# 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: 104-201811**
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Sponsor Contact: 

Medical Monitor: 

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**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]

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## PROTOCOL AMENDMENT, VERSION 2.0

The purpose of this protocol amendment is to incorporate information on the statistical methods and sample size estimations that are part of Verson 2.0 of the Statistical Analysis Plan (SAP) dated 22 July 2020 as summarized in this table. While there is some previous ("Was") and new ("Is") text included here, due to the extensive revisions to Section 11 (Statistical Methods), only the new text from the larger subsections ("New Text") is included in this table.

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| 4.1 General Considerations | Was:<br>Approximately 160 subjects will be enrolled at approximately 60 sites globally.<br>Is:<br>Approximately **142** subjects will be enrolled at approximately 60 sites globally. | Number of enrolled subjects updated from 160 to approximately 142 to reflect sample size calculations in the SAP Version 2.0.. |
| 11.1 Sample Size | New Text:<br>The target total sample size for the study is **142** subjects randomized with 1:1 allocation, drug:placebo, with **71** in each group.<br>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 previously conducted trials by the Sponsor in this indication. **The primary analysis will be conducted using a Negative Binomial model at Week 12. For the Negative Binomial analysis, a sample size of 142 subjects will provide approximately 90% power to detect a difference between groups in the 28-day average DVD. It is assumed that the 28-day average DVD will be 2.47 and 4.66 for OTO-104 and placebo, respectively, for an estimated ratio of 0.53. It is also assumed that the distribution shape parameter is 1.04. The assumptions used for the Negative Binomial model were based on the previously conducted study OTO-104-201508 (data on file). The calculations were conducted using EAST v6.5 from Cytel, Inc.** | Revision of sample size and the sample size calculation based on the revision to the primary analysis (Negative Binomial model at Week 12) replacing the generalized Poisson model) as described in the SAP Version 2.0. |
| 11.2 Analysis Sets | **Full Analysis Set definition**<br>Was: | Definitions revised for consistency with the SAP Version 2.0 |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| | **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 post-baseline daily diary entry. 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.<br><br>Is:<br><br>**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 post-baseline daily diary entry **for Week 12**. **All efficacy analyses** 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.<br><br>**Per Protocol Analysis Set definition**<br><br>Was:<br><br>**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, i.e. at least one post-baseline daily diary entry.<br><br>Is:<br><br>**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 **definitive vertigo measurement** and at least one post-baseline **daily diary entry within Week 9 through 12**.<br><br>**Intent to Treat Analysis Set:**<br><br>Was:<br><br>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 | reflecting primary analysis is at Week 12 [the 4-week (28 day) interval from Week 9 through Week 12] and clarification on when the ITT population will be used. |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| | group to which they were randomized regardless of the actual study drug received. The ITT set will be used to assess sensitivity to missing data.<br><br>Is:<br><br>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. The ITT set will be used to assess sensitivity to missing data. **The ITT set will be used to assess sensitivity to missing data.** | |
| 11.3 Description of Subgroups to be Analyzed | Subject Demographics<br><br>Was:<br><br>• Age (categories: 18-30, 31-40, 41-60, > 61yrs.)<br><br>Is<br><br>• Age (categories: 18-30, 31-40, 41-60, > 61-**64, 65-74, 75-84, ≥85** yrs.)<br><br>Baseline Disease Characteristics<br><br>New Text:<br><br>• **Betahistine use** | Added age categories at the higher end and also Betahistine use, which is a drug product approved in many countries in Europe for meniere's disease. |
| 11.5.1 Primary Effucacy Endpoint | Was:<br><br>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).<br><br>Is:<br><br>The primary efficacy endpoint is the **28-day average** definitive vertigo days (DVD) at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12). | Using the 28-day average number accounts for varying numbers of diary completion days; previously an offet was applied based on the number of diary days completed. |
| 11.5.2 Secondary Efficacy Endpoints | Was:<br><br>• Severity of vertigo episodes as measured by the mean Vertigo Score at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12) | Added 2 new secondary endpoints of 75% and 50% reduction from baseline in DVD and refined the definition of |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| | • The number of days Sick at home or Bedridden as a consequence of vertigo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)<br>• The change from baseline in vertigo frequency (VF) at Week 12 (the 4-week study interval from 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<br>Is:<br>• Severity of vertigo episodes as measured by the **Mean Severity** Vertigo Score (**MSVS**) at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)<br>• The **28-day average of** number of days Sick at home or Bedridden (**DSB**) as a consequence of vertigo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)<br>• **Percent of subjects achieving a 75% reduction from baseline in 28-day average DVD at Week 12**<br>• **Percent of subjects achieving a 100% reduction from baseline (i.e., count of zero) in 28-day average DVD at Week 12**<br>• The change from baseline in vertigo frequency (VF) at Week 12 (the 4-week study interval from Week 9 through Week 12), where vertigo frequency is defined as the **number of DVDs recorded** during the 4-week interval divided by the number of non-missing diary entries for the relevant interval | previously named secondary endpoints. |
| 11.5.3 Exploratory Efficacy Endpoints | Was:<br>• 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 | Added 1 newexploratory endpoint and refined the definition of previously named |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| | where a definitive vertigo episode was recorded divided by the number of non-missing diary entries for the relevant interval<br>• 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).<br>• Average daily count of vertigo episodes during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)<br>• The number of days Sick at home or Bedridden as a consequence of vertigo during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)<br>• The number of definitive vertigo days (DVD) during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)<br><u>Is:</u><br>• The change from baseline in vertigo frequency (VF) at Week 8, where vertigo frequency is defined as **the number of DVDs recorded** during the 4-week interval divided by the number of non-missing diary entries for the relevant interval<br>• Severity of vertigo episodes as measured by the **Mean Severity** Vertigo Score (**MSVS**) at Week 8<br>• Average daily count of vertigo episodes **at** Week 8<br>• The **28-day average** of number of days Sick at home or Bedridden as a consequence of vertigo during each 4-week study interval (**i.e., Week 4, Week 8, Week 12**)<br>• The **28-day average** definitive vertigo days (DVD) **at** Week 8<br><u>New Text:</u><br>• **Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bedridden events as a consequence of vertigo at Week 4, Week 8, and Week 12** | exploratory endpoints. |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| 11.5.4 Analytic methods for Efficacy | Revised Section (mix of previous and new text).<br><br>**The primary efficacy endpoint, the 28-day average DVD at Week 12 (the 4-week interval from Week 9 through Week 12), will be compared between OTO-104 and placebo at the 2-tailed, 0.05 alpha level using a Negative Binomial model. This model will include fixed effects for randomized treatment group (OTO-104 vs. placebo) and sex (male vs. female), with the 28-day average DVD from the lead-in period as a covariate.**<br><br>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.<br><br>The primary endpoint analysis also will be conducted using per-protocol and ITT analysis sets as sensitivity analyses.<br><br>The **key** secondary efficacy endpoint of the **Mean Severity Vertigo Score (MSVS) for Week 12** (Week 9 through Week 12) **will be analyzed using an ANCOVA model with fixed effects of randomized treatment, group (OTO-104 vs. placebo) and sex (male vs. female), with the subject's average mean severity vertigo score at lead-in period as a covariate.**<br><br>The **key** secondary endpoint of **the 28-day average of** number of days Sick at home or Bedridden (**DSB**) as a consequence of vertigo at Week 12 will be compared between the treatment groups **using using the same Negative Binomial model as specified for the primary analysis and using the 28-day average Lead-in DSB as a covariate.** The model will include fixed effects for randomized treatment group (OTO-104 vs. placebo) **and** sex (male vs. female).<br><br>**The key secondary endpoints of percent of subjects achieving a 75% and a 100% (i.e., count of zero) reduction from baseline in 28-day average of DVD will be compared between the treatment groups using a chi-square test. The risk difference and the** | Revised this section to reflect the primary analyses, secondary analyses, exploratpry analyses and the gate-keeping procedure that is provided in the SAP Version 2.0. |

