Intratympanic Administration of OTO-313 Reduces Tinnitus in Patients with Moderate to Severe, Persistent Tinnitus: A Phase 1/2 Study

Short running head: Phase 1/2 Study of OTO-313 in Patients with Tinnitus

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**Commented [edits1]:** Removed Rayne Fernandez since the preclinical data are now removed

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**ABSTRACT**

**Objective**:

To evaluate the safety and exploratory efficacy of intratympanic administration of OTO-313 in

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**Study Design**: Single intratympanic injection of OTO-313 evaluated in a randomized, double-

**Study Design**: Single intratympanic injection of OTO-313 evaluated in a randomized, double-blind, placebo-controlled Phase 1/2 clinical study.

**Setting**: Tertiary referral centers.

**Patients**: Patients with unilateral tinnitus (moderate to severe) with tinnitus duration 1 to 6 months.

**Interventions**: Intratympanic OTO-313.

**Main Outcome Measures**:

Safety and change from baseline in Tinnitus Functional Index (TFI), daily ratings of tinnitus loudness and annoyance, and Patient Global Impression of Change (PGIC).

**Results**: OTO-313 was well-tolerated with lower incidence of adverse events than placebo.

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**Results**: OTO-313 was well-tolerated with lower incidence of adverse events than placebo. Mean TFI reduction from baseline favored OTO-313 at Week 2, 4 and 8. A clinically meaningful, 13-point improvement on the TFI was observed in 43% (6/14) of OTO-313 patients at both Weeks 4 and 8 versus 13% (2/16) of placebo patients (ad hoc responder analysis, p-value

<0.05). Reductions in daily ratings of tinnitus loudness and annoyance favored OTO-313 compared with placebo. In OTO-313 responders, a strong correlation existed between change from baseline in TFI score and changes in tinnitus loudness, tinnitus annoyance, and PGIC. **Conclusions**: OTO-313 was well-tolerated and demonstrated a higher proportion of responders than placebo across consecutive visits (Weeks 4 and 8) supporting further clinical development of OTO-313 for the treatment of tinnitus.

## INTRODUCTION

Tinnitus or “ringing in the ears”, defined as a perception of sound without a correlated external auditory stimulus, is a common problem that affects millions (i.e., approximately 10% of the adult population in the United States or 21.4 million people suffer from tinnitus) (1). A significant proportion of patients experience moderate to severe tinnitus, which can negatively impact sleep, disrupt ability to focus, create feelings of distress, anxiety, and depression, and lower overall quality of life (2, 3, 4, 5, 6).

At present, there is no cure or approved medications to treat tinnitus (7). Nearly half of patients will seek medical treatment (1). Current management focuses on education and counseling, sound therapy, use of hearing aids, and cognitive behavioral therapy (8). These therapies focus primarily on modulation of patient’s attention and reactions to tinnitus rather than the sensation itself.

Tinnitus often arises as a consequence of noise or other cochlear insults. Although systemically administered agents have been tested in clinical studies in tinnitus aimed at influencing the putative imbalance in auditory firing rates produced by cochlear insults (9, 10), none have been approved to treat tinnitus. One potential pharmacologic approach to treating tinnitus would be to normalize altered neural activity within the cochlea. Excessive activation of the N-methyl-D-aspartic acid (NMDA) subtype of glutamate receptors at the level of the inner hair cell synapses with subsequent deafferentation may be key in altering activity of the auditory nerve and generating subjective tinnitus (11, 12). In animal models of acute tinnitus induced by acute traumatic noise or salicylate, intratympanic administration of NMDA receptor antagonists was shown to reduce “tinnitus-like” behavior (11, 12, 13). These findings suggest that activation of

cochlear NMDA receptors may be an important mechanism for generating tinnitus and that intratympanic NMDA receptor antagonists may have potential as a local cochlear treatment for tinnitus.

Gacyclidine is a high affinity NMDA-receptor antagonist (14), that has shown efficacy in animal models of tinnitus (11). In addition, gacyclidine was administered to the otic compartment in an open label study in patients with chronic tinnitus (15). The drug was generally safe and well-tolerated and reduced subjective ratings of tinnitus in 4 of 6 patients evaluated.

OTO-313 is a lipid-based formulation of gacyclidine that provides sustained exposure to the cochlea after a single intratympanic injection. Intratympanic delivery of drugs permits deposition over the round window membrane, allowing access to the inner ear for more localized delivery to the cochlea and less systemic drug exposure (16).
Herein, we report the safety
and exploratory efficacy of OTO-313 in a Phase 1/2 study.

## MATERIALS AND METHODS

### Phase 1/2 Study Part A: Safety Cohort

A randomized, double-blind, placebo-controlled, Phase 1/2 study was conducted in the United States in 2 parts, Part A: 1 site and Part B: 15 sites screened (12 sites randomized). This study was registered on ClinicalTrials.gov (NCT03918109) and conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical

Practice guidelines and applicable regulatory requirements. The Institutional Review Board (March 18, 2019 by IntegReview #4007596, Investigator: George Atiee, MD) approved the protocol and all participants provided written consent before enrollment.

An initial safety, tolerability and pharmacokinetic cohort was conducted where patients with subjective unilateral or bilateral tinnitus received a single intratympanic injection of either 0.11 mg OTO-313 or placebo (Part A, see Text, Supplemental Digital Content 1). Following review by a Safety Review Committee, a follow-on exploratory efficacy cohort took place in patients with subjective unilateral tinnitus of moderate to severe intensity who received a single intratympanic injection of either 0.32 mg OTO-313 or placebo (Part B).

**Phase 1/2 Study Part B: Safety and Exploratory Efficacy Cohort**

Part B objectives were to evaluate the safety and tolerability of OTO-313 (primary), assess plasma pharmacokinetics of gacyclidine (secondary), and assess preliminary efficacy of OTO-313 measured by change from Baseline visit in Tinnitus Functional Index (TFI) (17, 18) (secondary). Exploratory objectives were to evaluate efficacy of OTO-313 on tinnitus loudness and tinnitus annoyance using patient reported Numeric Rating Scales (NRS) and on tinnitus global status with Patient Global Impression of Change (19, 20, 21).

