OTONOMY®

Targeted Medicines for the Ear

OTO-313 Program Review

May 6, 2019

Forward-Looking Statements

Safe Harbor Statement

These slides and the accompanying oral presentation (the “Presentation”) contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements generally relate to future events or future financial or operating performance of Otonomy, Inc. (“Otonomy”). Forward-looking statements in this Presentation include, but are not limited to plans, trial design and conduct for the Phase 1/2 trial for OTO-313, and expectations regarding market opportunities and reimbursement for OTO-313. Otonomy’s expectations regarding these matters may not materialize, and actual results in future periods are subject to risks and uncertainties. Actual results may differ materially from those indicated by these forward-looking statements as a result of these risks and uncertainties, including but not limited to: Otonomy’s limited operating history and its expectation that it will incur significant losses for the foreseeable future; Otonomy’s ability to obtain additional financing; Otonomy’s dependence on the regulatory success and advancement of its product candidates; the uncertainties inherent in the drug development process, including, without limitation, Otonomy’s ability to adequately demonstrate the safety and efficacy of its product candidates, the nonclinical and clinical results for its product candidates, which may not support further development, and challenges related to patient enrollment in clinical trials; Otonomy’s ability to obtain regulatory approval for its product candidates; side effects or adverse events associated with Otonomy's product candidates; Otonomy’s ability to successfully commercialize its product candidates, if approved; competition in the biopharmaceutical industry; Otonomy’s dependence on third parties to conduct nonclinical studies and clinical trials; Otonomy’s dependence on third parties for the manufacture of its product candidates; Otonomy’s dependence on a small number of suppliers for raw materials; Otonomy’s ability to protect its intellectual property related to its product candidates in the United States and throughout the world; expectations regarding potential market size, opportunity, position and growth, and reimbursement; Otonomy’s ability to manage operating expenses; implementation of Otonomy’s business model and strategic plans for its business, products and technology; and other risks. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in Otonomy’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the "SEC") on May 6, 2019, and Otonomy’s future reports to be filed with the SEC. This Presentation is dated as of May 6, 2019 and based on information available to Otonomy as of that date, and Otonomy undertakes no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Persistent and Chronic Tinnitus **Affects Millions**

Tinnitus is perception of hearing noise when there is no sound

~ 10% OF U.S. ADULTS
experience tinnitus

Can severely impact
ABILITY TO SLEEP OR RELAX,
leads to anxiety and depression

#1 service-related disability in
U.S. MILITARY[1]

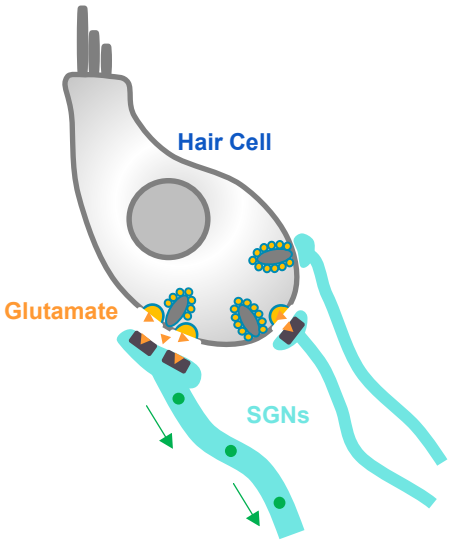
~ 8M report
MODERATE TO SEVERE
bothersome level[2]

NO FDA-APPROVED DRUG TREATMENTS
or standard of care for this condition

[1]United States Department of Defense; [2]ClearView Healthcare Partners analysis (2018)

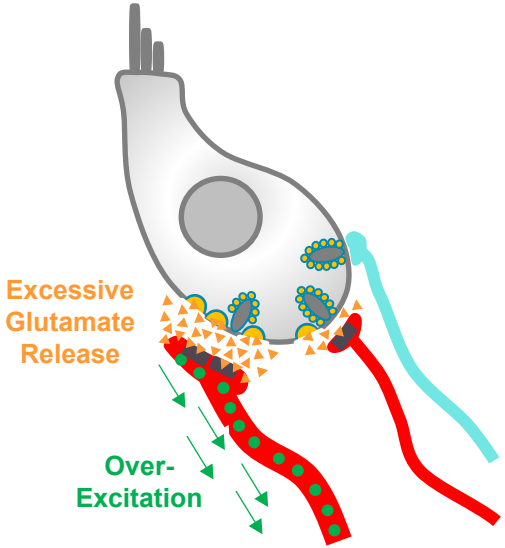
Rationale for NMDA Receptor Antagonist **to Treat Tinnitus**