| Section(s) | Description of Changes | Rationale |
|---|---|---|
| | **95% CI around the risk difference will also be provided.**<br><br>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 analyzed using **an ANCOVA model with treatment as a fixed effect and sex as fixed effects with the lead-in period VF as a covariate**.<br><br>The secondary efficacy endpoint of average daily count of vertigo episodes during 4-week study interval (Week 9 through Week 12) will be **using the ANCOVA model specified for the secondary efficacy endpoint of change from baseline in VF at Week 12, using the subject's Average Daily Vertigo Count (ADVC) at lead-in period as a covariate**.<br><br>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.<br><br>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:<br><br>1. Severity of vertigo episodes as measured by the mean Vertigo Score at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)<br><br>2. The **28-day average** number of days Sick at home or Bedridden as a consequence of vertigo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)<br><br>3. **Percent of subjects achieving a 75% reduction from baseline in 28-day average DVD at Week 12**.<br><br>**4. Percent of subjects achieving a 100% reduction from baseline (i.e., count of zero) in 28-day average DVD at Week 12.** | |

| Section(s) | Description of Changes | Rationale |
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| | 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 second key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in favor of OTO-104, then the third key secondary endpoint will be compared and tested. If the third key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in favor of OTO-104, then the fourth key secondary endpoint will be compared and tested. If the comparison between treatment groups is statistically significant for the fourth key secondary endpoint, then it can be claimed that all key secondary endpoints are statistically significant in favor of OTO-104.**<br><br>**At the first key secondary endpoint that does not demonstrate a statistically significant difference between groups in favor of OTO-104, the gate-keeping procedure ends and any subsequent key secondary endpoint p-values will be considered as a nominal p- value(s).**<br><br>**The gate-keeping procedure controls the Type I error for the four planned comparisons and, therefore, there will be no α spending penalty associated with the planned key secondary comparisons.**<br><br>**The remaining secondary endpoints comparisons will not follow the gate-keeping procedure and, therefore, the reported p-values will be reported as nominal p-values. These analyses will be conducted using the FAS only.**<br><br>**All efficacy hypothesis tests will be 2-sided and performed at α = 0.05 significance level, unless otherwise specifid in the SAP.** | |