Eligible patients were aged 18 to 75 years, were consistently aware of their tinnitus throughout much of the waking day, had tinnitus that was likely of cochlear origin (e.g., associated with acute hearing loss from noise trauma, barotrauma, blast trauma, middle ear surgery, age-related hearing loss, resolved otitis media, ototoxic drug exposure) and had an onset of tinnitus of 1 to 6

months prior to signing informed consent. Exclusion criteria included pulsatile tinnitus, tinnitus resulting from traumatic head or neck injury, active middle ear disease including Meniere's disease, abnormality or perforation of the tympanic membrane, any ongoing therapy known to be potentially tinnitus-inducing, severe or untreated depression or anxiety, and systemic or intratympanic steroids within 6 weeks prior to Screening. Stable prior treatments (≥1 month prior to Screening) of antidepressant and anti-anxiety medications, over-the-counter supplements or medications for tinnitus, or use of hearing aids, noise generators, sound therapy devices, and any behavioral therapy for tinnitus were allowed.

Patients were randomized 1:1 (OTO-313:placebo) using a permuted block randomization algorithm (Figure 1). Placebo was comprised of the vehicle (medium-chain triglycerides) that was used to formulate the active study drug OTO-313; there were no differences in viscosity or appearance between OTO-313 and placebo. Randomized patients received a single (0.2 mL volume) intratympanic injection of either OTO-313 or placebo to the affected (study) ear at the Baseline visit. After the intratympanic injection, patients completed the TFI at Weeks 2, 4 and 8. Patients rated their tinnitus loudness and annoyance daily using the electronic diary through the 8-week follow-up period. In a subset of 13 patients, blood samples for pharmacokinetic analysis were obtained at the Baseline visit (pre-dose and 1 hour post administration) and at Week 1.

Safety data were collected at all visits and included collection and evaluation of treatment-emergent adverse events, vital signs, clinical laboratory measurements, otoscopic examinations, audiograms, tympanometry, concomitant medications, and Columbia-Suicide Severity Rating Scale assessments.

**Statistical Analyses**

Part B served as an estimation study with no formal statistical considerations or planned hypothesis testing. The baseline TFI overall score was defined as the average of the TFI score at Screening and at Baseline visit (Day 1). The baseline tinnitus loudness and tinnitus annoyance were the average score for each measurement collected during the 14 days of Lead-In. Change from baseline in the 7-day average NRS ratings of tinnitus loudness or tinnitus annoyance was summarized descriptively at each of Weeks 1 through 8. Patients completed the PGIC, a patient-reported outcome that evaluated the change in overall "global" tinnitus status as perceived by the patient, at Weeks 2, 4, and 8.

The primary efficacy endpoint was the change from baseline to each study visit in TFI overall score. The key ad hoc efficacy endpoint was a responder analysis. Response was defined as achieving at least a 13-point reduction in TFI overall score (considered to be clinically meaningful) at Week 4 and Week 8. Additional TFI response levels were derived and included at least 15, 20, 25, and 30-point reductions. The 25 and 30-point reductions were derived ad hoc.

Secondary efficacy endpoints included: change from baseline to each visit in TFI overall score, change from baseline for each TFI subscale, and by-visit response at each visit. Exploratory endpoints included change from baseline by study week in the 7-day average NRS ratings of tinnitus annoyance and in tinnitus loudness and in PGIC scores at each visit. All efficacy and safety results are summarized descriptively. An ad hoc 1-sided, chi-square test was used to compare response rates between treatment groups.

## RESULTS

### Safety and Tolerability of OTO-313 in Patients with Tinnitus (Parts A and B)

Eight (8) patients were randomized in Part A and 35 patients in Part B (Figure 1). Thirty-one (31) patients in Part B were randomized and completed at least one post-baseline TFI assessment (Evaluable Set). Overall, treatment groups were similar with respect to demographic and baseline characteristics (Table 1). Two Part B patients assigned to OTO-313 deviated from eligibility criteria and were enrolled with bilateral rather than unilateral tinnitus (bilateral tinnitus was allowed in Part A). Based on audiometry, patients exhibited a wide range of hearing thresholds and most Part B patients had slight or mild hearing loss (based on PTA; 16-25 dB and 26-40 dB, respectively). The use of hearing aids as well as psychoactive medications including those for symptoms related to tinnitus (e.g., antidepressants, medications for anxiety and insomnia) was comparable for OTO-313 and placebo groups and therefore unlikely to have an impact on OTO-313 results in this study (Table 1). Of the OTO-313 treated patients, 3/6 responders were on stable doses of antidepressant and anti-anxiety medications compared to 3/8 non-responders, hence the use rate of these medications was similar between responders and non-responders.

A single intratympanic injection of OTO-313 was well-tolerated and patients who received OTO-313 had a lower incidence of adverse events than placebo (Table 2). There were no adverse events that led to withdrawal, and a very low incidence of tympanic membrane perforation (1 OTO-313 patient each in Parts A and B) which resolved by the end of the study. There was one serious adverse event (stress cardiomyopathy), but it was not considered related to study drug. Most adverse events were ear- or injection site-related, were mild to moderate in intensity, and resolved by the end of the study. There were no meaningful changes from baseline in

tympanometry, otoscopy or audiometry. There were no notable changes in clinical laboratory tests, vital signs, or assessment of suicidality.

Plasma concentrations of gacyclidine were below the limit of assay quantitation (≤ 0.1 ng/mL) for both dose levels at all timepoints confirming limited systemic exposure.

**Exploratory Efficacy in Patients with Tinnitus (Part B)**

The mean TFI overall score, NRS loudness and NRS annoyance reduction from baseline trended in favor of OTO-313 at each visit (Table 3). Subgroup analyses were performed and showed differences in favor of OTO-313 for the following subgroups: age ≤ median age (57) at baseline, tinnitus etiology of sensorineural hearing loss and age-related hearing loss, 3-6 months tinnitus duration, 76-100 baseline TFI overall score, and 41-70 dB hearing loss at baseline (see Table, Supplemental Digital Content 2).

One OTO-313 patient did not complete TFI at Week 4 and was not included in the responder analysis. A clinically meaningful, 13-point improvement on the TFI was observed in 43% (6/14) of OTO-313 patients at both Week 4 and Week 8 versus 13% (2/16) of placebo patients (ad hoc p-value for difference in response rates was 0.026) (Figure 2). The higher responder rate for OTO-313 versus placebo was maintained for all TFI improvement levels of 15, 20, 25 and 30 points.

