CLINICAL STUDY PROTOCOL

A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 3 EFFICACY AND SAFETY STUDY OF OTO-104 GIVEN AS A SINGLE INTRATYMPANIC INJECTION IN SUBJECTS WITH UNILATERAL MENIERE'S DISEASE

Protocol Number: 104-201508
EudraCT Number: 2015-004496-71

Sponsor Contact: 

Medical Monitor: 

Version:	3.0
Date of Protocol:	13 January 2016
Proprietary Notice	The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Otonomy, Inc.

A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 3 EFFICACY AND SAFETY STUDY OF OTO-104 GIVEN AS A SINGLE INTRATYMPANIC INJECTION IN SUBJECTS WITH UNILATERAL MENIERE'S DISEASE

APPROVED BY:

[redacted]

MEDICAL MONITOR:

I acknowledge that I have read and understood this protocol.

[redacted]

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PROTOCOL AMENDMENT, VERSION 3.0

This protocol amendment serves to make the following changes.

Item No.	Change	Section and Page Number
1	Updated date and version of protocol.	Title page, pg. 1 Footer, every page
2	Added additional exclusion criteria to hypersensitivity to dexamethasone or any of the OTO-104 excipients.	Synopsis, pg. 12 Section 4.3 Exclusion Criteria, pg. 20
3	Modified Section 1.1, Study Rationale to include rationale for dose selection.	Section 1.1 Rationale for Study and Dose Selection, pg. 18
4	Modified statement regarding contacting the medical monitor if an unblinding has occurred.	Section 5.3 Blinding, pg. 22
5	Safety reporting changed to ProPharma from INC.	Sponsor Contact Information, pg. 7 Section 9.3 Contacting Sponsor Regarding Safety, pg. 34

SPONSOR CONTACT INFORMATION

Medical Monitor:

Name	[redacted]
Title	[redacted]
Office Phone Number	[redacted]
Mobile Phone Number	[redacted]
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Other Appropriate Trial Contact Personnel:

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

Safety Email: [redacted]

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

INVESTIGATOR AGREEMENT

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

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

I will use only the informed consent form approved by the sponsor or its representative and approved by the Research Ethics Committee (REC) responsible for this study and will fulfill all responsibilities for submitting pertinent information to the REC responsible for this study. I will assure that each subject enrolled into the trial, 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 trial.

I further agree not to originate or use the name of the Otonomy, Inc. and/or OTO-104, 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 Otonomy, Inc.

Investigator's Signature	Date

Name of Investigator *(typed or printed)*

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery
C	Celsius
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DVD	Definitive Vertigo Day
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FAX	Facsimile
GCP	Good Clinical Practice
Hz	Hertz
ICH	International Conference on Harmonization
IT	Intratympanic
ITT	Intent to Treat
IVRS/IWRS	Interactive Voice/Web Randomization System
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
OTO-104	Investigational Product (Study Drug)
PTA	Pure Tone Average
QMP	Qualified Medical Professional
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF	Short Form
SOC	System Organ Class
TFI	Tinnitus Functional Index
VF	Vertigo Frequency
WHO Drug	World Health Organization Drug Dictionary

SYNOPSIS

NAME OF SPONSOR/COMPANY:	Otonomy, Inc.
NAME OF FINISHED PRODUCT:	OTO-104
NAME OF ACTIVE INGREDIENT(S):	Dexamethasone

Protocol No.: 104-201508

Title of Study: A prospective, randomized, double blind, placebo-controlled, multicenter, Phase 3 efficacy and safety study of OTO-104 given as a single intratympanic injection in subjects with unilateral Meniere's disease.

Study Center(s): This study will be conducted at approximately 50-70 sites in up to five countries in the European Union, including United Kingdom, Germany and Poland.

Study Period: 1-1.5 years | **Phase of Development:** 3

Study Design:

This is a randomized, double blind, placebo-controlled, multicenter 16-week Phase 3 study. Following an initial 4-week lead-in period, eligible subjects will be randomly assigned to either 12 mg OTO-104 or placebo using a 1:1 allocation ratio stratified by gender. Subjects will be observed for 12 weeks following a single intratympanic injection of either 12 mg OTO-104 or placebo.

Study Objectives:

Primary: To confirm the efficacy of OTO-104 in subjects with Meniere's disease, as measured by the number of definitive vertigo days (DVD) at Week 12 (the 4-week interval from Week 9 through Week 12).

Secondary: To describe the safety profile of OTO-104 in subjects with Meniere's disease.

Methods:

The duration of the study for each subject will be a maximum of approximately 16 weeks, including a 4-week lead-in period before dosing (a single injection), followed by a 12-week follow-up period.

After screening (Visit 1), all eligible subjects will enter into a 4-week lead-in period. During the lead-in period, subjects will record their daily vertigo experience to allow for a baseline assessment of these events. Any day with a recorded definitive vertigo episode, an episode lasting at least 20 minutes (corresponding to a Vertigo Severity Score of 2 or more), will be defined as a definitive vertigo day (DVD). Following the lead-in period, eligible subjects will be randomized to 12 mg OTO-104 or placebo using a 1:1 allocation ratio. The randomization is stratified by gender.

After a single intratympanic injection with OTO-104 or placebo on Day 1, subjects will continue to record their daily vertigo experience during the 12-week follow-up period. Subjects will visit the study site at Weeks 4 and 8 for additional efficacy and safety assessments. Efficacy and safety assessments will also be completed at the end of study (Week 12) or upon early discontinuation from the study.

Number of Subjects:

The planned sample size for this study is 160 subjects (80 assigned to 12 mg OTO-104 and 80 to placebo).

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in the study will have unilateral Meniere's disease as outlined by the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium in 1995 (Committee on Hearing and Equilibrium, 1995).

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 85 years, inclusive.

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2. Subject has a diagnosis of definite unilateral Meniere's disease by 1995 AAO-HNS criteria.
3. Subject self-reports active, definitive vertigo episodes for the 2 months prior to the study lead-in period.
4. Subject has documented asymmetric sensorineural hearing loss at screening or within the past 12 months according to AAO-HNS 1995 criteria defined as one of the following:
    a. The arithmetic mean of hearing thresholds (pure tone average, PTA) at 250, 500 and 1000 Hz of 15 dB or more higher than the PTA of 1000, 2000, and 3000 Hz,
    b. The arithmetic mean of PTA at 500, 1000, 2000 and 3000 Hz is 20 dB or more poorer in the ear in question than on the opposite side,
    c. It is the judgment of the investigator that the subject's hearing loss meets reasonable audiometric criteria for hearing loss characteristic of Meniere's disease, and if so, it should be justified and documented.
5. Subject agrees to maintain their current treatments for Meniere's disease while on-study.
6. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal (≥12 months since last menstrual period and 45 years of age or older)] must have a negative urine pregnancy test before enrollment. Women of childbearing potential who are not abstinent from sex with male partners may be entered into the study if they are using and willing to continue to use highly effective or "double barrier" contraceptive precautions for the duration of the study (e.g., oral contraceptives, contraceptive implant or injection, intrauterine device, or "double barrier" methods including condom with diaphragm, male condom with cervical cap, male condom with spermicide, or diaphragm and spermicide).
7. Subject is willing to comply with the protocol and attend all study visits.
8. Subject is able to use the telephone to complete their daily diary.
9. Subject is able to provide written informed consent, including agreement to local privacy language requirements either within the informed consent or in ancillary documents compliant with local privacy laws before the initiation of any study-related procedures.

At the completion of the first 28 days of the lead-in period:

10. Subject has experienced and recorded at least 4 and a maximum of 22 definitive vertigo days during the 4-week lead-in period.
11. Subject completed at least 22 of 28 diary entries during the 4-week lead-in period.

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 an infection in the ear, sinuses, or upper respiratory system at the time of randomization.
2. Subject is pregnant or lactating.
3. Subject has a history of immunodeficiency disease.
4. Subject has active or recent (<1 month prior to screening) middle ear disease, including but not limited to: chronic otitis media, acute otitis media, middle ear effusions, middle ear atelectasis, or cholesteatoma.
5. Subject has an abnormality of the tympanic membrane in the affected ear that would increase the risk associated with intratympanic injection including but not limited to monomeric tympanic membrane.