Normal



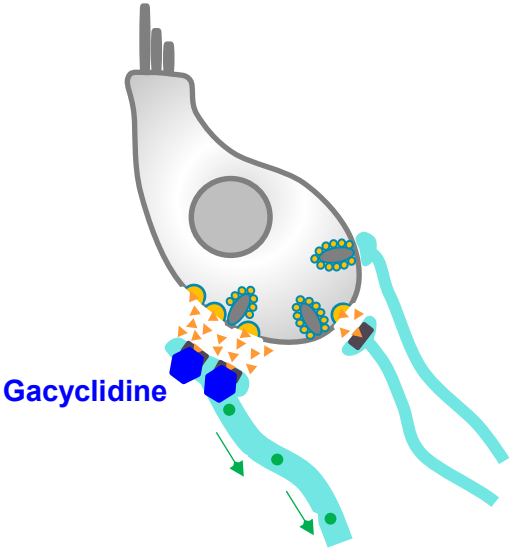
During normal hearing, hair cells release glutamate to activate NMDA receptors on spiral ganglion neurons (SGNs) to relay sound information to the brain

Damage ⟶ Tinnitus



Cochlear injury (e.g., from noise or trauma) can produce excessive glutamate release and over-activation of the NMDA receptor sub-type leading to tinnitus

Tinnitus Treatment

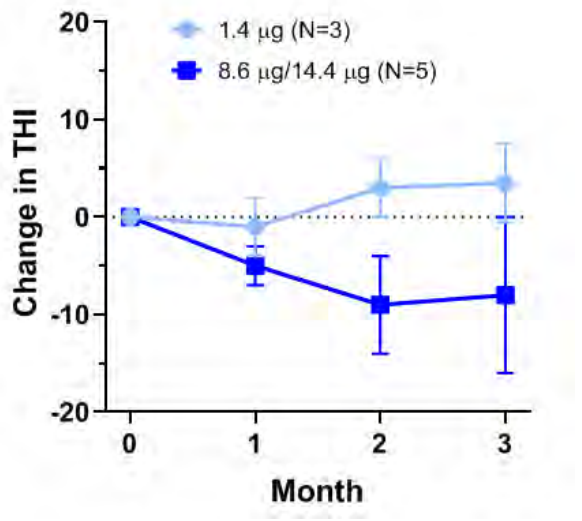


Inhibition of over-excited SGNs with a selective NMDA receptor antagonist can reduce tinnitus

OTO-313 Has Attractive Profile **for Tinnitus Treatment**

- OTO-313 is sustained-exposure formulation of gacyclidine – weeks of exposure from single IT injection
- Gacyclidine is a potent and selective NMDA receptor antagonist
- Preclinical data shows inhibition of spontaneous neuronal activity in SGNs and POC in tinnitus model
- Effect of gacyclidine on tinnitus demonstrated in pilot clinical study

Pilot Clinical Study Demonstrated Dose-Dependent Improvement in TINNITUS HANDICAP INVENTORY (THI)



In open-label Phase 1 study conducted by NeuroSystec, gacyclidine was infused into the cochlea for 48 hours

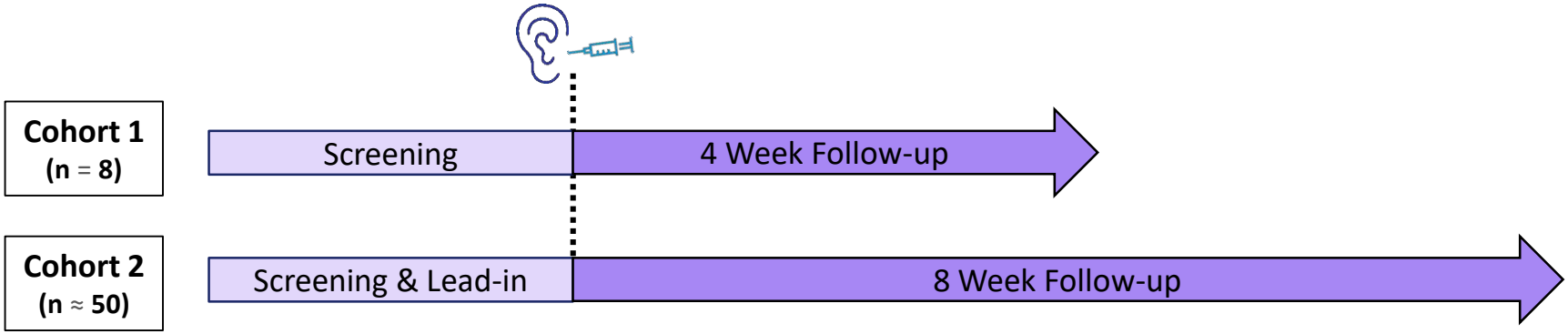
Successful Phase 1 Study Completed with Initial Formulation