All TFI subscales showed numerical improvement in the OTO-313 group versus placebo (see Table, Supplemental Digital Content 3; see Figure, Supplemental Digital Content 4). The

auditory subscale score displayed the greatest difference between OTO-313 and placebo, in favor of OTO-313. Mean change from baseline in TFI auditory subscale questions for the ability to hear clearly, understand people, and follow conversations for responders showed numerical improvement over time in patients who received OTO-313 compared with those who received placebo (see Table, Supplemental Digital Content 3). Additionally, quality of life, emotional, and sense of control subscales displayed a mean change from baseline in TFI subscale score of at least 13-points.

Treatment with OTO-313 led to numerical reductions in the daily ratings of tinnitus loudness and annoyance (Table 3). The 7-day average tinnitus loudness and annoyance NRS decreased over time in favor of OTO-313 compared with placebo, with a decrease from baseline for the OTO-313 group as early as Week 2 and the largest decrease at Week 8. For the 6 OTO-313 patients who were TFI responders, the mean decrease in tinnitus loudness was -1.7 (1.9) at Week 4 and -2.5 (2.2) at Week 8, and in tinnitus annoyance was -1.9 (1.9) at Week 4 and -2.4 (2.0) at Week 8.

All responders had an improved or unchanged PGIC response category at Week 8 (more details about PGIC in Text, Supplemental Digital Content 1). Correlations existed when assessing the relationship for change from baseline in TFI overall score versus each of PGIC (-0.75), change from baseline in tinnitus annoyance NRS (0.74), and change from baseline in tinnitus loudness NRS (0.79) across all evaluable patients. These correlations were very strong when assessing OTO-313 responders (-0.79, 0.85, 0.90, respectively).

**DISCUSSION**

In patients with persistent subjective tinnitus, intratympanic OTO-313 was well-tolerated and

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persistent subjective tinnitus, intratympanic OTO-313 was well-tolerated and reduced tinnitus across successive 4- and 8-week study visits. Four different tinnitus assessments were utilized: the TFI as a functional measure of tinnitus treatment-related change over the past week, daily ratings of tinnitus loudness and tinnitus annoyance averaged over 1-week intervals, and the PGIC as a self-report of global tinnitus status. The use of multiple measures assessing different aspects of the condition across several recall periods has been used successfully in chronic pain studies (22). Tinnitus has similarities to chronic pain (23) and using a multi-assessment approach may be an optimal method for evaluating efficacy in a subjective condition like tinnitus that relies on self-reports. Mean decreases from baseline in the TFI at each visit (Week 2, Week 4, and Week 8) favored OTO-313 treatment compared to placebo. Similarly, mean reductions from baseline in tinnitus loudness and tinnitus annoyance also trended in favor of OTO-313 versus placebo at each visit, further substantiating the clinical activity of OTO-313.

A reduction of at least 13 points on the TFI overall score is considered a clinically meaningful improvement (17). This TFI improvement level has been used in several tinnitus intervention studies to evaluate the effect of a particular investigational treatment (24, 25, 26). To assess durability of response, we have incorporated the requirement of at least a 13-point TFI improvement at successive study visits (Week 4 and Week 8). This is likely a more conservative estimate of response rather than at a single timepoint reflecting a sustained benefit. For patients who were responders at both Week 4 and Week 8, OTO-313 demonstrated a higher responder

rate (43%) than placebo (13%) at all TFI improvement levels considered to be clinically meaningful (TFI reduction ≥ 13, 15, 20, 25, and 30 points). The difference in the responder rate between OTO-313 and placebo was statistically significant on post hoc analysis (p-value < 0.05) for TFI reductions ≥ 13, 15, and 20 points. The responders also exhibited larger numerical reductions from baseline in tinnitus loudness and tinnitus annoyance scores relative to placebo, and all responders had an improved or unchanged PGIC response category at Week 8. There was a strong relationship between the improvement in TFI score reported by these OTO-313 responders and their improvement in tinnitus loudness and annoyance levels as well as the PGIC based on the calculated correlation coefficients of ≥ 0.8 for these endpoints. These correlations suggest consistency in improvements across the different tinnitus assessments in this study.

Although all TFI subscales were numerically improved in the OTO-313 group versus placebo, the auditory subscale score demonstrated the greatest difference between OTO-313 and placebo, in favor of OTO-313. While the validity of this subscale of the TFI has been questioned (27), speech comprehension and speech-in-noise hearing difficulty are common complaints of tinnitus patients (28). It seems plausible that if a patient's tinnitus has been reduced, the patient would have improved ability to hear clearly, understand people, and follow conversations (the 3 items that comprise the auditory subscale), especially if the patient also had speech-in-noise hearing difficulty. Whether this effect is due to improved attention and cognitive control because of diminished tinnitus is uncertain (29).

Mechanistically, NMDA receptor antagonists like OTO-313 may be effective in the treatment of tinnitus by blocking cochlear NMDA receptors that become overactivated as a result of noise and

other cochlear injuries (11, 12). In this study, only patients who exhibited tinnitus likely of cochlear origin (e.g., associated with acute hearing loss from noise or other trauma, age-related hearing loss, or sensorineural hearing loss) were eligible; those with tinnitus that originated centrally were excluded to better restrict the study population to tinnitus of cochlear origin. In addition, animal studies suggest an optimal time frame after the induction of tinnitus during which NMDA receptor antagonists may be most effective (13). Therefore, we studied patients with relatively recent onset tinnitus of no more than 6 months to better target acute tinnitus. Other clinical studies have evaluated NMDA receptor antagonists in tinnitus using intratympanic administration (21, 30), oral dosing (31), or inhalation (24) with relatively good safety although limited signs of efficacy, perhaps owing to the low potency of those agents or poor target site bioavailability. Gacyclidine is a high affinity
and selective NMDA receptor antagonist and the OTO-313 intratympanic formulation provides pharmacologically-relevant concentrations of gacyclidine to the inner ear (32) – requirements for an effective medication to treat tinnitus.

