Supplemental Digital Content

Supplemental Digital Content 1. Text that describes more details about the clinical study methods and results.

**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, Visit, and Subgroup (Part B/Evaluable Set)

| **Subgroup Visit** | **OTO-313 0.32 mgN=15** | **PlaceboN=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 Baselinea: 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.

aBased 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** **Change from Baseline Category** | **OTO-313 0.32 mgN=6** | **PlaceboN=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



C. Week 4



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.