SPONSOR CONTACT INFORMATION

**Medical Monitor:**

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

**Other Appropriate Trial Contact Personnel:**

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

**Safety:**

| | |
|---|---|
| **USA** | [redacted] |
| Telephone | [redacted] |
| Email | [redacted] |
| **Europe** | [redacted] |
| Telephone | [redacted] |
| Email | [redacted] |

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

## INVESTIGATOR AGREEMENT

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

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

I will use only the informed consent form approved by Otonomy, Inc. (hereafter, "the Sponsor") or its representative and approved by the Institutional Review Board (IRB) or Research Ethics Committee (REC) responsible for this study and will fulfill all responsibilities for submitting pertinent information to the IRB or 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 Sponsor 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 the Sponsor.

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|---|---|
| Investigator's Signature | Date |

Name of Investigator *(typed or printed)*

## ABBREVIATIONS

| | |
|---|---|
| ADVC | Average Daily Vertigo Count |
| 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 |
| DSB | Days Sick at Home or Bedridden |
| DVD | Definitive Vertigo Day |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| Hz | Hertz |
| ICH | International Council for Harmonisation |
| ICHD-III | International Classification of Headache Disorders III |
| IT | Intratympanic |
| ITT | Intent to Treat |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Randomization System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mL | Milliliter |
| MSVS | Mean Severity Vertigo Score |
| OTO-104 | Investigational Product (Study Drug) |
| PTA | Pure Tone Average |
| PGIC | Patient Global Impression of Change |
| QMP | Qualified Medical Professional |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SF-36 | Short Form 36 Health Survey |
| SOC | System Organ Class |
| VF | Vertigo Frequency |
| WHO Drug | World Health Organization Drug Dictionary |

# SYNOPSIS

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

**Protocol No.:** 104-201811

**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 60 sites globally.

**Study Period:** Approximately 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 investigate 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 investigate the safety profile of OTO-104 in subjects with Meniere's disease.

**Methods:**

The duration of the study for each subject will be 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, which is 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 of 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 142 subjects (71 assigned to 12 mg OTO-104 and 71 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.
2. Subject has a diagnosis of definite unilateral Meniere's disease by 1995 AAO-HNS criteria.

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| NAME OF SPONSOR/COMPANY: | Otonomy, Inc. |
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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 1995 AAO-HNS 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 must be justified and documented, and discussed with the medical monitor.
5. If taking medication for Meniere's disease (e.g., diuretics, vestibular suppressants, betahistine, antidepressants, or anxiolytics), subject must be on stable doses of the medication for at least 2 weeks prior to Screening and agrees to remain on stable doses of the medication for the duration of the 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 privacy language compliant with country and/or local requirements, 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.

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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 significant middle ear or inner ear surgery, or endolymphatic sac surgery in the affected ear.
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 in the affected ear.
9. Subject has used systemic steroids within 1 month prior to entering the lead-in period.
10. Subject has a history of previous use of intratympanic steroids in the affected ear.
11. Subject has experienced an adverse reacton to dexamethasone.
12. Subject has a history of vestibular migraine. International Classification of Headache Disorders III criteria for vestibular migraine includes a current or past history of migraine with or without aura, vestibular symptoms of moderate or severe intensity lasting between 5 minutes and 72 hours, and at least half of episodes are associated withat least 1 of the 4 following migraineous features: unilateral headache, pulsating quality, photophobia, and visual aura.
13. Subject has history of drop attacks.
14. Subject is not able to accurately identify and report episodes of vertigo.
15. 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.
16. Subject has used an investigational drug or device in the 3 months prior to screening.
17. Subject has a history of serious substance abuse (e.g. cocaine, heroin) within the preceding 6 months prior to screening.
18. Subject has previously been randomized to a clinical study 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:**

16% poloxamer solution (placebo), single 0.2 mL intratympanic injection to the affected ear

**Outcome Measures for Evaluation:**

Primary Efficacy Endpoint:

The primary efficacy endpoint is the 28-day average 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:

- Severity of vertigo episodes as measured by the Mean Severity Vertigo Score (MSVS) at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]

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

- The the 28-day average of number of days Sick at home or Bedridden as a consequence of vertigo at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]
- The change from baseline in vertigo frequency (VF) at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12], where vertigo frequency is defined as the number of DVDs recorded during the 4-week interval divided by the number of non-missing diary entries for the relevant interval
- Average daily count of vertigo episodes at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]