A single intratympanic injection of OTO-313 in the clinical study was well-tolerated at both dose levels with a low incidence of adverse events. All plasma samples at all timepoints had gacyclidine concentrations that were below the limit of quantitation of the bioanalytical assay, which demonstrates limited exposure following
intratympanic administration of OTO-313. Intratympanic administration of steroids and other medications is becoming more commonplace in the treatment of inner ear disorders (33, 34) because it not only provides more sufficient drug concentrations to the inner ear compared to systemic dosing, but also yields limited plasma exposure, consequently reducing the risk of

systemic side effects. Interestingly, the maximal effect of OTO-313 occurred at 8 weeks post-dose, suggesting that improvements in tinnitus and the functional effects of tinnitus may not be immediate after an OTO-313 injection. This delayed response may be due to time required for NMDA receptor blockade to reverse the tinnitus-related aberrant neuronal activity and to subsequently impact tinnitus perception and the functional effects of tinnitus (e.g., cognition, sleep, emotions), which may themselves take time to ameliorate. Future studies will extend the observation period to evaluate this and the durability of the treatment effect further.

Limitations of this study include the small sample size and limited statistical comparisons, which are common for early-stage clinical studies and will be addressed by evaluating a larger population in future studies. In addition, there was an imbalance between TFI scores at baseline between OTO-313 and placebo groups such that the OTO-313 group had slightly higher scores. It is unknown if the greater degree of functional impact of tinnitus at baseline influenced the response to OTO-313. One could argue either that OTO-313 patients had more opportunity to improve because their tinnitus was more severe, or conversely, that they had a greater barrier to improvement. In future studies, randomization will be stratified to ensure a proper balance in baseline TFI scores between treatment groups. Lastly, this study focused on unilateral tinnitus patients. Since bilateral tinnitus comprises a significant portion of tinnitus patients (35), testing bilateral intratympanic administration will be a future goal for OTO-313 clinical development.

**CONCLUSIONS**

In conclusion, OTO-313 treatment was well-tolerated and demonstrated a higher proportion of

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In conclusion, OTO-313 treatment was well-tolerated and demonstrated a higher proportion of responders versus placebo based on a 13-point clinically meaningful reduction in TFI scores across consecutive study visits (Week 4 and Week 8). Mean improvements from baseline in TFI, tinnitus loudness, and tinnitus annoyance were numerically higher for OTO-313 compared with placebo. Reductions in TFI scores strongly correlated with improvements in tinnitus loudness, tinnitus annoyance, and PGIC. These findings demonstrate safety and exploratory efficacy of OTO-313 and support further clinical development for the treatment of tinnitus.

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TABLES

Table 1. Patient Demographics and Baseline Characteristics.

| | Part A | | Part B | |
|---|---|---|---|---|
| | **OTO-313 0.11 mg N=6** | **Placebo N=2** | **OTO-313 0.32 mg N=15** | **Placebo N=16** |
| Sex, n (%) | | | | |
| Male | 3 (50.0) | 2 (100.0) | 8 (53.3) | 9 (56.3) |
| Female | 3 (50.0) | 0 | 7 (46.7) | 7 (43.8) |
| Age in years, mean (SD) | 62.5 (5.17) | 57.0 (0) | 56.9 (14.5) | 54.5 (10.9) |
| Race, n (%) | | | | |
| White | 6 (100.0) | 2 (100.0) | 14 (93.3) | 14 (87.5) |
| Black or African American | 0 | 0 | 0 | 1 (6.3) |
| Asian | 0 | 0 | 0 | 1 (6.3) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 1 (6.3) | 0 |
| "How did you perceive the beginning of your tinnitus?", n (%) | | | | |
| Abrupt | 4 (66.7) | 0 | 13 (86.7) | 12 (75.0) |
| Gradual | 2 (33.3) | 2 (100.0) | 2 (13.3) | 4 (25.0) |
| "Please describe the pitch of your tinnitus", n (%) | | | | |
| Very High Frequency | 2 (33.3) | 1 (50.0) | 7 (46.7) | 3 (18.8) |
| High Frequency | 3 (50.0) | 1 (50.0) | 7 (46.7) | 10 (62.5) |
| Medium Frequency | 0 | 0 | 1 (6.7) | 2 (12.5) |
| Low Frequency | 1 (16.7) | 0 | 0 | 1 (6.3) |
| Hearing loss based on Baseline PTA (dB), n (%)[c] | | | | |
| Normal: ≤15 and slight hearing loss: 16-26 | 0 | 0 | 5 (33.3) | 8 (50.0) |
| Mild: 26-40 | 1 (16.7) | 0 | 2 (13.3) | 6 (37.5) |
| Moderate: 41-55 | 2 (33.3) | 2 (100.0) | 4 (26.7) | 2 (12.5) |
| Moderate-severe: 56-70 | 2 (33.3) | 0 | 1 (6.7) | 0 |
| Severe: 71-90 and profound hearing loss: >90 | 1 (16.7) | 0 | 2 (13.3) | 0 |
| No response at 2000 and 4000 Hz | 0 | 0 | 1 (6.7) | 0 |
| Use of Hearing Aids, n (%) | 4 (66.7) | 2 (100.0) | 3 (20.0) | 2 (12.5) |

| | Part A | | Part B | |
|---|---|---|---|---|
| | **OTO-313 0.11 mg N=6** | **Placebo N=2** | **OTO-313 0.32 mg N=15** | **Placebo N=16** |
| Relevant Medication Use, n (%) | | | | |
| Psychoanaleptics (e.g., antidepressants) | 2 (33.3) | 1 (50.0) | 5 (33.3) | 5 (31.3) |
| Psycholeptics (e.g., medications for anxiety and insomnia) | 4 (66.7) | 1 (50.0) | 4 (26.7) | 6 (37.5) |
| Other nervous system drugs (e.g., gabapentin, betahistine) | 1 (16.7) | 1 (50.0) | 0 | 0 |
| Analgesics (e.g., tramadol) | 0 | 1 (50.0) | 0 | 0 |
| Unspecified herbal and traditional medicine (e.g., Gingko Biloba) | 0 | 0 | 0 | 1 (6.3) |
| Baseline TFI Total Score, mean (SD) [range][a] | 70.7 (11.5) [55-85] | 86.5 (0.71) [86-87] | 65.9 (17.7) [32-90] | 57.9 (19.6) [29-86] |
| Months since tinnitus onset, mean (SD) [range][b] | 95.8 (87.1) [19.7-238.1] | 49.0 (16.4) [37.4-60.6] | 4.5 (2.0) [1.6-7.6] | 4.2 (1.6) [1.9-6.8] |
| Baseline NRS Loudness, mean (SD)[c] | NA | NA | 7.3 (1.7) | 7.2 (1.5) |
| Baseline NRS Annoyance, mean (SD)[d] | NA | NA | 7.2 (1.8) | 6.7 (1.8) |

NA=not applicable; NRS=Numeric Rating Scale; PTA= pure tone average; SD=standard deviation; TFI=Tinnitus Functional Index.