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6. Subject has a history of previous endolymphatic sac surgery.
7. Subject has a history of previous use of intratympanic gentamicin in the affected ear.
8. Subject has a history of tympanostomy tubes with evidence of perforation or lack of closure.
9. Subject has used systemic steroids within 1 month prior to entering the lead-in period.
10. Subject has had intratympanic steroids within 1 month prior to entering the lean-in period.
11. Subject has experienced an adverse reaction to intratympanic injection of steroids.
12. Subject has a hypersensitivity to dexamethasone or any of the excipients in OTO-104.
13. Subject has history of migrainous vertigo.
14. Subject has history of drop attacks.
15. Subject is not able to accurately identify and report episodes of vertigo.
16. Subject has any other clinically significant illness, medical condition or medical history that, in the investigator's or the medical monitor's opinion, would prohibit the subject from participating in the study at screening or at the time of randomization.
17. Subject has used an investigational drug or device in the 3 months prior to screening.
18. Subject has a history of substance abuse within the preceding 6 months prior to screening.
19. Subject has previously been randomized to a trial of OTO-104.

Test Product, Dose and Mode of Administration:

12 mg OTO-104, single 0.2 mL intratympanic injection to the affected ear

Duration of Treatment:

Single 0.2 mL intratympanic injection to the affected ear

Reference Therapy, Dose and Mode of Administration:

OTO-104 Diluent (placebo), single 0.2 mL intratympanic injection to the affected ear

Outcome Measures for Evaluation:

Primary Efficacy Endpoint:

The primary efficacy endpoint is the number of definitive vertigo days (DVD) at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]. A DVD is defined as a day where the subject recorded at least one vertigo episode lasting at least 20 minutes and corresponds to a Vertigo Severity Score of 2 or more. If multiple episodes occur on a given day, subjects will be instructed to record the Vertigo Severity Score for the worst episode experienced during the day.

Secondary Efficacy Endpoints:

- The number of definitive vertigo days (DVD) at Week 8 [the 4-week (28-day) interval from Week 5 through Week 8]
- The number of definitive vertigo days (DVD) at Week 4 [the 4-week (28-day) interval from Week 1 through Week 4]
- The change from baseline in vertigo frequency (VF) during the 4-week study interval (Week 9 through Week 12), where vertigo frequency is defined as the proportion of days during the 4-week interval where a definitive vertigo episode was recorded divided by the number of non-missing diary entries for the relevant interval

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- The change from baseline with respect to severity of vertigo episodes as measured by the mean Vertigo Score during the 4-week study interval (Week 9 through Week 12)
- The change from baseline in average daily count of vertigo episodes, during the 4-week study interval (Week 9 through Week 12)
- Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bed ridden events as a consequence of vertigo at Week 12
- SF-36 at Week 12
    - Physical Health Summary Measure
    - Mental Health Summary Measure
    - 8 Scales

Exploratory Efficacy Endpoints:

- The change from baseline in vertigo frequency (VF) during the 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8), where vertigo frequency is defined as the proportion of days during the 4-week interval where a definitive vertigo episode was recorded divided by the number of non-missing diary entries for the relevant interval
- The change from baseline with respect to severity of vertigo episodes as measured by the mean Vertigo Score during each 4-week study interval (Week 1 through Week 4) and (Week 5 through 8).
- The change from baseline in average daily count of vertigo episodes, during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)
- Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bed ridden events as a consequence of vertigo at Week 4 and 8
- SF-36 at Weeks 4 and 8
    - Physical Health Summary Measure
    - Mental Health Summary Measure
    - 8 Scales
- Tinnitus Functional Index (TFI) at Weeks 4, 8, and 12

Safety Assessments:

Safety assessments include:

- Adverse events
- Audiometry assessments
- Tympanometry
- Local tolerability (otoscopic examinations)
- Clinical laboratory measurements
- Vital sign measurements
- Columbia-Suicide Severity Rating Scale (C-SSRS): Baseline and Since Last Visit versions

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Statistical Methods:

The primary efficacy endpoint is the number of DVD at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]. The target total sample size for the study is 160 randomized with1:1 allocation, 80 in each treatment group, stratified by gender. The sample size estimate was chosen to achieve more than 90% power with significance level of 0.05 two-sided to reject the null hypothesis of no treatment difference for the primary endpoint of DVD.

The power estimate was based on the estimated treatment group means for DVD at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12] from the recently completed Phase 2b trial in this indication. The OTO-104 and placebo treatment groups in that study received a single dose of the study drug at Day 1. The OTO-104 treatment group received the same dose as will be evaluated in this Phase 3 study. A Poisson generalized linear regression model was used to estimate the mean number of DVDs for the OTO-104 and placebo groups during the primary endpoint 4-week study interval. The model included treatment group as a factor (categorical), and the lead-in period as a covariate. An offset for the number of diary entries recorded for that 4-week interval (interval from Week 9 through 12) was included for each subject to account for missing diary entries. The number of lead-in period DVD was adjusted to 28 days. The model was also adjusted for over-dispersion using Pearson residuals as the scale factor. The estimated mean number of DVD for the OTO-104 and placebo groups were 4.5 and 2.1, respectively with an estimated mean difference of (active – placebo) -2.4 days, adjusted for lead-in period number of DVD. The model residual variance was 4.79. For the purpose of the sample size calculation the residual variance and true mean difference was considered as 5.0 and 2.2, respectively.

The Poisson regression model will be used to analyze the primary endpoint in this study. The primary analysis population for this study is full analysis set (FAS). The full analysis set will include all subjects who are randomized, receive study drug, have a baseline DVD measurement for the 4-week lead-in period, and have at least one 4-week DVD measurement post-baseline.

In the primary efficacy analysis if a subject misses all diary data for the primary endpoint then an imputation method which will be specified in the Statistical Analysis Plan (SAP) will used. .

Subjects will be included in the treatment group to which they were randomized regardless of the actual study drug received.

If the primary endpoint comparison between the two treatment groups is statistically significant in favor of OTO-104 then a closed testing, gate-keeping procedure, will be used to compare the following secondary efficacy endpoints sequentially:

1. The number of DVD at Week 8 [the 4-week (28-day) interval from Week 5 through Week 8]
2. The number of DVD at Week 4 [the 4-week (28-day) interval from Week 1 through Week 4]

In this procedure if the first secondary endpoint comparison between the two treatment groups is statistically significant in favor of OTO-104 then the second secondary endpoint will be compared and tested. If the comparison of the first secondary endpoint is not statistically significant in favor of OTO-104 then the reported p-value for the second secondary endpoint will be considered as a nominal p-value.

The remaining secondary endpoints comparison will not go through the gate keeping procedure and therefore the reported p-values will be reported as nominal p-values. This procedure controls the study-wise Type I error. Since the study-wise error is maintained with the above procedure, there is no α penalty associated with it. All efficacy hypothesis tests will be 2-sided and performed at $\alpha = 0.05$ significance level.

Time and Events Schedule: See Table 1.

Table 1: Time and Events Schedule

Procedure	Screening	Lead-In	Baseline[1] / Treatment Visit	Follow-up Visit	Follow-up Visit	End-of-Study/ Early Termination	Unscheduled Visit
	Visit 1	–	Visit 2	Visit 3	Visit 4	Visit 5[2]	Unscheduled
	–	–	–	Week 4	Week 8	Week 12	N/A
	Up to 14 days prior to start of lead-in	Day -28 to -1 (+3 days)	Day 1	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (+4 days)	N/A
Informed consent (including privacy language/documents)	X						
Eligibility criteria	X	X[3]	X				
Medical history[4]	X		X				
Concomitant medications	X		X	X	X	X	X
Vital sign measurements[5]	X		X	X	X	X	X
Height and weight measurements	X					X[6]	
Pregnancy test[7]	X		X			X	
Clinical laboratory test[8]	X		X			X	X as indicated
Tympanometry	X		X	X	X	X	X as indicated
Audiometry	X		X	X	X	X	X as indicated
Otoscopy	X		X	X	X	X	X
TFI-25			X	X	X	X	
SF-36 assessment			X	X	X	X	
C-SSRS assessment[9]	X		X	X	X	X	X
Review subject IVRS diary compliance and instruct subject on IVRS diary use[10]	X		X	X	X		
Randomization[11,12]			X				

Procedure	Screening	Lead-In	Baseline[1] / Treatment Visit	Follow-up Visit	Follow-up Visit	End-of-Study/ Early Termination	Unscheduled Visit
	Visit 1	–	Visit 2	Visit 3	Visit 4	Visit 5[2]	Unscheduled
	–	–	–	Week 4	Week 8	Week 12	N/A
	Up to 14 days prior to start of lead-in	Day -28 to -1 (+3 days)	Day 1	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (+4 days)	N/A
Administer study drug			X				
Adverse event monitoring			X	X	X	X	X

[1] Baseline assessments on Day 1 are to be performed before administration of study drug shown. Review eligibility criteria at the baseline visit to ensure subjects remain eligible following the lead-in period.