Exploratory Efficacy Endpoints:

- The change from baseline in vertigo frequency (VF) at Week 8, where vertigo frequency is defined as the number of DVDs recorded during the 4-week interval divided by the number of non-missing diary entries for the relevant interval
- Severity of vertigo episodes as measured by the Mean Severity Vertigo Score (MSVS) at Week 8
- Average daily count of vertigo episodes at Week 8
- The 28-day average number of days Sick at home or Bedridden as a consequence of vertigo during each 4-week study interval (i.e., at Week 4, Week 8 and Week 12)
- The number of 28-day average definitive vertigo days (DVD) during each 4-week study interval (Week 1 through Week 4) and (Week 5 through Week 8)
- Patient Global Impression of Change (PGIC) at Weeks 8 and 12
- SF-36 Social Functioning Subscale assessment at Weeks 8 and 12
- Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bedridden events as a consequence of vertigo at Week 4, Week 8, and Week 12

Safety Assessments:

Safety assessments include:

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

**Statistical Methods:**

The primary efficacy endpoint is the 28-day average 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 142 randomized with 1:1 allocation, 71 in each treatment group

The primary analysis will be conducted using a Negative Binomial model at Week 12. For the Negative Binomial analysis, a sample size of 142 subjects will provide approximately 90% power to detect a difference between groups in the 28-day average DVD. It is assumed that the 28-day average DVD will be 2.47 and 4.66 for OTO-104 and placebo, respectively, for an estimated ratio of 0.53. It is also assumed that the distribution shape parameter is 1.04. The assumptions used for the Negative Binomial model were based on the previously

conducted study 104-201508 (data on file). The calculations were conducted using EAST v6.5 from Cytel, Inc. The primary analysis population for this study is the full analysis set (FAS). The FAS 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 day of DVD measurement at Week 12 [the 4-week (28 day) interval from Week 9 through Week 12].

In the primary efficacy analysis if a subject is missing their Week 12, 28-day average DVD in FAS, the subject will enter the analysis having a missing value. It is assumed that data will be missing at random. Sensitivity analyses will be undertaken to examine the effect of missing daily diary (DD) data on the results of the primary endpoint analysis for the FAS and for subjects whom discontinued the study prior to entering the Week 12 interval. which include various imputation methods as specified in the Statistical Analysis Plan (SAP). 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. Severity of vertigo episodes as measured by the Mean Vertigo Severity Score (MSVS) at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]
2. The 28-day average of number of days Sick at home or Bedridden as a consequence of vertigo at Week 12 [the 4-week (28-day) interval from Week 9 through Week 12]
3. Percent of subjects achieving a 75% reduction from baseline in 28-day average DVD at Week 12
4. Percent of subjects achieving a 100% reduction from baseline (i.e., count of zero) in 28-day average DVD at Week 12.

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 second key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in favor of OTO-104, then the third key secondary endpoint will be compared and tested. If the third key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in favor of OTO-104, then the fourth key secondary endpoint will be compared and tested. If the comparison between treatment groups is statistically significant for the fourth key secondary endpoint, then it can be claimed that all key secondary endpoints are statistically significant in favor of OTO-104.

At the first key secondary endpoint that does not demonstrate a statistically significant difference between groups in favor of OTO-104, the gate-keeping procedure ends and any subsequent key secondary endpoint p-values will be considered as a nominal pvalue(s).

The gate-keeping procedure controls the Type I error for the four planned comparisons and, therefore, there will be no α spending penalty associated with the planned key secondary comparisons.

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. All efficacy hypothesis tests will be 2-sided and performed at $\alpha = 0.05$ significance level unless otherwise specified in the SAP.

**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 |
| PGIC | | | | | X | X | |
| SF-36 Social Functioning Subscale assessment | | | X | | X | X | |
| C-SSRS assessment[9] | X | | X | X | X | X | X |
| Instruct subject on IVRS diary use and review any compliance issues[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. 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. If Visit 5 is performed outside the visit window and prior to Day 84, subjects will continue to record their daily vertigo experience after the completion of Visit 5 visit until Day 84 unless the subject is an early discontinuation or withdrew consent.

[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. Subjects may be entered into the Lead-in period before clinical laboratory test results are available.

[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, betahistine, 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 (Clyde et al, 2017). 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 safe and effective therapies to address this debilitating disease.

OTO-104 is a suspension of dexamethasone [redacted] Single and repeat-dose nonclinical safety studies in guinea pigs, rats and cats have been conducted to support clinical development. 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. A summary of these studies and results can be found in the Investigator's Brochure.

## 1.1. Rationale for Study and Dose Selection

Otonomy has completed 4 placebo-controlled, double-blind, multi-center clinical studies with OTO-104 in Meniere's disease: an exploratory Phase 1b study, 104-200901, a Phase 2b study, 104-201102, and two Phase 3 studies, 104-201506 and 104-201508. 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 addition, the trends in the data suggest treatment with 12 mg OTO-104 was 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 the two Phase 3 studies was 12 mg OTO-104 and the Week 12 interval, respectively.