[a]Average Baseline TFI overall score was computed as the average of the TFI overall scores at the Screening and Baseline visits, prior to exposure to study drug. A negative change in TFI overall score from Baseline indicated improvement in tinnitus.

[b]Months since tinnitus onset was calculated by ([date of informed consent – date of tinnitus onset]/365.25)*12.

[c]Baseline tinnitus loudness NRS score was defined as the sum of all scores over the 2 weeks of the Lead-in period immediately prior to exposure to study product divided by the number of non-missing days over the same period.

[d]Baseline tinnitus annoyance NRS score was defined as the sum of all scores over the 2 weeks of the Lead-in period immediately prior to exposure to study product divided by the number of non-missing days over the same period.

Includes all patients randomized in Part A and the Evaluable Set in Part B (all randomized patients who received study drug and had at least one post-baseline TFI assessment).

Table 2. All Adverse Events and Treatment-Emergent Adverse Events (Safety Set) (Part B)

| | **OTO-313 0.32 mg N=17** | | **Placebo N=18** | |
|---|---|---|---|---|
| **System Organ Class Preferred Term** | **All Adverse Events** | **Treatment Related TEAE** | **All Adverse Events** | **Treatment Related TEAE** |
| Number (%) of patients with at least 1 TEAE reported[a] | 5 (29.4) | 2 (11.8) | 10 (55.6) | 3 (16.7) |
| Ear and labyrinth disorders | 3 (17.6) | 2 (11.8) | 7 (38.9) | 3 (16.7) |
| Ear pain | 2 (11.8) | 1 (5.9) | 1 (5.6) | 0 |
| Ear discomfort | 1 (5.9) | 1 (5.9) | 1 (5.6) | 1 (5.6) |
| Hypoacusis | 1 (5.9) | 1 (5.9) | 1 (5.6) | 1 (5.6) |
| Tinnitus[b] | 1 (5.9) | 1 (5.9) | 4 (22.2) | 2 ( 11.1) |
| Conductive deafness | 0 | 0 | 1 (5.6) | 1 (5.6) |
| Ear pruritus | 0 | 0 | 1 (5.6) | 0 |
| Ear haemorrhage | 0 | 0 | 1 (5.6) | 0 |
| General disorders and administration site conditions | 1 (5.9) | 0 | 1 (5.6) | 0 |
| Injection site erythema | 0 | 0 | 1 (5.6) | 0 |
| Injection site haemorrhage | 1 (5.9) | 0 | 0 | 0 |
| Infections and infestations | 0 | 0 | 2 ( 11.1) | 0 |
| Acute sinusitis | 0 | 0 | 1 (5.6) | 0 |
| Gastroenteritis viral | 0 | 0 | 1 (5.6) | 0 |
| Nasopharyngitis | 0 | 0 | 1 (5.6) | 0 |

| | | | | |
|---|---|---|---|---|
| Injury, poisoning and procedural complications | 1 (5.9) | 0 | 1 (5.6) | 0 |
| Back injury | 1 (5.9) | 0 | 0 | 0 |
| Ear injury | 1 (5.9) | 0 | 0 | 0 |
| Face injury | 1 (5.9) | 0 | 0 | 0 |
| Fall | 1 (5.9) | 0 | 0 | 0 |
| Nerve injury | 0 | 0 | 1 (5.6) | 0 |
| Nervous system disorders | 0 | 0 | 2 (11.1) | 0 |
| Sciatica | 0 | 0 | 1 (5.6) | 0 |
| Tension headache | 0 | 0 | 1 (5.6) | 0 |
| Skin and subcutaneous tissue disorders | 0 | 0 | 2 (11.1) | 0 |
| Eczema | 0 | 0 | 1 (5.6) | 0 |
| Rash | 0 | 0 | 1 (5.6) | 0 |
| Cardiac disorders | 1 (5.9) | 0 | 0 | 0 |
| Stress cardiomyopathy | 1 (5.9) | 0 | 0 | 0 |

MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
[a]If a patient experienced more than 1 episode of an adverse event, the patient was counted once for that preferred term. If a patient had more than 1 AE in a system organ class, the patient was counted only once in that system organ class.
[b]One placebo patient had a tinnitus TEAE with unknown relationship to study treatment
n=number of patients reporting at least 1 adverse event with that system organ class; (%)=percentage of patients in treatment group (N).
Incidences are displayed in descending order of frequency of system organ class and then by descending order of preferred term within each system organ class, based on the OTO-313 frequency. System organ class was based on Version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Safety set includes all patients who received study drug in Part B.

Table 3. Change from Baseline in TFI Overall Score, Tinnitus Loudness and Tinnitus Annoyance (Part B; Evaluable Set)

| | **OTO-313 N=15** | **Placebo N=16** |
|---|---|---|
| Week 2 – mean (SD) | | |
| TFI Overall Score | -9.3 (19.7) | -4.1 (14.5) |
| NRS Loudness | -0.6 (1.3) | -0.2 (1.0) |
| NRS Annoyance | -0.5 (1.3) | -0.1 (1.1) |
| Week 4 – mean (SD) | | |
| TFI Overall Score | -9.4 (20.0) | -6.6 (16.2) |
| NRS Loudness | -0.7 (1.7) | -0.01 (0.9) |
| NRS Annoyance | -0.6 (1.7) | 0.05 (1.1) |
| Week 8 – mean (SD) | | |
| TFI Overall Score | -12.9 (25.2) | -4.3 (18.2) |
| NRS Loudness | -1.1 (1.8) | -0.3 (1.4) |
| NRS Annoyance | -1.2 (1.8) | -0.4 (1.4) |

NRS=Numeric Rating Scale; SD=standard deviation; TFI=Tinnitus Functional Index.
Average Baseline TFI overall score was computed as the average of the TFI overall scores at the Screening and Baseline visits, prior to exposure to study drug. A negative change in TFI overall score from Baseline indicated improvement in tinnitus.
Baseline tinnitus loudness NRS score was defined as the sum of all scores over the 2 weeks of the Lead-in period immediately prior to exposure to study product divided by the number of non-missing days over the same period.
Baseline tinnitus annoyance NRS score was defined as the sum of all scores over the 2 weeks of the Lead-in period immediately prior to exposure to study product divided by the number of non-missing days over the same period.
Evaluable Set includes all randomized patients in Part B who received study drug and had at least one post-baseline TFI assessment.

