OTONOMY®

Targeted Medicines for the Ear

Corporate Presentation

March 2021

Forward-Looking Statements

Safe Harbor Statement

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Broad Pipeline Targeting Large Market Opportunities

Total Market Potential by Condition:

~39 M in U.S.

Vertigo ~11 M

OTIVIDEX®: additional Phase 3 trial in Ménière's Disease failed primary endpoint; analysis of results ongoing

Tinnitus ~7.8 M

OTO-313: positive Phase 1/2 trial results; expect to initiate Phase 2 trial in 1Q21 with results mid-2022

Hearing Loss ~20.5 M

OTO-413: positive Phase 1/2 trial results; expect to initiate expansion study in 2Q21 with results mid-2022

OTO-825: GJB2 gene Tx for congenital hearing loss

OTO-510: cisplatin-induced hearing loss

OTO-6XX: severe hearing loss

Source: ClearView Healthcare Partners (2018): analysis based on **patients with moderate to severe symptoms**

OTIVIDEX Phase 3 Trial Failed Primary Endpoint

- Enrolled 149 Ménière's Disease patients in U.S. and Europe
- Primary endpoint: count of definitive vertigo days in Month 3 for OTIVIDEX vs. placebo

p-value for Primary Endpoint	Intent-to-Treat Population (n=148)	Per Protocol Population (n=136)
Negative Binomial Model	**0.312**	**0.031**
Generalized Poisson Model	**0.340**	**0.030**

- Analysis underway to understand difference observed between ITT and per protocol

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]

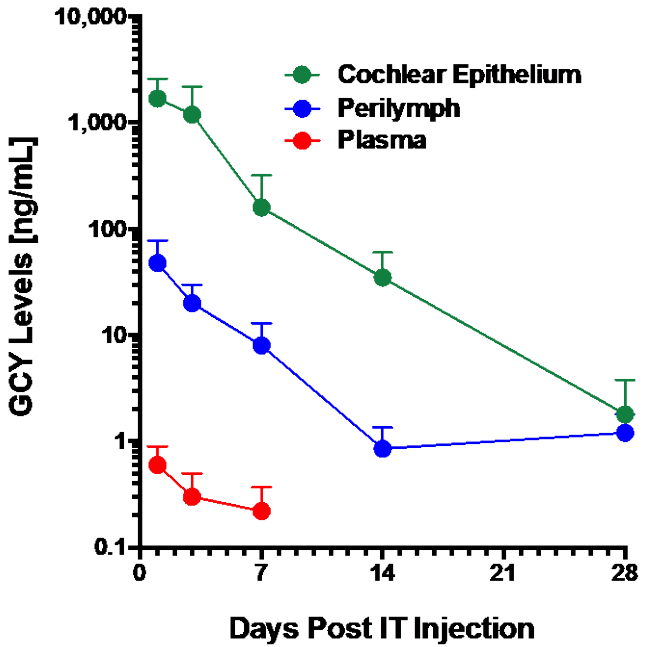
NO FDA-APPROVED DRUG TREATMENTS
or standard of care for this condition