[2] Procedures scheduled for Visit 5 will be performed at the end of the follow-up period (+4 days) or upon early discontinuation from the study.

[3] Once the subject has met the inclusion/exclusion criteria as appropriate at screening, the subject will enter a 4-week lead-in period. During the lead-in, the subject will record their daily vertigo experience. A determination of whether the subject meets Inclusion Criteria No. 10 and 11 will be determined 28 days after subjects enter the lead-in period.

[4] Medical history to include information on demographics.

[5] Vital sign measurements include blood pressure and pulse rate.

[6] Only weight is to be measured at Visit 5.

[7] Female subjects of childbearing potential will have a serum pregnancy test at screening and a urine pregnancy test at baseline, prior to randomization. If the screening or baseline pregnancy test result is positive, the subject is not eligible for enrollment into the study. If a subject is found to be pregnant after dosing with study drug, they will complete the follow-up period. All serum pregnancy tests will be analyzed by a central laboratory. Serum pregnancy test results from Visit 1 as well as the urine pregnancy test at baseline prior to randomization must be included in eligibility assessment at Visit 2.

[8] Clinical laboratory tests include hematology, clinical chemistry, and urinalysis and will be analyzed by a central laboratory.

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

[10] Subjects will be instructed and trained how to record daily vertigo experience using the IVRS diary.

[11] A subject is considered randomized when a randomization number has been assigned by IWRS. Randomization must occur prior to administration of study drug. Study sites log in to the IWRS to execute each randomization after a subject has met all prerequisites for randomization and has completed all scheduled procedures for Day 1.

[,12] Subjects will be randomized using laboratory results from Visit 1; laboratory results from Visit 2 are not required for randomization.

1. BACKGROUND

Meniere's disease is an idiopathic syndrome of endolymphatic hydrops (Committee on Hearing and Equilibrium, 1995). It is associated with a distinct pattern of clinical symptoms comprised of vertigo, hearing loss, tinnitus and aural fullness. It is more frequently unilateral than bilateral. Episodic vertigo is considered the most prominent symptom, with episodes typically lasting at least 20 minutes and resulting in significant patient morbidity. The diagnosis is primarily a clinical one, since there are no specific diagnostic tests for Meniere's disease. The disease is known to wax and wane, but eventually results in irreversible sensorineural hearing loss at all frequencies in the affected ear. While the pathogenesis of Meniere's disease has not been elucidated, one well-accepted mechanism involves the dysregulation of labyrinth fluid volume/ion balance resulting in endolymphatic hydrops (Shea, 1993). The increase in fluid volume and consequent increased labyrinth pressure may then be expressed as the Meniere's spectrum of symptoms.

There is no cure for Meniere's disease. Treatment tends to focus on relieving the vertigo symptoms, where it is hypothesized that reducing inner ear fluid volume will relieve the hydrops and associated clinical picture. It is for this reason that many subjects are initially started on low salt diets and diuretics (Barritt, 2008). A number of medical systemic treatments are also used to relieve Meniere's disease symptoms, including but not limited to antihistamines, anticholinergics, phenothiazines, benzodiazepines, and corticosteroids; however, these interventions are often inadequate in relieving the symptoms of Meniere's disease. A device that generates low-pressure pulses, the Meniett® device, is indicated for the symptomatic treatment of Meniere's disease. However, the device is not widely used and is not currently considered standard of care (Kim et al, 2005). Surgical decompression may be attempted in severe cases unresponsive to medical intervention, but surgical outcomes are frequently unsatisfactory. Finally, patients with unresponsive disease may undergo chemical or surgical neuroablation, resulting in symptom relief at the cost of destruction of the 8th cranial nerve. Thus, there continues to be an unmet medical need for therapies to address this debilitating disease.

OTO-104 is a suspension of dexamethasone in a buffered solution [redacted] Otonomy has formulated dexamethasone, a [redacted] for the purpose of studying the potential benefits of intratympanic (IT) injections of OTO-104 in subjects with Meniere's disease. Single and repeat-dose nonclinical safety studies in guinea pigs, rats and cats have been conducted to support clinical development. Special emphasis in the toxicology studies has been placed on the effects of OTO-104 and [redacted] vehicle control on middle and inner ear compartments, where both functional and histological assessments have been conducted. Additionally, pharmacokinetic assessments have been conducted in guinea pigs, rats, cats, and sheep that provide a complete profile of exposure of OTO-104 to the inner ear compartment, as well as systemic exposure.

1.1. Rationale for Study and Dose Selection

Otonomy has completed 2 placebo-controlled, double-blind, multi-center clinical studies with OTO-104 in Meniere's disease: a Phase 1b study, 104-200901, and a Phase 2b study, 104-201102. The Phase 1b study demonstrated that a single intratympanic injection of OTO-104 at doses of 3 mg or 12 mg was safe and well tolerated in subjects with Meniere's disease. In the exploratory Phase 1b study, the trends in the data suggest treatment with 12 mg OTO-104 is associated with a clinically meaningful reduction in vertigo frequency at 3 months after treatment compared to 3 mg OTO-104 or placebo. The Phase 2b study therefore randomized 154 subjects with unilateral Meniere's disease to treatment with 12 mg OTO-104 or placebo. This study demonstrated improvement in number of definitive vertigo days compared to the lead-in period with a single IT injection of OTO-104 compared to placebo during the Week 12 interval with a smaller improvement observed at Week 16. Therefore, the final dose selected and primary observation point for this study is 12 mg OTO-104 and the Week 12 interval, respectively.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is to confirm the efficacy of OTO-104 in subjects with Meniere's disease, as measured by the number of definitive vertigo days (DVD) at Week 12 (the 4-week interval from Week 9 through Week 12).

2.2. Secondary Objective

The secondary objective is to describe the safety profile of OTO-104 in subjects with Meniere's disease.

3. OVERVIEW OF STUDY DESIGN

This is a randomized, double blind, placebo-controlled, multicenter 16-week Phase 3 study. Following an initial 4-week lead-in period, eligible subjects will be randomly assigned to either 12 mg OTO-104 or placebo using a 1:1 allocation ratio stratified by gender. Subjects will be observed for 12 weeks following a single intratympanic injection of either 12 mg OTO-104 or placebo.

The duration of the study for each subject will be a maximum of approximately 16 weeks, including a 4-week lead-in period before dosing (a single injection), followed by a 12-week follow-up period.

After screening (Visit 1), all eligible subjects will enter into a 4-week lead-in period. During the lead-in period, subjects will record their daily vertigo experience to allow for a baseline assessment of these events. Any day with a recorded definitive vertigo episode, an episode lasting at least 20 minutes (corresponding to a Vertigo Severity Score of 2 or more), will be defined as a definitive vertigo day (DVD). Following the lead-in period, eligible subjects will be randomized to 12 mg OTO-104 or placebo using a 1:1 allocation ratio.

After a single intratympanic injection with OTO-104 or placebo on Day 1, subjects will continue to record their daily vertigo experience during the 12-week follow-up period. Subjects will visit the study site at Weeks 4 and 8 for additional efficacy and safety assessments. Efficacy and safety assessments will also be completed at the end of study (Week 12) or upon early discontinuation from the study.

4. STUDY POPULATION

4.1. General Considerations

Approximately 160 subjects will be enrolled at 50-70 sites in up to five countries in the European Union, including United Kingdom, Germany and Poland. Subjects will be randomized only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.2. Inclusion Criteria

Subjects enrolled in the study will have unilateral Meniere's disease as outlined by the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium in 1995 (Committee on Hearing and Equilibrium, 1995).