The 104-201508 Phase 3 study demonstrated a significant effect on the primary endpoint at Week 12 with OTO-104 subjects experiencing a greater decrease in the count of definitive vertigo days compared to placebo subjects. OTO-104 treatment also met key Week 12 secondary endpoints in this study including significant decreases in the mean vertigo severity score, decreases from baseline in vertigo frequency, and reductions in number of days at home sick or bedridden. The 104-201506 Phase 3 study, in contrast, did not demonstrate a statistical difference between OTO-104 and placebo subjects in definitive vertigo days at Week 12 or for any of the secondary endpoints. On analysis of the differences between the two Phase 3 studies, a key finding was that the placebo response in 104-201506 was greater than that observed in study 104-201508 as well the placebo response in all other OTO-104 clinical trials in Meniere's disease patients. The purpose of the current Phase 3 study, 104-201811, therefore, is to further investigate the efficacy of OTO-104 in subjects with Meniere's disease, informed by the results of studies 104-201506 and 104-201508.

# 2. OBJECTIVES

## 2.1. Primary Objective

The primary objective is to investigate 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 investigate 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. Randomization will be stratified based on 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 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/or 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 142 subjects will be enrolled at approximately 60 sites globally. 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 1995 AAO-HNS 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 must be justified and documented, and discussed with the medical monitor.

5. If taking medication for Meniere's disease (e.g., diuretics, vestibular suppressants, betahistine, antidepressants, or anxiolytics), subject must be on stable doses of the medication for at least 2 weeks prior to Screening and agrees to remain on stable doses of the medication for the duration of the 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 privacy language compliant with country and/or local requirements, 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 significant middle ear or inner ear surgery, or endolymphatic sac surgery in the affected ear.
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 in the affected ear.
9. Subject has used systemic steroids within 1 month prior to entering the lead-in period.
10. Subject has a history of previous use of intratympanic steroids in the affected ear.
11. Subject has experienced an adverse reaction to dexamethasone.
12. Subject has a history of vestibular migraine. International Classification of Headache Disorders III criteria for vestibular migraine includes a current or past history of migraine with or without aura, vestibular symptoms of moderate or severe intensity lasting between 5 minutes and 72 hours, and at least half of episodes are associated withat least 1 of the 4 following migraineous featires: unilateral headache, pulsating quality, photophobia, and visual aura.
13. Subject has history of drop attacks.
14. Subject is not able to accurately identify and report episodes of vertigo.
15. 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.
16. Subject has used an investigational drug or device in the 3 months prior to screening.
17. Subject has a history of serious substance abuse (e.g. cocaine, heroin) within the preceding 6 months prior to screening.
18. Subject has previously been randomized to a clinical study 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, 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. 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 Manual. The subject identification number and kit number must both be recorded in the subject's record at the Baseline visit.

### 5.2.3. Randomization Algorithm

Subjects will be randomized in a 1:1 ratio treatment groups, stratified 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 QMP 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, blinding procedures must be followed according to the Site Blinding Plan and briefly described below:

Treatment syringes will be pre-loaded by an unblinded QMP. Each syringe will be prepared according to the detailed instructions in the Pharmacy Manual 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. Investigators may also unblind via the Interactive Response Technology (IRT) randomization system for the study, which permits rapid unblinding. In all cases, the Investigator must contact the medical monitor as soon as is practical after unblinding has occurred and emergency 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 the Sponsor.

# 6. DOSAGE AND ADMINISTRATION

## 6.1. Study Drug Administration

OTO-104 and placebo are provided in a Study Drug Kit and prepared by a QMP in a clean location at room temperature. To maintain study blind, preparation should be conducted in a location separate from blinded study personnel. OTO-104 12 mg will be administered as a single, 0.2 mL intratympanic injection of 60 mg/mL OTO-104. Refer to the Pharmacy Manual for instructions on preparing one syringe with OTO-104 or placebo.

OTO-104 or placebo should be prepared with a 1 mL luer-lock sterile syringe only. Luer slip tip syringes are not acceptable for use due to the viscosity of OTO-104. Administration needles can be 25, 26, or 27 gauge and typically range from 1.5 to 3.5 inches in length. Note, OTO-104 and placebo are thermosensitive and will gel when warmed, therefore handling of the section of the syringe barrel containing the study drug and any location on the needle should be limited. If OTO-104 or placebo gels prior to administration, it can be cooled to a liquid by either placing the syringe on an ice pack covered by a sterile drape or in the refrigerator for several minutes.

The recommended injection procedure for intratympanic administration of OTO-104 in Meniere's disease subjects is as follows. A ventilation hole in the tympanic membrane is not needed due to the small injection volume.