FIGURES

Figure 1. Patient Disposition for Part B

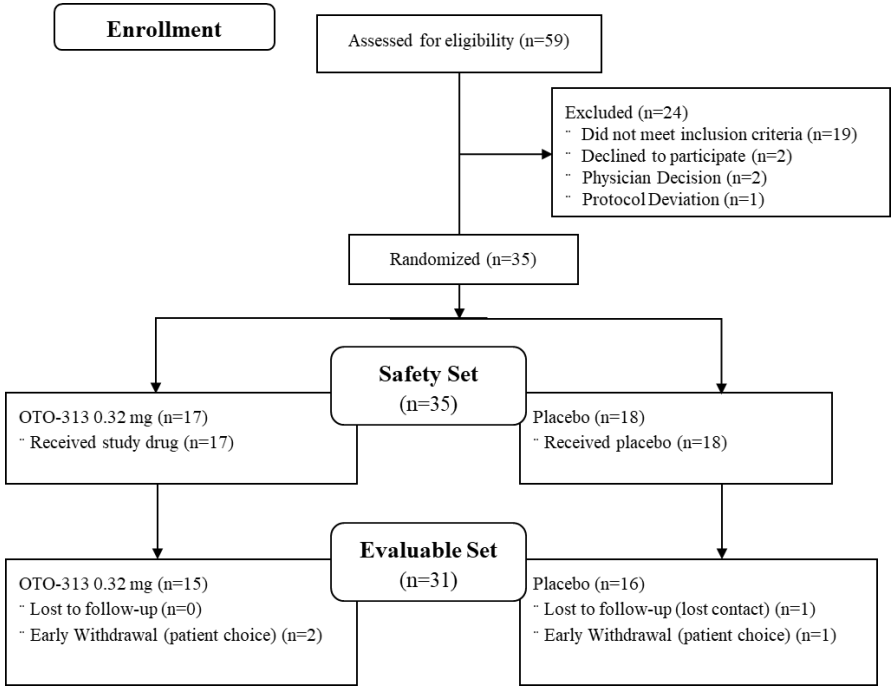
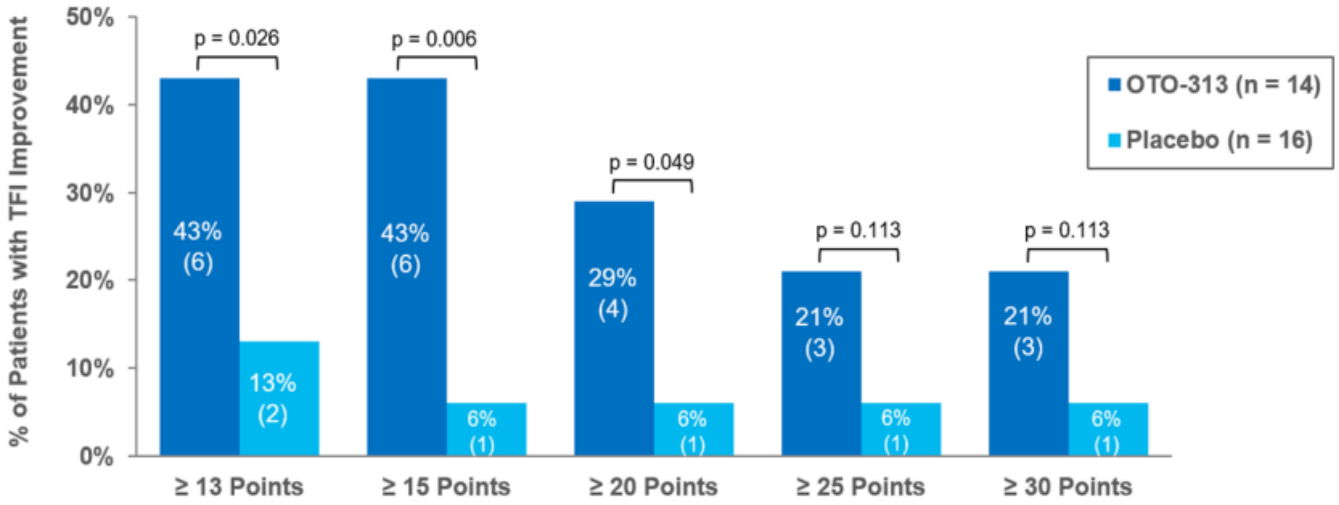


Figure 2. TFI Responder Analysis (Part B; Evaluable Set)
Responders with TFI Improvement at Both Week 4 and Week 8




TFI=Tinnitus Functional Index.
P-values based on 1-sided test of response rate difference between OTO-313 and placebo (post hoc).
Number of patients shows below percentage
One OTO-313 patient did not complete the TFI at Week 4 and was not a responder at Week 8.

SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1.

**Part A**

Objectives in Part A were to evaluate the safety and tolerability of OTO-313 (primary) and assess plasma pharmacokinetics of gacyclidine (secondary). Part A consisted of a 2-week Screening period and a 4-week Follow-up period. Patients underwent serial blood sampling for pharmacokinetic analysis at the Baseline visit (Day 1 through 24 hours post-administration), and Day 8 with follow-up visits for safety and efficacy assessments at Week 1, Week 2, and Week 4. Because acceptable safety and tolerability was observed for 8 days post-administration of the 0.11 mg dose level in Part A, Part B was initiated with the 0.32 mg dose level of OTO-313. Sample size for Part A was selected based on clinical judgment and not on statistical considerations.