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 85 years, inclusive.
2. Subject has a diagnosis of definite unilateral Meniere's disease by 1995 AAO-HNS criteria.
3. Subject self-reports active, definitive vertigo episodes for the 2 months prior to the study lead-in period.
4. Subject has documented asymmetric sensorineural hearing loss at screening or within the past 12 months according to AAO-HNS 1995 criteria defined as one of the following:
    a. The arithmetic mean of hearing thresholds (pure tone average, PTA) at 250, 500 and 1000 Hz of 15 dB or more higher than the PTA of 1000, 2000, and 3000 Hz,
    b. The arithmetic mean of PTA at 500, 1000, 2000 and 3000 Hz is 20 dB or more poorer in the ear in question than on the opposite side,
    c. It is the judgment of the investigator that the subject's hearing loss meets reasonable audiometric criteria for hearing loss characteristic of Meniere's disease, and if so, it should be justified and documented.
5. Subject agrees to maintain their current treatments for Meniere's disease while on-study.
6. Female subjects of childbearing potential [i.e., not surgically sterile and/or not post-menopausal (≥12 months since last menstrual period and 45 years of age or older)] must have a negative urine pregnancy test before randomization. Women of childbearing potential who are not abstinent from sex with male partners may be entered into the study if they are using and willing to continue to use highly effective or "double barrier" contraceptive precautions for the duration of the study (e.g., oral contraceptives,

contraceptive implant or injection, intrauterine device, "double barrier" methods including male condom with diaphragm, male condom with cervical cap, male condom with spermicide, or diaphragm and spermicide).

7. Subject is willing to comply with the protocol and attend all study visits.
8. Subject is able to use the telephone to complete their daily diary.
9. Subject is able to provide written informed consent, including agreement to local privacy language requirements either within the informed consent or in ancillary documents compliant with local privacy laws before the initiation of any study-related procedures.

At the completion of the first 28 days of the lead-in period:

10. Subject has experienced and recorded at least 4 and a maximum of 22 definitive vertigo days during the 4-week lead-in period.
11. Subject completed at least 22 of 28 diary entries during the 4-week lead-in period.

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 an infection in the ear, sinuses, or upper respiratory system at the time of randomization.
2. Subject is pregnant or lactating.
3. Subject has a history of immunodeficiency disease.
4. Subject has active or recent (<1 month prior to screening) middle ear disease, including but not limited to: chronic otitis media, acute otitis media, middle ear effusions, middle ear atelectasis, or cholesteatoma.
5. Subject has an abnormality of the tympanic membrane in the affected ear that would increase the risk associated with intratympanic injection including but not limited to monomeric tympanic membrane.
6. Subject has a history of previous endolymphatic sac surgery.
7. Subject has a history of previous use of intratympanic gentamicin in the affected ear.
8. Subject has a history of tympanostomy tubes with evidence of perforation or lack of closure.
9. Subject has used systemic steroids within 1 month prior to entering the lead-in period.
10. Subject has had intratympanic steroids within 1 month prior to entering the lead-in period.
11. Subject has experienced an adverse reaction to intratympanic injection of steroids.
12. Subject has a hypersensitivity to dexamethasone or any of the excipients in OTO-104.
13. Subject has history of migrainous vertigo.

14. Subject has history of drop attacks.
15. Subject is not able to accurately identify and report episodes of vertigo.
16. Subject has any other clinically significant illness, medical condition, or medical history that, in the investigator's or the medical monitor's opinion, would prohibit the subject from participating in the study at screening or at the time of randomization.
17. Subject has used an investigational drug or device in the 3 months prior to screening.
18. Subject has a history of substance abuse within the preceding 6 months prior to screening.
19. Subject has previously been randomized to a trial of OTO-104.

5. RANDOMIZATION AND BLINDING

5.1. Overview

At the conclusion of the screening/lead-in period, eligible subjects will be randomly assigned to either OTO-104 or placebo in a 1:1 allocation ratio, stratified by gender, based on a computer-generated randomization schedule.

- 12 mg OTO-104; single, intratympanic injection
- Placebo; single, intratympanic injection

5.2. Enrollment Procedures

5.2.1. Assignment of Subject Identification Numbers

At the screening visit, Visit 1, subjects signing the informed consent will be assigned a unique subject identification number via the Electronic Data Capture system (EDC). 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.

5.2.2. Treatment Assignment

Study sites will log in to the IWRS to execute each randomization after a subject has met all prerequisites for randomization and has completed all scheduled procedures for Day 1 (Visit 2). Study site personnel, who are blinded to treatment assignment, will receive a randomization notification indicating the kit number (packaged study drug), and the date and time of randomization for each subject. Once assigned, kit numbers cannot be re-assigned. Subjects will be considered enrolled into the study once they are randomized and assigned a unique randomization number.

Study sites will provide the information contained in the IWRS randomization notification to the unblinded qualified medical professional (QMP) responsible for preparation of the syringe containing study drug. The unique kit number provided by the IWRS will correspond to a kit of packaged study drug labeled with the identical kit number. The QMP will prepare the syringe

from the contents of the study drug package corresponding to the IWRS kit number according to the instructions in the study Pharmacy Binder. The subject identification number and kit number must both be recorded in the subject's record.

5.2.3. Randomization Algorithm

Subjects will randomized in a 1:1 ratio treatment groups stratifying by gender using a permuted block randomization algorithm. The randomization process will be deployed via an internet-based IWRS which is accessible 24 hours a day to authorized users. The subject's randomization number will determine the randomized treatment assignment. Numbered kits will be dispensed by the qualified medical professional based on the treatment assignment. Study drug kits will be labeled with a unique kit number using a separate and independent randomization algorithm.

5.3. Blinding

The study will be double-blinded. To maintain the blind for site personnel involved in study assessments, the following procedures will be followed:

Treatment syringes will be pre-loaded by an unblinded QMP. Each syringe will be prepared according to the detailed instructions in the Pharmacy Binder in a manner that prevents visualization of syringe contents by all other study staff through the use of a syringe overlabel. In addition, any interaction with subjects with regard to the collection, review or discussion of study assessments, with the exception of otoscopic exams, will be done by the study coordinator, audiologist or someone other than the QMP who prepared the syringe and the physician who administered the intratympanic injection of study drug. Every effort should be made to ensure that otoscopic exams are conducted by the physician who administered the study drug or another physician involved in the study, but not responsible for other assessments for the specific subject. Physicians administering study drug and conducting the otoscopic exams will be instructed not to discuss any potential visual differences observed in study material with subjects or study staff.

The blind should be broken only if knowing the subject's treatment allocation would facilitate specific emergency treatment. The physician who administered the study drug is unblinded at the time of injection. If the physician who administered the study drug is not available or does not recollect the treatment administered, the investigator can access the unblinded drug accountability records completed and retained by the QMP when preparing OTO-104 or placebo. In all cases, the investigator must contact the medical monitor as soon as 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 Sponsor representatives until all subjects have completed the trial and the database has been finalized by Otonomy.

6. DOSAGE AND ADMINISTRATION

6.1. Study Drug Administration

OTO-104 12 mg will be administered as a single, 0.2 mL intratympanic injection of 60 mg/mL OTO-104. The recommended injection procedure for intratympanic administration of OTO-104 in Meniere's disease subjects is as follows:

1. Place the subject in a recumbent position with the treated ear upwards. Anesthetize the tympanic membrane by covering the external surface of the posterior inferior quadrant with topical lidocaine/prilocaine cream [redacted] until the tympanic membrane is numb. If applicable, suction away the topical lidocaine/prilocaine cream.
2. Using the 1 mL syringe pre-loaded with OTO-104 and equipped with a 25 or 26 gauge needle, insert the needle through the tympanic membrane with the bevel facing in an inferoposterior direction to a depth of approximately 2-3 mm just inferior to the round window niche, and with firm but gentle pressure, inject 0.2 mL taking care not to insert the needle further than necessary. Use of this technique will minimize the possibility of OTO-104 adhering to the underside of the tympanic membrane. Do not incise the tympanic membrane to form a ventilation hole as this is not needed due to the small injection volume.

6.2. Compliance

OTO-104 will be administered by site medical professionals as a single, intratympanic injection at Visit 2. Any deviations in administration will be documented in the source documents and the eCRF.

The site will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the trial.

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

7.1. Proscribed Therapy During the Study Period

The following therapies are prohibited during the study:

- Systemic corticosteroids
- Immunosuppressive medications
- Intratympanic injection other than that outlined in the current study

- Surgery for treatment of Meniere's disease
- Other investigational drug(s) or device(s)

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

7.2. Symptomatic Relief Medications

It is recognized that subjects may at times use certain medications for relief of symptoms related to Meniere's disease during the course of the study. Use of vestibular suppressants, anti-emetics and betahistine is allowed as symptomatic relief medications. The use of gentamicin or ear surgery at any time during the study will be considered a protocol deviation. Any changes reported by the subjects in concomitant medications should be recorded in the subject's eCRF.