1. Place the subject in a recumbent position with the study drug ear upwards.
2. Prior to administration, confirm the ear to be treated is the affected study drug ear.

3. Anesthetize the tympanic membrane by covering the external surface of the inferior-posterior quadrant with a topical preparation containing lidocaine, prilocaine, or other related anesthetic (e.g. [redacted] or lidocaine spray) until the tympanic membrane is numb. If applicable, suction away the topical lidocaine or lidocaine/prilocaine cream. Phenol should not be used to anesthetize the tympanic membrane.
4. Using the prepared syringe, insert the needle into the inferior-posterior quadrant of the tympanic membrane at the level of the round window, taking care not to insert the needle further than necessary.
5. With the needle bevel facing in the inferior-posterior direction, inject 0.2 mL of OTO-104 or placebo towards the round window.

## 6.2. Compliance

OTO-104 or placebo 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 Screening, which will be considered prior therapy. Only stable doses (at least 2 weeks prior to Screening and continuing for the duration of the study) of medications for Meniere's disease symptoms (e.g. diuretics, vestibular suppressants, betahistine, antidepressants, or anxiolytics) are allowed. 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. The medical monitor should be alerted to any changes in concomitant medications. Any changes in concomitant medications will be recorded in the subject's eCRF.

## 7.1. Prohibited Therapy During the Study Period

The following therapies are prohibited during the study:

- 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 prohibited 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 and anti-emetics is allowed as symptomatic relief medications. Medications taken for the acute treatment of a vertigo attack must be recorded as such in the eCRF. The use of intratympanic steroids, intratympanic 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
- SF-36 Social Functioning Subscale assessment
- 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
- Patient Global Impression of Change (PGIC) – Week 8 only
- SF-36 Social Functioning Subscale assessment – Week 8 only
- 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)

If Visit 5 is performed outside the visit window and prior to Day 84, subjects will continue to record their daily vertigo experience after completion of the Visit 5 visit until Day 84 unless the subject is an early discontinuation or withdrew consent.

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
- PGIC
- SF-36 Social Functioning Subscale assessment
- C-SSRS assessment, Since Last Visit version
- Adverse events

## 8.2. Efficacy Evaluations

Efficacy assessments include:

- Characterization of Daily Vertigo Experience
- PGIC (exploratory endpoint)
- SF-36 Social Functioning Subscale assessment (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 a trained staff member 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 = Bedridden

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. Patient Global Impression of Change (PGIC)

The PGIC is a patient-reported outcome that evaluates the change in overall "global" Meniere's disease status as perceived by the subject. The subject is asked: "Since the beginning of the clinical study, how would you rate your Meniere's disease?". The beginning of the clinical study in this context is the time prior to study drug administration. The 7 response categories (and point scores) for the PGIC are:

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

### 8.2.3. Short Form 36 (SF-36) Health Survey – Social Functioning Subscale

The 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, but only the Social Functioning Subscale consisting of 2 questions will be administered.

The 2 questions of the Social Functioning Subscale are:

1) During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
    - 1 – Not at all
    - 2 – Slightly
    - 3 – Moderately
    - 4 – Quite a bit
    - 5 – Extremely
2) During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
    - 1 – All of the time
    - 2 – Most of the time
    - 3 – Some of the time
    - 4 – A little of the time
    - 5 – None of the time

## 8.3. Safety Evaluations

Safety assessments include:

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

### 8.3.1. Vital Signs, 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, unless the examiner determines that there is a contraindication to performing the procedure. 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 250, 500, 1000, 2000, 3000, 4000 and 8000 Hz at Screening and at 500, 1000, 2000, 4000, and 8000 Hz for all other study visits (Baseline, Week 4, Week 8, and Week 12) for air conduction and at 1000, 2000, and 4000 Hz for bone conduction at all study visits. Both air and bone conduction thresholds will be assessed. Pure tone averaging for 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 or certified audiologist or a qualified assistant with appropriate training under the direct supervision of a licensed or certified 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 or qualified healthcare professional. 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.

### 8.3.6. Columbia Suicide Severity Rating Scale (C-SSRS) Assessment

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner 2011). The U.S. Food and Drug Administration requires that a prospective assessment for suicidal ideation and behavior be included in clinical trials involving all drugs and biological products for neurological indications. This is true whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. The C-SSRS assessment fulfills this requirement. 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 Baseline (Screening) or an appearance of any new suicidal ideation or suicide behavior since Baseline 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 Drug 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 Institutional Review Board (IRB) or Research Ethics Committee (REC) in accordance with local regulations.

### 9.2.2. Serious Adverse Events

All SAEs occurring during clinical trials must be reported to Medpace Clinical Safety within 24 hours of Investigator knowledge of event.