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

OTO-313 Has Attractive Profile for Tinnitus Treatment

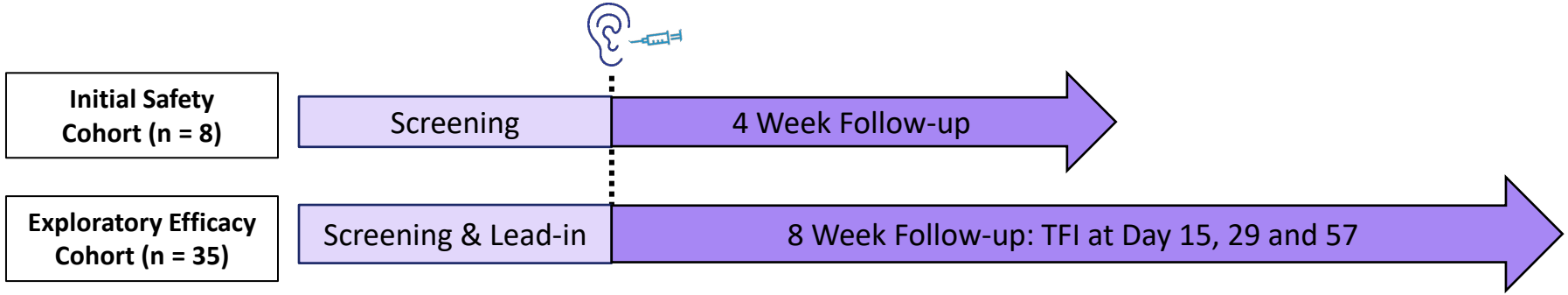
- Tinnitus is often caused by injury to the cochlea (e.g., excessive noise, trauma, persistent ear infection and exposure to ototoxic drugs)
- N-Methyl-D-Aspartate (NMDA) receptor antagonists shown to reduce the over-activation of auditory nerve fiber signaling that results from the injury
- Gacyclidine is a potent and selective NMDA receptor antagonist
- OTO-313 is a sustained-exposure formulation of gacyclidine – several weeks of drug exposure from single intratympanic (IT) injection
- Preclinical and previous pilot clinical data support the development of gacyclidine for treating tinnitus

Preclinical PK for OTO-313



Design of OTO-313 Phase 1/2 Proof-of-Concept Trial

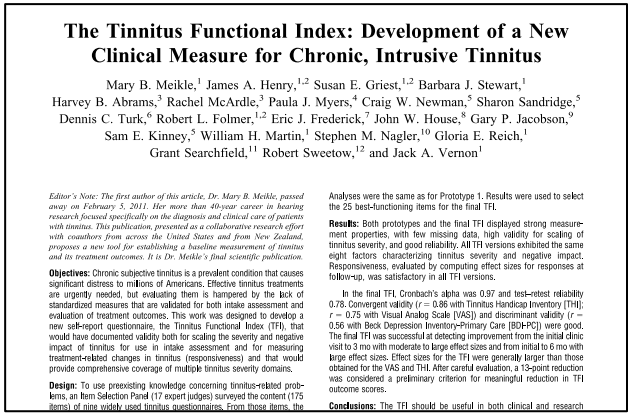
Randomized, double-blinded, placebo-controlled safety and exploratory efficacy study of OTO-313 given as a single intratympanic injection in subjects with tinnitus



- Exploratory efficacy cohort included 31 evaluable patients (4 early terminations split between groups and not related to AE's)
- Patients had unilateral, persistent tinnitus of cochlear origin, less than 6 months since onset
- Required at least moderate tinnitus severity at baseline based on Tinnitus Functional Index (TFI)
- **Goal: demonstrate safety and clinical signal for OTO-313 treatment (not powered for stat sig)**

Exploratory Efficacy Endpoints in Phase 1/2 Clinical Trial

- **Tinnitus Functional Index (TFI)** is ”primary” endpoint
  - Clinically validated instrument that assesses tinnitus severity and treatment-related changes
  - 25 item questionnaire completed by patient during screening visit and on Day 1, 15, 29 and 57
  - 8 subscales: Intrusive, Sense of Control, Cognitive, Sleep, Auditory, Relaxation, QoL and Emotional
  - 100-point scale with **13-point reduction considered clinically meaningful improvement (“Responder”)**
- Patients reported Tinnitus Loudness and Tinnitus Annoyance using daily phone diary
- 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 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.