8. STUDY EVALUATIONS

8.1. Study Procedures by Visit

8.1.1. Visit 1: Up to 14 days prior to initiation of lead-in period (Screening)

Because audiology, tympanometry and otoscopic exams are considered routine for this patient population, data obtained from assessments performed prior to documentation of informed consent can be used as screening data. In these cases, the data should have been collected within 14 days of initiation of the lead-in period.

The following assessments will be performed at Visit 1.

- Informed consent
- Confirm eligibility criteria
- Medical history
- Concomitant medications
- Vital signs
- Height and weight measurements
- Serum pregnancy test (for female subjects of childbearing potential only)
- Clinical laboratory test
- Tympanometry
- Audiometry
- Otoscopy
- C-SSRS assessment: Baseline version
- Review IVRS diary instructions with subject

8.1.2. Lead-In Period (Day -28 through -1 (+3 days))

The subject will record their daily vertigo experience during the entire lead-in period until randomization, ineligibility or withdrawal of consent. The determination of whether subjects meet Inclusion Criteria No. 10 and 11 will be conducted 28 days after initiation of the lead-in period.

8.1.3. Visit 2: Day 1 (Baseline/Dose Administration)

The following assessments will be performed at Visit 2.

- Confirm eligibility criteria
- Medical history
- Concomitant medications
- Vital signs
- Urine pregnancy test (for female subjects of childbearing potential only)
- Clinical laboratory test
- Tympanometry
- Audiometry
- Otoscopy
- TFI-25
- SF-36 Health Survey
- C-SSRS assessment, Since Last Visit version
- Randomize and administer OTO-104 or placebo (all assessments in the above list must be conducted prior to OTO-104 or placebo administration)
- Review subject IVRS diary instructions
- Adverse events (to be collected during or after OTO-104 administration)

8.1.4. Visit 3, 4: Week 4 and 8 (± 2 days) (Follow Up)

The following assessments will be performed at Visit 3 and 4.

- Concomitant medications
- Vital signs
- Tympanometry
- Audiometry
- Otoscopy
- TFI-25
- SF-36 Health Survey

- C-SSRS assessment, Since Last Visit version
- Review subject IVRS diary instructions
- Adverse events

8.1.5. Visit 5: Week 12 (± 4 days) (End of Study/Early Termination)

The following assessments will be performed at Visit 5.

- Concomitant medications
- Vital signs
- Urine pregnancy test (for female subjects of childbearing potential only)
- Clinical laboratory test
- Tympanometry
- Audiometry
- Otoscopy
- TFI-25
- SF-36 Health Survey
- C-SSRS assessment, Since Last Visit version
- Adverse events

8.2. Efficacy Evaluations

Efficacy assessments include:

- Characterization of Daily Vertigo Experience
- TFI-25 (exploratory endpoint)
- Short Form 36 Health Survey (SF-36) (exploratory endpoint)

To maintain the double-blind of the study, it is required that any interaction with subjects in the collection, review, or discussion of these assessments be done by the study coordinator or someone other than the investigator who administered the intratympanic injection of study drug. An exception may be made only if it involves the safety of the subject.

8.2.1. Daily Diary – Vertigo Experience

Subjects will record their daily vertigo experience via an IVRS daily diary by recording the severity of the worst vertigo episode experienced during the day, the effect of vertigo on their daily activities, and the number of vertigo episodes experienced during the day. Subjects eligible at screening will begin using the IVRS daily diary at the start of the lead-in period, and if randomized, will continue to record their daily vertigo experience throughout the remainder of the study. Subjects will be able to record missed diary entries for 1 day after a missed entry. Compliance with the IVRS vertigo diary will be monitored.

Using the daily vertigo scales developed by Gates (Gates, 2000; Gates, 2004; Gates 2005; Gates, 2006) and adapted to an IVRS, subjects are instructed to record the score that best corresponds to the worst vertigo episode experienced each day and the effect on their daily activities of their total vertigo experience that day using a 5-point scoring system:

Vertigo Severity Score

0 = Vertigo-free day

1 = Mild - an attack lasting less than 20 minutes

2 = Moderate - an attack lasting more than 20 minutes

3 = Severe - an attack lasting more than 20 minutes and accompanied by nausea and/or vomiting

4 = The worst attack experienced to date

Effect of Vertigo on Activity Level

0 = Normal Activity

1 = Slight limitation

2 = Moderate limitation

3 = Sick at home

4 = Bed ridden

The occurrence of a definitive vertigo episode for a given day is defined as a recorded Vertigo Severity Score of 2 or more for that day. If multiple attacks occur on the same day, only the worst attack should be scored.

8.2.2. Tinnitus Functional Index (TFI-25)

The TFI-25 is a validated, 25-item questionnaire that can be used to quantify treatment-related change in tinnitus (Meikle et al., 2013; Henry et al., 2015). The total TFI score is a sum of the 25 items with a maximum score of 250, with higher scores representing greater perceived handicap. The 25 items can also be grouped into 8 subscales: 1) Intrusive, 2) Sense of Control, 3) Cognitive, 4) Sleep, 5) Auditory, 6) Relaxation, 7) Quality of Life, and 8) Emotional.

The TFI-25 will be administered to subjects at Visits 2, 3, 4, and 5.

8.2.3. Short Form 36 (SF-36) Health Survey

SF-36 is a validated, 36-item, multi-purpose, short-form health survey (Ware et al., 1993; Ware et al., 1994). It consists of 8 subscales: 1) Physical Functioning, 2) Role-Physical, 3) Bodily Pain, 4) General Health, 5) Vitality, 6) Social Functioning, 7) Role-Emotional, and 8) Mental Health.

The SF-36 health survey will be administered to subjects at Visits 2, 3, 4, and 5.

8.3. Safety Evaluations

Safety assessments include:

- Vital Signs, Height and Weight Measurements
- Clinical Laboratory Test
- Tympanometry
- Audiometry
- Otoscopy
- C-SSRS Assessment
- Concomitant Medications
- Adverse events (see Section 9)

8.3.1. Vital Sign, Height and Weight Measurements

Vital sign measurements (including systolic and diastolic blood pressure and pulse rate) will be collected at all study visits. Vital signs will be measured after subjects have been seated for 5 minutes and while subjects are in a sitting position. Height and weight will be measured at Visit 1 and weight will be measured again at Visit 5.

8.3.2. Clinical Laboratory Test

All clinical laboratory tests will be processed by a Central Laboratory.

Blood and urine samples for hematology, serum chemistry, urinalysis, and pregnancy tests will be prepared using standard procedures. Clinical laboratory testing will be completed at Visits 1, 2 and 5. In addition, female subjects of childbearing potential will have serum pregnancy test at Visit 1 and a urine pregnancy test at Visits 2 and 5.

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

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

Serum Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, carbon dioxide, calcium, chloride, creatinine, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein.

Urinalysis: appearance, color, glucose, ketones, nitrite, pH, protein, specific gravity, occult blood, leukocyte esterase, and urobilinogen.

8.3.3. Tympanometry

Tympanometry assessments will be used to assess the mobility and compliance of the tympanic membrane, pressure and volume in the middle ear, and function of the tympanic membrane, ossicles and eustachian tube. Tympanograms will be completed in both ears at all study visits. Subjects wearing hearing aids should be instructed not to wear their hearing aids during the tympanometry assessment.

8.3.4. Audiometry

Audiometric assessments will be used to assess hearing function in both ears. Audiograms should be conducted at 500, 1000, 2000, 4000 and 8000 Hz for both air and bone conduction at all study visits. Both air and bone conduction thresholds will be assessed. Pure tone averaging bone and air conduction testing will be done at 500, 1000, and 2000 Hz frequencies. Subjects wearing hearing aids should be instructed not to wear their hearing aids during the audiogram.

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 audiologist or a qualified assistant with appropriate training under the direct supervision of a licensed audiologist.

8.3.5. Otoscopy

Otoscopic exams will be used to assess the auditory canal, the appearance of the tympanic membrane, and the healing of the intratympanic injection site. Otoscopic examinations will be performed in both ears at all study visits during the study by the physician. Presence and size of tympanic membrane perforations will be recorded. Perforations of the tympanic membrane will be captured as AEs only if the perforation increases in size and does not resolve by the end of the study. Subjects wearing hearing aids should be instructed not to wear their hearing aids during the otoscopic exam.

