in the delegation log.

13.2. Institutional Review Board (IRB) and Ethics Committee (EC)

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

The IRB or EC 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 or EC 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 or EC. 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 or EC 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 or EC 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 or EC 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 efficacy and safety data recorded in the EDC system.

14.5. Termination

Closure of a center or study termination can be initiated at any time by the Sponsor, 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 (study-wide or specific to a center)
- 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 or EC in accordance with the IRB or EC 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, IRBs, ECs as appropriate.

14.6.1. Safety Review Committee

An independent Safety Review Committee will review accumulated individual safety data for the first 25% (35 subjects), 50% (70 subjects), and 75% (105 subjects) of subjects randomized and who have post-administration safety data. Blinded safety data including adverse events, concomitant medications, medical history, clinical safety laboratory measurements, audiometry, otoscopy, tympanometry, and C-SSRS data will be reviewed. 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. The decision to continue with the study will be based recommendations from the Safety Review Committee on the clinical significance of any adverse events or suspected investigational product-related or procedure-related findings. Additional information on the Safety Data Review and composition of the independent Safety Review Committee is provided in the Safety Review Committee Charter.

14.7. Monitoring

The Sponsor or its representatives will perform monitoring visits (on-site and/or remote as permitted by local regulations) 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.

Prior to site screening of the initial subject, site-specific source documents will be compared to the eCRF, and any findings will be discussed with the Investigator.

At all visits, the monitor will compare the data entered onto the eCRFs with the hospital or clinic records (source documents) in accordance with the Clinical Monitoring Plan. 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. 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 or designee 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

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