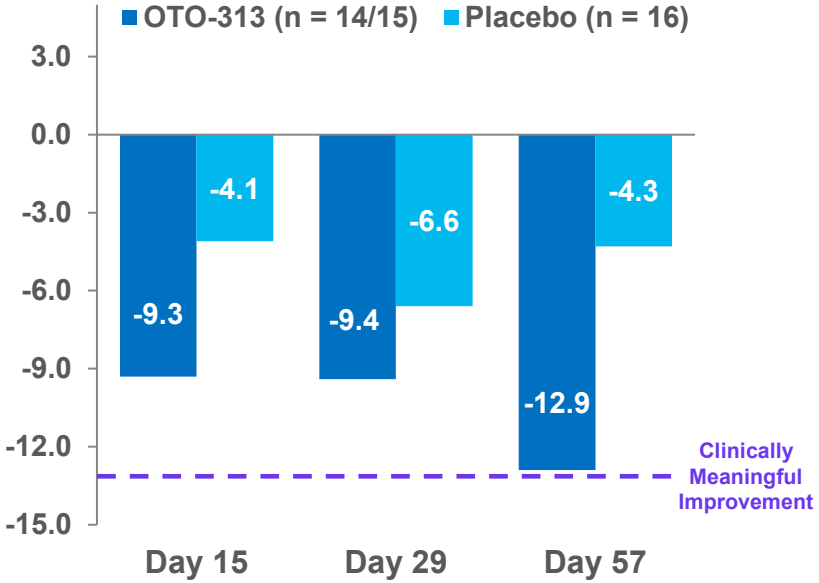
Conclusions: The TFI should be useful in both clinical and research

Reference: Meikle et al., Ear & Hearing (2011)

TFI Severity Ranges
< 25: mild
25-50: moderate
> 50: severe

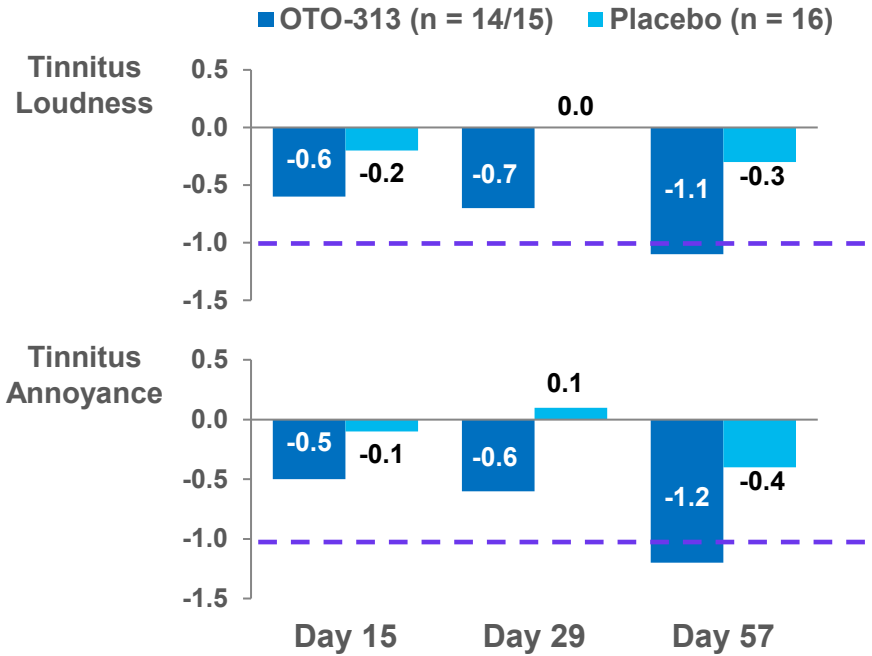
OTO-313 Treatment Benefit for Total Study Population

TFI Change from Baseline
(100-point scale, reduction is improvement)