8.3.6. C-SSRS Assessment

The C-SSRS assessment will be administered at all study visits. The Baseline version will be used at Visit 1 for all subjects. For Visits 2 through 5, the Since Last Visit version will be used. Any subject with a positive score at on the Baseline version or an appearance of any new suicidal ideation or suicide behavior since the Baseline version should be referred to their primary care provider for follow-up.

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

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

9. ADVERSE EVENT REPORTING

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

All AEs, including serious adverse events (SAEs) reported or observed during or after dosing with the study drug will be recorded on the AE page of the eCRF for all enrolled subjects. Information to be collected includes description of event, date of onset, investigator-specified assessment of the severity and relationship to study drug, 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 only if the perforation increases in size and does not resolve by the end of the study.

If the existing medical condition worsens at any time after application of study drug, it should be recorded as an AE.

9.1. Adverse Event Classification Definitions

Adverse Event:

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

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

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

Serious Adverse Event (SAE):

An SAE is defined as any untoward medical occurrence that:

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

- is a congenital anomaly/birth defect.

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

9.1.1. Assessment of Severity

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

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

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

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

Grade 4 – Life Threatening: These events are those for which the subject was at risk of death at the time of the event rather than an event which hypothetically might have caused death if it were more severe.

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

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

9.1.2. Assessment of Causality

The investigator's assessment of an AE's relationship to study drug will be part of the documentation process, but will not be a factor in determining what is or is not reported in the study.

The investigator will assess the relationship or association of the study drug in causing or contributing to the AE, which will be characterized using the following classification and criteria:

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

Probable: Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the study drug. The following characteristics will apply:

- a reasonable temporal relationship exists between the event and exposure to the study drug, and
- the event is a known reaction to the study drug that cannot be explained by an alternative cause commonly occurring in the population/individual, or

- the event is not a known reaction to the study drug but cannot be reasonably explained by an alternative cause.

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

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

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

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

9.1.3. Follow up of Adverse Events

The investigator will follow a non-serious AE until resolution, stabilization, or the End of Study Visit. The investigator will follow an SAE (regardless of relationship to study drug) 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 the current status (ongoing or resolved) will be noted. In addition, SAEs will be reported to Product Safety according to the reporting guidelines identified in Section 9.2.2.

9.2. Monitoring of Adverse Events

9.2.1. All Adverse Events

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

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, 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 study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Any non-serious AE that occurs after the dose of study drug 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 study drug, seriousness, any required treatment or evaluations, and outcome.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigators all serious AEs that are unlisted and associated with the use of the drug. The investigators must report these events to the appropriate Research Ethics Committee (REC) in accordance with local regulations.

9.2.2. Serious Adverse Events

All SAEs occurring during clinical trials must be reported within 24 hours to Product Safety.

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

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

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

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

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

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

9.2.3. Pregnancies

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

9.3. Contacting Sponsor Regarding Safety

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

[redacted]

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

10. SUBJECT COMPLETION

10.1. Completion

Study subject participation is complete after Visit 5. Subjects who withdraw their consent to be followed or are lost-to-follow-up before completion of Visit 5 (Week 12) will not be considered to have completed the study.

10.2. Withdrawal

All subjects have the right to withdraw from study evaluations at any time, for any reason, without prejudice; nonetheless, investigators should attempt to encourage subjects to complete the protocol so that continued observation and follow-up measurements may be obtained. The investigator may discontinue a subject's participation in the study at his/her discretion for reasons including, but not limited to, the following:

1. Subject experiences a serious or intolerable AE that, in the opinion of the investigator, requires withdrawal from the study.
2. Subject is in violation of the protocol.
3. Subject develops a condition during the course of the study that makes it unwise to continue with the trial.
4. Subject requires a medication that is prohibited by the protocol.
5. Subject requests an early discontinuation for any reason.

At any point, the investigator may discontinue the subject's study participation at his/her discretion 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 study drug administration and further follow-up the study at any time. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Whenever possible, all subjects who withdraw from study drug administration should be encouraged to remain on-study for further follow-up through the subject last scheduled visit. However, 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 administration of study drug or the study prior to completing Visit 5 (Week 12), 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.

11. STATISTICAL METHODS

The primary objective of this Phase 3 study is to test the hypothesis that subjects randomized to OTO-104 will demonstrate fewer definitive vertigo days (DVD) than subjects randomized to placebo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12). The secondary objective of the study is to describe the safety profile of a 12 mg dose of OTO-104 compared to placebo when administered as a single intratympanic injection in subjects with Meniere's disease.

The following statistical sections describe the general analytic methods to be implemented to assess the overall study objectives. More detailed descriptions of the methodology will be provided in the Statistical Analysis Plan (SAP). The SAP will be prepared and finalized before unblinding the subjects' randomized treatment assignments.

11.1. Sample Size

The target total sample size for the study is 160 randomized with 1:1 allocation, 80 in each treatment group stratified by gender. The sample size estimate was chosen to achieve more than 90% power with significance level of 0.05 two-sided to reject the null hypothesis of no treatment difference for the primary endpoint of DVD.

The power estimate was based on the estimated treatment means for DVD at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12) from the recently completed Phase 2b trial in this indication. The OTO-104 and placebo treatment groups received a single dose of the study drug at Day 1. In the 2b trial, the OTO-104 treatment group received the same dose as will be evaluated in this Phase 3 study. A Poisson generalized linear regression model was used to estimate the mean number of DVD for the OTO-104 and placebo groups during the primary endpoint 4-week study interval. The model included treatment group as a factor (categorical), and the lead-in period as a covariate. An offset for the number of diary entries recorded for that 4-week interval (interval from Week 9 through 12) was included for each subject to account for missing diary entries. The number of lead-in period DVD was adjusted to 28 days. The model was also adjusted for over-dispersion using the Pearson residuals as the scale factor. The estimated mean number of DVD for the OTO-104 and placebo groups were 4.5 and 2.1, respectively with an estimated mean difference of (active – placebo) -2.4 days, adjusted for lead-in period number of DVD. The model residual variance was 4.79. For the purpose of the sample size calculation the residual variance and true mean difference was considered as 5.0 and 2.2, respectively.

11.2. Analysis Sets

The following definitions will be used to derive the analysis sets for this study.

Full Analysis Set (FAS): The full analysis set will include all subjects who are randomized, receive study drug, have a baseline definitive vertigo measurement for the 4-week lead-in period and at least one 4-week definitive vertigo measurement post-baseline. The primary analysis for the primary endpoint of DVD will be conducted using the FAS. Subjects will be included in the treatment group to which they were randomized regardless of the actual study drug received.

Completers Analysis Set: The completers analysis set will include all subjects who are randomized, receive study drug, and have all baseline and post-baseline definitive vertigo measurements for each 4-week study interval. Subjects will be included in the treatment group to which they were randomized regardless of the actual study drug received.

Per Protocol Analysis Set: The per protocol analysis set will include all subjects who are randomized, receive study drug, meet eligibility criteria, have no major protocol deviations, and have a baseline and at least one 4-week definitive vertigo measurement post-baseline. Subjects will be included in the treatment group of the actual study drug received.

Intent-to-Treat Analysis Set (ITT): The ITT analysis set will include all randomized subjects who receive study drug. Subjects will be included in the treatment group to which they were randomized regardless of the actual study drug received.

Safety Analysis Set: The safety analysis set will include all subjects who receive study drug. Subjects will be included in the treatment group according to the actual treatment received regardless of their randomized assignment. When the ear is the unit of analysis, the safety analysis will categorize an ear by whether it was a treated or an untreated ear, irrespective of whether it was the affected ear.

11.3. Description of Subgroups to be Analyzed

Descriptive analyses will be performed for the primary efficacy endpoint for the following subgroups using the FAS with details provided in the Statistical Analysis Plan (SAP):

- Subject Demographics
  - Gender
  - Race/Ethnicity
  - Age (categories: 18-30, 31-40, 41-60, > 61yrs.)
- Baseline Disease Characteristics
  - Duration of Meniere's Disease
  - Previous intratympanic steroid injection for Meniere's Disease
  - Degree of hearing loss

11.4. Subject Demographics, Baseline Disease Status, and Disposition

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

11.5. Efficacy Evaluations

11.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the number of definitive vertigo days (DVD) at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12). A DVD is defined as each day the subject recorded a vertigo episode lasting at least 20 minutes and corresponds to a Vertigo Score of 2 or more. If multiple episodes occur on a given day, only the worst episode in terms of score should be recorded.