**Part B**

Part B consisted of a 2-week Screening period, a 2-week Lead-in assessment period, and an 8-week Follow-up period. Patients completed the TFI at Screening and Baseline visits and must have had a score of ≥25 at each TFI assessment for eligibility. During the 2-week Lead-in period, patients entered ratings of tinnitus loudness and tinnitus annoyance (using NRS for each measure) each day into an electronic diary. Additional safety and/or exploratory assessments were completed at the Baseline visit and Weeks 1, 2, 4 and 8 (end of study).

**Patient Global Impression of Change (PGIC)**

Three (3) of 15 patients who received OTO-313 reported their symptoms were very much improved on the PGIC at Week 8 compared with no patients in the placebo group at any visit

(Baseline, Weeks 1, 2, 4 or 8). A higher percentage of patients in the placebo group reported their symptoms unchanged at Week 1 (10/16, 62.5%), Week 2 (9/16, 56.3%), Week 4 (7/15, 43.8%), and Week 8 (10/16, 62.5%) compared with those in the OTO-313 group at Weeks 1 and 2 (7/15, 46.7%), Week 4 (4/15, 26.7%), and Week 8 (5/15, 33.3%). Of the 6 OTO-313 TFI responders, 5/6 (83.3%) patients scored much improved or minimally improved on the PGIC at Week 4. Similarly, at Week 8, 5/6 patients (83.3%) scored very much improved, much improved, or minimally improved on the PGIC.

Supplemental Digital Content
2. Table of the Mean (SD) Change from Baseline in TFI Overall Scores by Treatment Group,

| **Subgroup**<br>**Visit** | **OTO-313 0.32 mg**<br>**N=15** | **Placebo**<br>**N=16** |
|---|---|---|
| Male | | |
| Week 4 | -8.4 (17.95) (n=7) | -1.9 (15.37) (n=9) |
| Week 8 | -13.3 (26.05) (n=8) | 0.1 (14.77) (n=9) |
| Tinnitus etiology: Sensorineural hearing loss | | |
| Week 4 | -7.4 (13.99) (n=5) | -6.9 (22.49) (n=8) |
| Week 8 | -13.0 (22.21) (n=5) | -5.1 (23.04) (n=8) |
| Tinnitus etiology: Age-related hearing loss | | |
| Week 4 | -33.5 (26.16) (n=2) | -14.0 (NC) (n=1) |
| Week 8 | -39.5 (33.23) (n=2) | -27.0 (NC) (n=1) |
| Duration of tinnitus: >3-6 months | | |
| Week 4 | -13.9 (20.25) (n=9) | -5.4 (19.54) (n=11) |
| Week 8 | -17.4 (26.79) (n=10) | -5.3 (21.42) (n=11) |
| Average Baseline TFI overall score: 76-100 | | |
| Week 4 | -15.0 (23.87) (n=6) | -6.8 (3.03) (n=5) |
| Week 8 | -22.2 (31.57) (n=6) | -5.2 (7.09) (n=5) |
| Degree of hearing loss at Baseline[a]: 41-70 dB | | |
| Week 4 | -21.4 (21.84) (n=5) | -11.5 (2.12) (n=2) |
| Week 8 | -33.0 (28.08) (n=5) | 3.5 (6.36) (n=2) |

dB=decibel; NC=not calculable; SD=standard deviation; TFI =Tinnitus Functional Index.
[a]Based on Pure Tone Average at 1000, 2000, and 4000 Hz.
Average Baseline TFI overall score was computed as the average of the TFI overall scores at the Screening and Baseline visits, prior to exposure to study drug. A negative change in TFI overall score from Baseline indicated improvement in tinnitus.
Change from Baseline was defined as visit value – Baseline value.

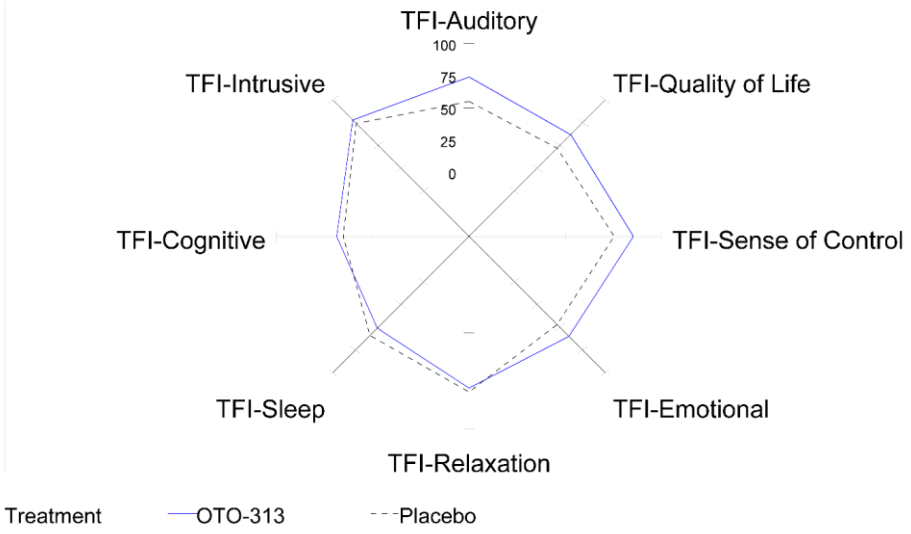
Supplemental Digital Content 3. Table of the Change from Baseline in TFI Auditory Subscale Questions in Responders (Part B; Evaluable Set, Responders)

| **Visit**<br>**Change from Baseline Category** | **OTO-313 0.32 mg**<br>**N=6** | **Placebo**<br>**N=2** |
|---|---|---|
| Week 4 – mean (SD) | | |
| Ability to hear clearly | -3.1 (2.8) | -2.3 (3.2) |
| Ability to understand people | -3.0 (2.6) | -2.0 (2.8) |
| Ability to follow conversations | -4.3 (2.2) | -1.8 (2.5) |
| Week 8 – mean (SD) | | |
| Ability to hear clearly | -4.9 (2.3) | -2.8 (3.9) |
| Ability to understand people | -4.8 (2.4) | -3.0 (4.2) |
| Ability to follow conversations | -5.3 (2.1) | -2.8 (3.9) |