- Phase 1 safety study in normal volunteers completed with OTO-311 (formulation of gacyclidine in thermosensitive polymer)
- Single intratympanic administration was safe and well-tolerated
- No serious adverse events reported
- Decision to move to different formulation based on improved pharmacokinetic properties with **OTO-313**

Phase 1/2 POC Trial for OTO-313 in Tinnitus Patients

Randomized, double-blinded, placebo-controlled safety and exploratory efficacy study of OTO-313 given as a single intratympanic injection in subjects with tinnitus

- Initial patient cohort for safety and tolerability assessment (**enrollment completed**)
- Followed by ≈ 50 patients with subjective, unilateral, persistent tinnitus of cochlear origin
- Inclusion requires that patient's tinnitus severity exceeds specified level
- Randomized 1:1 for single intratympanic injection of OTO-313 or placebo



Exploratory Efficacy Endpoints in Phase 1/2 Clinical Trial

- Tinnitus Functional Index (TFI):
  - Validated clinical instrument that assesses tinnitus severity and functional impact on patient
  - Can be used to measure treatment-related changes
- Tinnitus Loudness Rating Scale
- Tinnitus Annoyance Rating Scale
- Patient Global Impression of Change (PGIC)

The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus

Mary B. Meikle,[1] James A. Henry,[1,2] Susan E. Griest,[1,2] Barbara J. Stewart,[1] Harvey B. Abrams,[3] Rachel McArdle,[3] Paula J. Myers,[4] Craig W. Newman,[5] Sharon Sandridge,[5] Dennis C. Turk,[6] Robert L. Folmer,[1,2] Eric J. Frederick,[7] John W. House,[8] Gary P. Jacobson,[9] Sam E. Kinney,[5] William H. Martin,[1] Stephen M. Nagler,[10] Gloria E. Reich,[1] Grant Searchfield,[11] Robert Sweetow,[12] and Jack A. Vernon[1]

Editor's Note: The first author of this article, Dr. Mary B. Meikle, passed away on February 5, 2011. Her more than 40-year career in hearing research focused specifically on the diagnosis and clinical care of patients with tinnitus. This publication, presented as a collaborative research effort with coauthors from across the United States and from New Zealand, proposes a new tool for establishing a baseline measurement of tinnitus and its treatment outcomes. It is Dr. Meikle's final scientific publication.

Objectives: Chronic subjective tinnitus is a prevalent condition that causes significant distress to millions of Americans. Effective tinnitus treatments are urgently needed, but evaluating them is hampered by the lack of standardized measures that are validated for both intake assessment and evaluation of treatment outcomes. This work was designed to develop a new self-report questionnaire, the Tinnitus Functional Index (TFI), that would have documented validity both for scaling the severity and negative impact of tinnitus for use in intake assessment and for measuring treatment-related changes in tinnitus (responsiveness) and that would provide comprehensive coverage of multiple tinnitus severity domains.

Design: To use preexisting knowledge concerning tinnitus-related problems, an Item Selection Panel (17 expert judges) surveyed the content (175 items) of nine widely used tinnitus questionnaires. From those items, the Panel identified 13 separate domains of tinnitus distress and selected 70 items most likely to be responsive to treatment effects. Eliminating redundant items while retaining good content validity and adding new items to achieve the recommended minimum of 3 to 4 items per domain yielded 43 items, which were then used for constructing TFI Prototype 1.

Prototype 1 was tested at five clinics. The 326 participants included consecutive patients receiving tinnitus treatment who provided informed consent—constituting a convenience sample. Construct validity of Prototype 1 as an outcome measure was evaluated by measuring responsiveness of the overall scale and its individual items at 3 and 6 mo follow-up with 65 and 42 participants, respectively. Using a predetermined list of criteria, the 30 best-functioning items were selected for constructing TFI Prototype 2.

Prototype 2 was tested at four clinics with 347 participants, including 155 and 86 who provided 3 and 6 mo follow-up data, respectively. Analyses were the same as for Prototype 1. Results were used to select the 25 best-functioning items for the final TFI.

Results: Both prototypes and the final TFI displayed strong measurement properties, with few missing data, high validity for scaling of tinnitus severity, and good reliability. All TFI versions exhibited the same eight factors characterizing tinnitus severity and negative impact. Responsiveness, evaluated by computing effect sizes for responses at follow-up, was satisfactory in all TFI versions.