11.5.2. Secondary Efficacy Endpoints

Secondary Efficacy Endpoint:

- The number of definitive vertigo days (DVD) at Week 8 [the 4-week (28-day) interval from Week 5 through Week 8]
- The number of definitive vertigo days (DVD) at Week 4 [the 4-week (28-day) interval from Week 1 through Week 4]
- The change from baseline in vertigo frequency (VF) during the 4-week study interval (Week 9 through Week 12), where vertigo frequency is defined as the proportion of days during the 4-week interval where a definitive vertigo episode was recorded divided by the number of non-missing diary entries for the relevant interval
- The change from baseline with respect to severity of vertigo episodes as measured by the mean Vertigo Score during the 4-week study interval (Week 9 through Week 12)
- The change from baseline in average daily count of vertigo episodes, during the 4-week study interval (Week 9 through Week 12)
- Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bed ridden events as a consequence of vertigo at Week 12
- SF-36 at Week 12
    - Physical Health Summary Measure
    - Mental Health Summary Measure
    - 8 Scales

11.5.3. Exploratory Efficacy Endpoints

Exploratory Efficacy Endpoints are:

- The change from baseline in vertigo frequency (VF) during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8), where vertigo frequency is defined as the proportion of days during the 4-week interval where a definitive vertigo episode was recorded divided by the number of non-missing diary entries for the relevant interval

- The change from baseline with respect to severity of vertigo episodes as measured by the mean Vertigo Score during each 4-week study interval (Week 1 through Week 4) and (Week 5 through 8)
- The change from baseline in average daily count of vertigo episodes, during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)
- Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bed ridden events as a consequence of vertigo at Week 4 and Week 8
- SF-36 at Weeks 4 and 8
    - Physical Health Summary Measure
    - Mental Health Summary Measure
    - 8 Scales
- Tinnitus Functional Index (TFI) at Weeks 4, 8, and 12

Details regarding imputation of missing data, including items for questionnaires, will be provided in the Statistical Analysis Plan (SAP).

11.5.4. Analytic Methods for Efficacy

The primary efficacy endpoint is the number of DVD at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12). Poisson regression model will be used to estimate and compare the mean number of DVD for OTO-104 and placebo groups during the primary endpoint 4-week study interval. The model will include treatment group (OTO-104 vs. placebo) and gender as factors (categorical), and the lead-in period as a covariate. An offset for the number of diary entries recorded for that 4-week interval (interval from Week 9 through 12) will be included for each subject. The number of lead-in period DVD will be adjusted to 28 days. The model will also adjust for over-dispersion using Pearson residuals as the scale factor.

The primary analysis population for the comparison of the primary endpoint between the treatment groups in this study is full analysis set (FAS). Subjects will be included in the treatment group to which they were randomized regardless of the actual study drug received.

The primary endpoint analysis also will be conducted using per-protocol, ITT, and completers analysis sets as sensitivity analyses.

If a subject has no recorded diary data for the Vertigo Severity Score during Week 12 interval then an imputation method which will be specified in the SAP will be used.

The secondary efficacy endpoints of number of DVD during 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8) will be compared between the treatment groups separately using the same Poisson regression model specified for the primary endpoint.

The secondary efficacy endpoint of change from baseline in vertigo frequency (VF) at Week 12 (the 4-week interval from Week 9 through Week 12), will be compared between the treatment groups using analysis of covariance (ANCOVA). The model will contain treatment group (OTO-104 vs. placebo) and gender as factors (categorical) and baseline vertigo frequency as a covariate.

The secondary efficacy endpoint of change from baseline in severity of vertigo during 4-week study interval (Week 9 through Week 12) will be compared between the treatment groups using ANCOVA including treatment groups, gender, and severity score at baseline as a covariate.

The secondary efficacy endpoint of change from baseline in average daily count of vertigo episodes, during 4-week study interval (Week 9 through Week 12) will be compared between the treatment groups using ANCOVA including treatment groups, gender, and average daily count of vertigo episode at baseline as a covariate.

The secondary endpoint of occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bed ridden events as a consequence of vertigo at Week 12 will be compared between the treatment groups using Mantel-Haenszel Row Mean Scores stratified by gender.

Alternative models will be pre-specified in the SAP should certain assumptions regarding data and models do not hold. In addition, the SAP will include pre-specified data transformations should evaluation of the residuals suggest a data transformation is more suitable.

If the primary endpoint comparison between the two treatment groups is statistically significant in favor of OTO-104 then a closed testing, gate-keeping procedure will be used to compare the following secondary efficacy endpoints sequentially:

1. The number of DVD at Week 8 [the 4-week (28-day) interval from Week 5 through Week 8]
2. The number of DVD at Week 4 [the 4-week (28-day) interval from Week 1 through Week 4]

In this procedure if the first secondary endpoint comparison between the two treatment groups is statistically significant in favor of OTO-104 then the second secondary endpoint will be compared and tested. If the comparison of the first secondary endpoint is not statistically significant in favor of OTO-104 then the reported p-value for the second secondary endpoint will be considered as a nominal p-value.

The remaining secondary endpoints comparison will not follow the gate keeping procedure and therefore the reported p-values will be reported as nominal p-values. This procedure controls the study-wise Type I error. Since the study-wise error is maintained with the above procedure, there is no α penalty associated with it. All efficacy hypothesis tests will be 2-sided and performed at $\alpha = 0.05$ significance level.

11.6. Safety Evaluations

Safety endpoints to be examined include:

- Vital Signs, Height and Weight Measurements
- Clinical Laboratory Test
- Tympanometry
- Audiometry
- Otoscopy
- C-SSRS Assessment

- Concomitant Medications
- Adverse events

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

11.6.1. Adverse Events

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

The primary analysis of AEs will consider only treatment-emergent AEs, events occurring for the first time, or worsening during or after the first dose of study drug. Subject incidence of TEAEs and SAEs will be tabulated by preferred terms and system organ class. Severity and relationship to study drug 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 system organ class and preferred term.

Subgroup analyses for age, race, and gender will also be examined provided a reasonable number of subjects in each subgroup are available for analysis. Listings of all SAEs, AEs leading to study withdrawal, and deaths on-study will also be included. Duration and outcome of each AE will be reported in subject listings.

Adverse events occurring during the lead-in period prior to exposure to study drug will be reported in data listings. Further details will be provided in the SAP.

11.6.2. Vital Signs and Laboratory Parameters

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

11.6.3. Otoscopic Examinations

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

11.6.4. Audiometry Assessments

Descriptive summary statistics for audiometric assessments of air and bone conduction thresholds at each frequency will be provided by treatment group and study visit. In addition, the PTA computed as the average air conduction threshold for the 500, 1000, and 2000 Hz will also be calculated.

Air-Bone Gap assessments at each frequency for treatment group and study visit will be tabulated as the proportion of subjects with air minus bone conduction thresholds of:

1. ≤ 10 dB or
2. > 10 dB.

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

11.6.5. Tympanometry

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

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

The C-SSRS will be administered at each visit using the appropriate version i.e. Baseline or Since Last Visit. Analysis of this scale will be performed on the Safety Analysis Set.

11.6.6.1. Baseline Version

The Baseline version of the C-SSRS will be administered at the Screening visit (Visit 1). This version of the scale captures both suicide ideation and suicide behavior (lifetime). There are 5 suicidal ideation questions, each captured as yes/no for the subject's lifetime. Additionally a sixth suicidal ideation variable will be created to indicate if there was any ideation, regardless of type. There are 4 suicidal behavior questions, each captured as yes/no for the subject's lifetime. A fifth suicidal behavior variable will be created to capture if there was any suicidal behavior regardless of type. 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. All C-SSRS data will be included in data listings. There is no inclusion or exclusion criterion associated with the Baseline C-SSRS score. Subjects with a positive score should be referred to their primary care provider for follow-up.