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

[redacted]

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

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

### 9.2.3. Pregnancies

Pregnancies occurring after the first dose of investigational product and during participation of the study are considered immediately reportable events. While not considered a SAE unless a serious criterion is met, pregnancies occurring in subjects enrolled on the study must be reported and followed to outcome. The Investigator should complete the pregnancy report eCRF within one (1) working day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the follow-up pregnancy report form should be completed on the pregnancy CRF. Spontaneous abortions should always be reported as SAEs. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

# 10. SUBJECT COMPLETION

## 10.1. Completion

Study subject participation is complete after Visit 5 and completion of the Day 84 diary of their vertigo experience. 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.

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

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

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

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

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

### 10.2.1. Handling of Withdrawals

Subjects will be free to withdraw from the study, including discontinuing study drug administration, and further follow-up of 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 with rationale documented.

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

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

### 10.2.2. Replacements

Subjects who discontinue participation in the study for any reason after dosing will not be replaced.

# 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 main secondary objective of the study is to investigate 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 142 subjects randomized with 1:1 allocation, drug:placebo, with 71 in each group.

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 previously conducted trials by the Sponsor in this indication. The primary analysis will be conducted using a Negative Binomial model at Week 12. For the Negative Binomial analysis, a sample size of 142 subjects will provide approximately 90% power to detect a difference between groups in the 28-day average DVD. It is assumed that the 28-day average DVD will be 2.47 and 4.66 for OTO-104 and placebo, respectively, for an estimated ratio of 0.53. It is also assumed that the distribution shape parameter is 1.04. The assumptions used for the Negative Binomial model were based on the previously conducted study OTO-104-201508 (data on file). The calculations were conducted using EAST v6.5 from Cytel, Inc.

## 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 post-baseline daily diary entry for Week 12. All efficacy analyses 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.

**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 definitive vertigo measurement and at least one post-baseline daily diary entry within Week 9 through 12. 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. The ITT set will be used to assess sensitivity to missing data.

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, 61-64, 65-74, 75-84, ≥85 yrs.)
- Baseline Disease Characteristics
  - Duration of Meniere's Disease
  - Degree of hearing loss
  - Betahistine use

## 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 28-day average 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:

- Severity of vertigo episodes as measured by the Mean Severity Vertigo Score (MSVS) at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)
- The 28-day average of number of days Sick at home or Bedridden (DSB) as a consequence of vertigo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)

- Percent of subjects achieving a 75% reduction from baseline in 28-day average DVD at Week 12
- Percent of subjects achieving a 100% reduction from baseline (i.e., count of zero) in 28-day average DVD at Week 12
- The change from baseline in vertigo frequency (VF) at Week 12 (the 4-week study interval from Week 9 through Week 12), where vertigo frequency is defined as the number of DVDs recorded during the 4-week interval divided by the number of non-missing diary entries for the relevant interval
- Average daily count of vertigo episodes at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)

### 11.5.3. Exploratory Efficacy Endpoints

Exploratory Efficacy Endpoints are:

- The change from baseline in vertigo frequency (VF) at Week 8, where vertigo frequency is defined as the number of DVDs recorded during the 4-week interval divided by the number of non-missing diary entries for the relevant interval
- Severity of vertigo episodes as measured by the Mean Severity Vertigo Score (MSVS) at Week 8
- Average daily count of vertigo episodes at Week 8
- The 28-day average of number of days Sick at home or Bedridden as a consequence of vertigo during each 4-week study interval (i.e., Week 4, Week 8, Week 12)
- The number of 28-day average definitive vertigo days (DVD) at Week 8
- Patient Global Impression of Change (PGIC) at Weeks 8 and 12
- SF-36 Social Functioning Subscale at Weeks 8 and 12

Occurrence of Normal activity, Slight limitation, Moderate limitation, Sick at home, and Bedridden events as a consequence of vertigo at Week 4, Week 8, and Week 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, the 28-day average DVD at Week 12 (the 4-week interval from Week 9 through Week 12), will be compared between OTO-104 and placebo at the 2-tailed, 0.05 alpha level using a Negative Binomial model. This model will include fixed effects for randomized treatment group (OTO-104 vs. placebo) and sex (male vs. female), with the 28-day average DVD from the lead-in period as a covariate.

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 and ITT analysis sets as sensitivity analyses.

The key secondary efficacy endpoint of the Mean Severity Vertigo Score (MSVS) for Week 12 (Week 9 through Week 12) will be analyzed using an ANCOVA model with fixed effects of randomized treatment, group (OTO-104 vs. placebo) and sex (male vs. female), with the subject's average mean severity vertigo score at lead-in period as a covariate.

The key secondary endpoint of the 28-day average of number of days Sick at home or Bedridden (DSB) as a consequence of vertigo at Week 12 will be compared between the treatment groups using using the same Negative Binomial model as specified for the primary analysis and using the 28-day average Lead-in DSB as a covariate. The model will include fixed effects for randomized treatment group (OTO-104 vs. placebo) and sex (male vs. female).