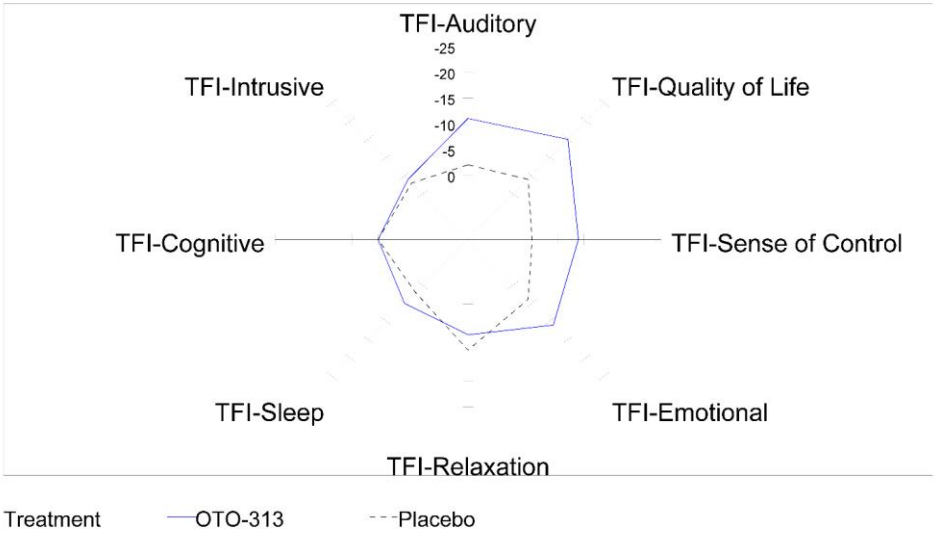
SD=standard deviation; TFI=Tinnitus Functional Index.
Average Baseline TFI overall score was computed as the average of the TFI overall scores at the Screening and Baseline visits, prior to exposure to study drug. A negative change in TFI overall score from Baseline indicated improvement in tinnitus.
Responders were defined as patients with at least a 13-point improvement on the TFI at Weeks 4 and 8.

Supplemental Digital Content 4. Radar Plots of Change from Baseline in TFI Subscale Scores by Treatment and Visit (Part B/Evaluable Set). A greater separation in lines indicates a greater difference between OTO-313 and placebo.

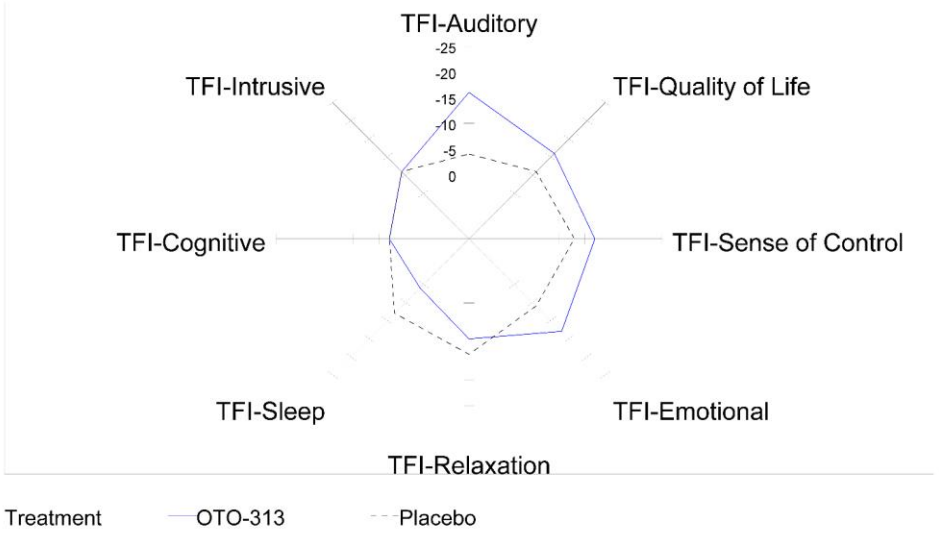
A. Baseline Visit



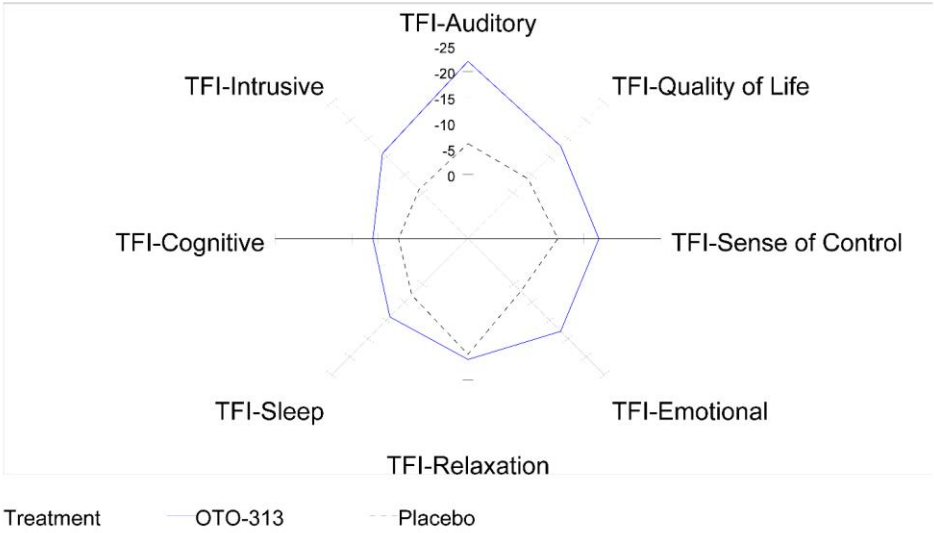
B. Week 2


TFI-Auditory
-25
-20
-15
-10
-5
0
TFI-Intrusive
TFI-Quality of Life
TFI-Cognitive
TFI-Sense of Control
TFI-Sleep
TFI-Emotional
TFI-Relaxation
Treatment
OTO-313
Placebo

C. Week 4


TFI-Auditory
-25
-20
-15
-10
-5
0
TFI-Quality of Life
TFI-Sense of Control
TFI-Emotional
TFI-Relaxation
TFI-Sleep
TFI-Cognitive
TFI-Intrusive
Treatment
OTO-313
Placebo

D. Week 8




TFI=Tinnitus Functional Index.
Average baseline TFI score for each question was computed as the average of the TFI question score at the Screening and Baseline visits, prior to exposure to study drug. Change from baseline was defined as visit value – baseline value.