In the final TFI, Cronbach's alpha was 0.97 and test–retest reliability 0.78. Convergent validity ($r = 0.86$ with Tinnitus Handicap Inventory [THI]; $r = 0.75$ with Visual Analog Scale [VAS]) and discriminant validity ($r = 0.56$ with Beck Depression Inventory–Primary Care [BDI-PC]) were good. The final TFI was successful at detecting improvement from the initial clinic visit to 3 mo with moderate to large effect sizes and from initial to 6 mo with large effect sizes. Effect sizes for the TFI were generally larger than those obtained for the VAS and THI. After careful evaluation, a 13-point reduction was considered a preliminary criterion for meaningful reduction in TFI outcome scores.

Conclusions: The TFI should be useful in both clinical and research settings because of its responsiveness to treatment-related change, validity for scaling the overall severity of tinnitus, and comprehensive coverage of multiple domains of tinnitus severity.

(Ear & Hearing 2011;32;1–➔)

INTRODUCTION

Chronic subjective tinnitus (ringing or other sounds audible only to the affected individual) is a prevalent condition affecting millions of Americans, many of whom experience significant distress as a result (Hoffman & Reed 2004). The disabling effects of severe tinnitus resemble many effects associated with chronic pain (Moller 2007), typically including sleep interference; cognitive difficulties (particularly with concentration); difficulties at work, at home, and in social relationships; and negative emotional reactions including anxiety, frustration, anger, and depression (Tyler & Baker 1983; Stouffer & Tyler 1990; Axelsson 1992; Meikle 1992; Dobie 2004b).

Despite many efforts to provide relief for tinnitus over the past three decades, there is little agreement concerning the relative merits of the various treatments used (Noble & Tyler 2007). Evaluating the efficacy of tinnitus treatments is hampered by the lack of standardized outcome measures (Axelsson 1992; Meikle 1992; Dobie 2004a; Kamalski et al. 2010). Clinical trials of proposed treatment efforts would benefit greatly from standardization of tinnitus measures. Standardization would improve comparability of treatment effects between different treatment

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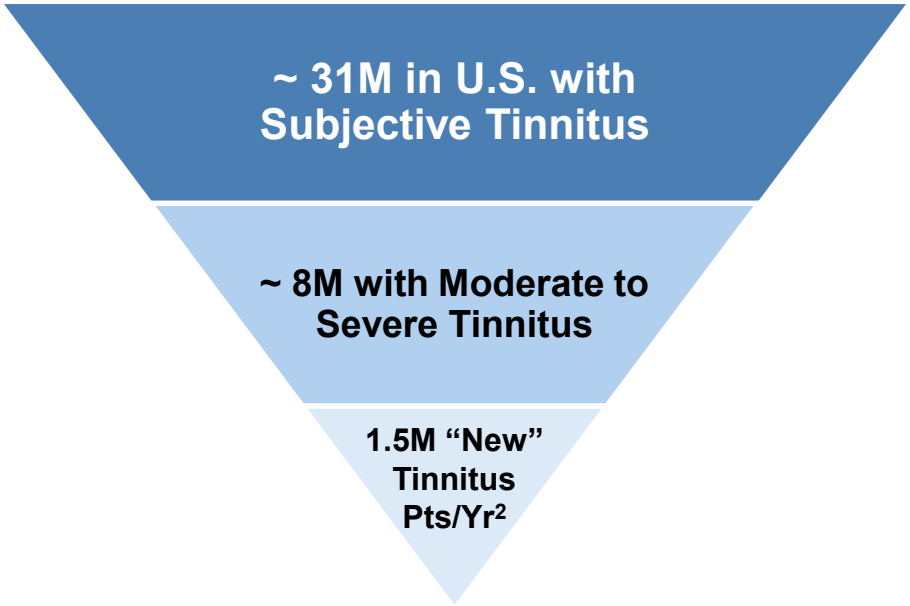
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and text of this article on the journal's Web site (www.ear-hearing.com).

OTO-313 Program Summary: **Phase 1/2 Results in 1H20**

- NMDA receptor antagonists represent a viable treatment approach for tinnitus based on the mechanism of action and preclinical data
- Gacyclidine is a potent and selective NMDA receptor antagonist
- An initial formulation of gacyclidine (OTO-311) was safe and well-tolerated in a Phase 1 safety study
- OTO-313 is an improved formulation, which provides increased inner ear exposure of gacyclidine
- Phase 1/2 clinical trial has been initiated with results expected in 1H20

OTO-313 Market Opportunity **is Significant**

Current Landscape[1]



OTO-313 Market Potential

- No drug treatments approved by FDA; current therapies help patients cope but do not treat tinnitus pathophysiology
- Opportunity to create SOC treatment
- Initial focus on patients early after onset
- Buy-and-bill model; disease burden supports pricing comparable to CGRP's
- > $1B U.S. sales potential[1]

[1]Clearview Healthcare Partners analysis; [2]IMS patient-centric data: patients treated for tinnitus in a single year with no tinnitus diagnosis in prior 2 years