11.6.6.2. Since Last Visit Version

The Since Last Visit version of the C-SSRS will be administered at each study visit after the Screening visit (Visit 1). The same overall individual variables for suicidal ideation and behavior will be assessed as in the Baseline version. In addition, overall suicidality (yes/no) will be defined as any subject having any suicidal ideation or behavior since the last visit. All suicidal ideation and behavior variables will be tabulated overall and by treatment group for each study visit. All C-SSRS data will be included in data listings.

Any subject with an appearance of any new suicidal ideation or suicide behavior since Screening should be referred to their primary care provider for follow-up.

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

recorded as an AE. This information is reported as indicated in Section 9.2.1. (Possible AE terms: Suicidal plans, Suicidal ideation, Suicidal tendency, Suicidal behavior, Suicidal intention, Suicidal depression, Active suicidal ideation, Passive suicidal ideation, Self-injurious behavior without suicidal intent).

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

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

In addition to the primary analysis of the primary endpoint, if needed several sensitivity analyses will also be evaluated. These analyses will be included in the SAP with appropriate details prior to unblinding the database.

The SAP will include greater detail regarding the handling of missing data as well as the algorithms for scoring the SF-36, including the handling of missing questionnaire items.

Every effort will be made to follow subjects for study observation and encourage compliance with study measurements to minimize the amount of missing data.

Except for partial dates, safety data will not be imputed. The imputation algorithm for partial dates will be defined in the SAP.

11.8. Interim Analyses

There are no formal interim analyses planned. Blinded reviews of safety data will be conducted as described in Section 14.7; however, the review of such data is not intended to impact the study conduct unless there are safety concerns. As such, it is expected that the trial will continue to its scheduled completion barring any unexpected safety issues.

12. STUDY DRUG INFORMATION

12.1. Physical Description of Study Drug(s)

The investigational drug product administered to subjects in this study will be OTO-104 and placebo. The OTO-104 final product suspension for dosing will be prepared from two separate components, OTO-104 Diluent (one vial needed) and OTO-104 Active (one vial needed). An appropriate volume of OTO-104 Diluent will be withdrawn and delivered into the OTO-104 Active vial to achieve a visually homogeneous suspension of a target drug concentration of 60 mg/mL. Placebo will consist of the vehicle used to formulate OTO-104 and will be supplied from one vial (OTO-104 Diluent).

The following drug supplies will be used in the study:

Product	Supplied as:
OTO-104	A kit containing: one vial of OTO-104 Active and one vial of OTO-104 Diluent.
Placebo	A kit containing: one vial of OTO-104 Diluent.

12.2. Directions for Use

OTO-104 and placebo will be prepared by an unblinded QMP in a clean, secure location with a room temperature preferably at or below 23°C (73°F). The location will not be accessed by the blinded personnel during study drug preparation. Please refer to the Pharmacy Manual for detailed study drug preparation instructions.

12.3. Packaging and Labeling

12.3.1. Packaging

All study drug 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-104 Active and Diluent vials indicating contents and storage instructions. A syringe blinding label will be provided to mask the syringe contents for injection.

12.4. Management of Clinical Supplies

The clinical supplies will be managed by the IWRS. The IWRS 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 the IWRS system and sent to the clinical supplies vendor. Upon shipment and receipt of the clinical trial material, the site personnel (e.g., pharmacy) will acknowledge the shipment using the IWRS and identify any damaged, missing, or unusable kits so they will not be dispensed.

12.4.1. Storage of Kits

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

12.5. Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug 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 QMP will be instructed to return all original containers, whether empty or containing study drug, when instructed by the study monitor to return. Study drug returned by the clinical site staff will be stored and disposed of according to the sponsor's instructions. Drug accountability will be verified by the sponsor's unblinded study monitor during the course of the study. Study drug will be stored in a limited access area or in a locked refrigerator under appropriate environmental conditions.

The investigator agrees not to supply the study drug to any person other than sub-investigators, designated staff and the subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects except under special circumstances approved by Otonomy.

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 study drug, to the sponsor as instructed by the study manager. The investigator agrees to neither dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

The sponsor will ensure proper disposition of original containers empty or full with returned or unused study drug. Appropriate documentation will be maintained. Permission may be granted for local disposition, with supporting documentation.

13. ETHICAL ASPECTS

13.1. Investigator Responsibilities

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

13.2. Research Ethics Committee (REC)

This trial will be undertaken only after full approval of the protocol and addenda has been obtained from a designated REC and the sponsor has received a copy of this approval.

The REC must be informed of all subsequent protocol amendments issued by the sponsor.

Reports on, and reviews of, the trial and its progress will be submitted to the REC 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) according to local requirements after the nature of the study has been fully explained. The consent form must be signed 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 REC. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and Otonomy policy.

The investigator must explain to potential subjects the aims, methods, reasonably anticipated benefits and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part, and that such refusal 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 trial, consent should be appropriately recorded by means of the subject's dated signature. 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 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 REC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor, change of telephone number). Responsibilities for reporting protocol amendments to any Regulatory Authority (if applicable) and/or REC are further described in the Ethical Aspects section of the protocol.

In situations requiring a departure from the protocol, the investigator or other physician in attendance will contact the site manager, Medical Monitor, or other appropriate sponsor representative by fax, 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 in order to discuss the situation and agree on an appropriate course of action. The eCRF and source document will describe any departure from the protocol and the circumstances requiring it.

14.2. Regulatory Documentation

Documents that must be provided to the sponsor prior to study drug shipment are as follows:

- Up-to-date curriculum vitae for each investigator and sub-investigator.

- Signed and dated Investigator Agreement.
- Applicable local regulatory documentation
- A copy of the formal written notification to the investigator regarding approval of the protocol by an REC that is in compliance with regulatory guidelines. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an REC member has a known conflict of interest, abstention of that individual from voting should be documented; an investigator (or sub-investigator) may be a member of the REC, but may not vote on any research in which he or she is involved.
- Financial disclosure documentation for each investigator and sub-investigator.
- Name and address of the REC with a statement that it is organized and operates according to GCP and the applicable laws and regulations, and a current list of the REC members. The REC Attestation form can be used to capture this information.
- A copy of the REC approved informed consent form and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of REC approval of these items.
- Required financial agreement.

In addition to the documents required prior to the study, other documentation may be required during the course of the study.

14.3. Subject Identification Register

The investigator agrees to complete a subject identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential, and will be filed by the investigator in the Trial Site File. Otherwise, all reports and communications relating to the study will identify subjects by initials and assigned number only.

14.4. Record Retention

In compliance with the ICH/GCP guidelines the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two 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/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 person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

14.5. Electronic Case Report Form

Electronic Case Report Forms (eCRFs) will be completed for each subject. Access for data entry will be provided to appropriate site staff members. 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 they always reflect the latest observations on the subjects participating in the trial.

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 recorded safety and efficacy data.

14.6. Termination

An initiative for center closure or trial termination can be taken at any time either by the sponsor or by the investigator, provided there is reasonable cause and sufficient notice is 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 trial at the center
- The maximum number of eligible subjects for the trial has been enrolled
- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the investigator
- Business reasons

14.7. 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-104. In order to comply with this, the sponsor and CRO medical personnel will have the ability to review blinded safety information as it is entered and verified in the electronic data capture system (Section 14.5). Depending on the enrollment rate, all AEs in the ear and labyrinth disorders SOC will be reviewed at least every other month. In addition, reasons for study discontinuation will be reviewed to see if any trends in study discontinuation are identified.

Investigators are instructed to contact the Product 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 study drug. The sponsor assumes responsibility for appropriate reporting to the regulatory authorities. The investigator assumes responsibility for reporting events to the REC in accordance with the REC requirements. All SAE's will be part of the CRO medical personnel/sponsor safety review.

If, through this ongoing review, the sponsor determines that OTO-104 presents an unreasonable and significant risk to subjects, the sponsor shall take appropriate steps to suspend or discontinue the study and notify regulatory authorities, investigators and RECs as appropriate.

14.8. Monitoring

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

14.9. 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. Case report forms 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.

14.10. On-Site Audits

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

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

14.11. Use of Information and Publication

All information concerning OTO-104, Otonomy operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the sponsor to the investigator and not previously published, is considered confidential and remains the sole property of Otonomy. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The investigator understands that the information developed in the clinical study will be used by Otonomy in connection with the continued development of OTO-104, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review and written approval of Otonomy. Draft abstracts, manuscripts, and materials for presentation at scientific meetings should be provided to the sponsor at least 30 working days prior to abstract or other relevant submission deadlines. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

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