The key secondary endpoints of percent of subjects achieving a 75% and a 100% (i.e., count of zero) reduction from baseline in 28-day average of DVD will be compared between the treatment groups using a chi-square test. The risk difference and the 95% CI around the risk difference will also be provided.

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 analyzed using an ANCOVA model with treatment as a fixed effect and sex as fixed effects with the lead-in period VF as a covariate.

The secondary efficacy endpoint of average daily count of vertigo episodes during 4-week study interval (Week 9 through Week 12) will be using the ANCOVA model specified for the secondary efficacy endpoint of change from baseline in VF at Week 12, using the subject's Average Daily Vertigo Count (ADVC) at lead-in period as a covariate.

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. Severity of vertigo episodes as measured by the mean Vertigo Score at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)
2. The 28-day average number of days Sick at home or Bedridden as a consequence of vertigo at Week 12 (the 4-week (28-day) interval from Week 9 through Week 12)
3. Percent of subjects achieving a 75% reduction from baseline in 28-day average DVD at Week 12.
4. Percent of subjects achieving a 100% reduction from baseline (i.e., count of zero) in 28-day average DVD at Week 12.

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 second key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in favor of OTO-104, then the third key secondary endpoint will be compared and tested. If the third key secondary endpoint comparison between the two treatment groups is tested and the result is statistically significant in

favor of OTO-104, then the fourth key secondary endpoint will be compared and tested. If the comparison between treatment groups is statistically significant for the fourth key secondary endpoint, then it can be claimed that all key secondary endpoints are statistically significant in favor of OTO-104.

At the first key secondary endpoint that does not demonstrate a statistically significant difference between groups in favor of OTO-104, the gate-keeping procedure ends and any subsequent key secondary endpoint p-values will be considered as a nominal p- value(s).

The gate-keeping procedure controls the Type I error for the four planned comparisons and, therefore, there will be no α spending penalty associated with the planned key secondary comparisons.

The remaining secondary endpoints comparisons will not follow the gate-keeping procedure and, therefore, the reported p-values will be reported as nominal p-values. These analyses will be conducted using the FAS only.

All efficacy hypothesis tests will be 2-sided and performed at $\alpha = 0.05$ significance level, unless otherwise specifid in the SAP.

## 11.6. Safety Evaluations

Safety endpoints to be examined include:

- Vital Signs 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, including overall, 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 and overall.

### 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 for air conduction testing will be calculated as the average threshold for the 500, 1000, and 2000 Hz frequencies.

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:

- $\leq 10$ dB or
- $> 10$ 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).

### 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, as well as shift tables displays subjects who move from 'No' to 'Yes' at 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, 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 any algorithms for scoring, 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 14.6; however, the review of such data is not intended to impact the study conduct unless there are safety concerns. As such, it is expected that the 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, [redacted] (one vial needed) and OTO-104 Active (one vial needed).

An appropriate volume of [redacted] 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 [redacted]).

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 [redacted] solution. |
| Placebo | A kit containing: one vial of [redacted] solution. |

## 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 16% poloxamer solution 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 in accordance with instructions on the product label. 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 the Sponsor.

The Investigator will retain and store all original containers returned by the clinical site staff until these containers are inventoried by the study monitor. Unless otherwise instructed by the sponsor, the Investigator agrees at the end of the study to return all original containers, whether empty or containing 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. Institutional Review Board (IRB) and Research Ethics Committee (REC)

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

The IRB or 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 IRB or 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 is typically signed at the Screening Visit (Visit 1) and 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 IRB or REC. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and Sponsor 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 IRB or 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 IRB 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 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

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

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

## 14.3. Record Retention

In compliance with the ICH/GCP guidelines the Investigator/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.

## 14.4. 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.

## 14.5. 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

## 14.6. Data and Safety Monitoring Plan

The Sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from this clinical study and any other clinical study conducted with OTO-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 14.4). 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 Drug Safety within 24 hours following the identification of a SAE (Section 9.2.2). All SAEs will be reviewed by the Sponsor and CRO medical personnel within 1-2 days after receipt whether or not the event was considered associated with study drug. The Sponsor assumes responsibility for appropriate reporting to the regulatory authorities. The Investigator assumes responsibility for reporting events to the IRB or REC in accordance with the IRB or 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 IRBs or RECs as appropriate.

## 14.7. Monitoring

The Sponsor or its representatives will perform on-site monitoring visits as frequently as necessary based on site activity to review protocol compliance, compare eCRFs with individual subject's medical records and clinic charts, and ensure that the study is being conducted according to pertinent regulatory requirements. The dates of the visits will be recorded by the monitor in a 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.

## 14.8. Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to study initiation, and periodic monitoring visits by the Sponsor

or its representatives. 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.

## 14.9. On-Site Audits

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

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

## 14.10. Use of Information and Publication

All information concerning OTO-104, Sponsor 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 the Sponsor. 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 the Sponsor 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 the Sponsor. 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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