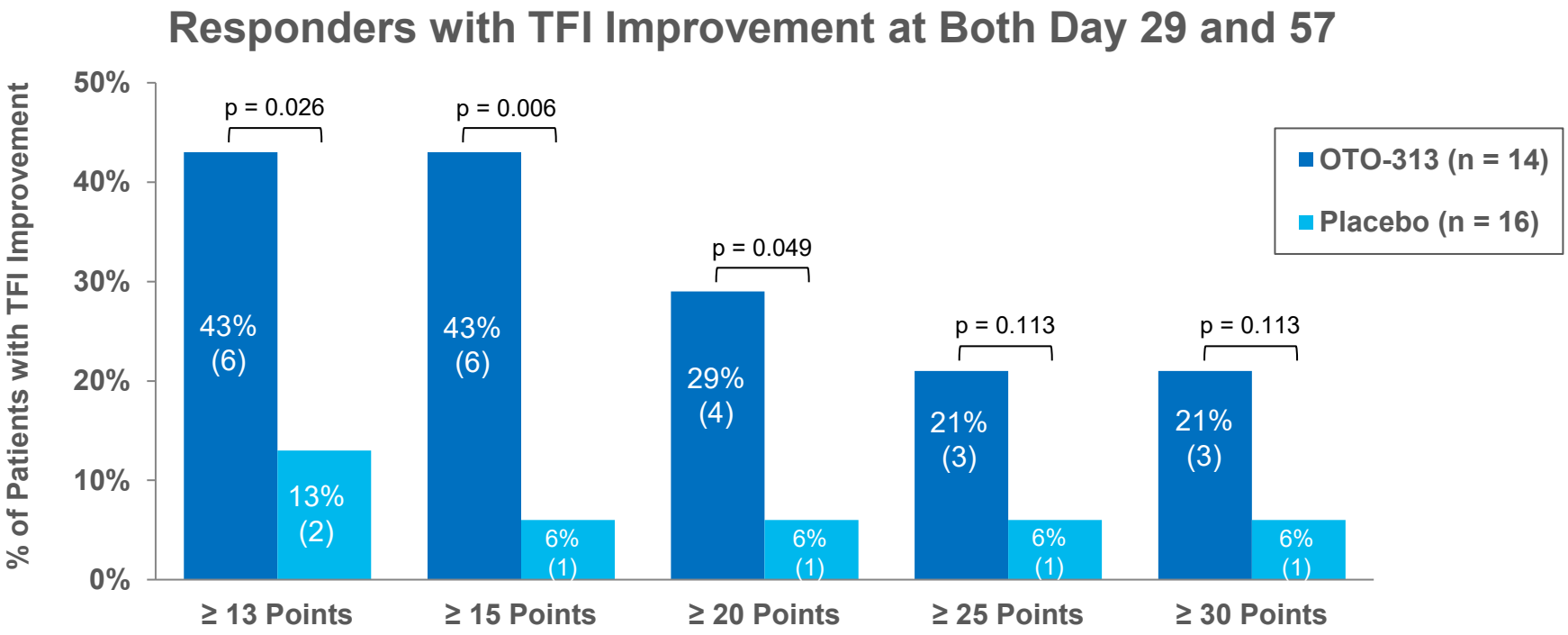


Baseline TFI values: OTO-313 = 65.9; Placebo = 57.9

Loudness and Annoyance Change from Baseline
(10-point scale, reduction is improvement)



Clear OTO-313 Efficacy Signal Based on Responder Analysis

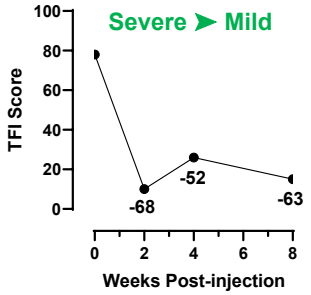


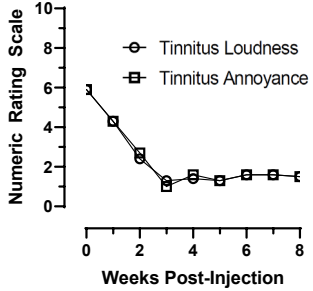
Notes: p-values based on 1-sided test of response rate difference between OTO-313 and placebo (post hoc); # of patients shown below %; one OTO-313 patient did not complete the TFI at Day 29 and was not a responder at Day 57

OTO-313 Responders also Improved on Other Endpoints

(Case Studies below for 4 OTO-313 Patients with TFI reduction ≥ 20 points)

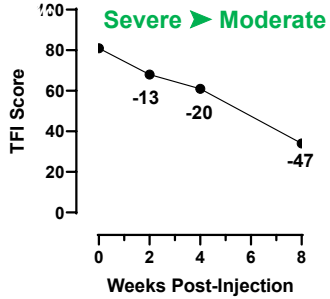
OTO-313: 1

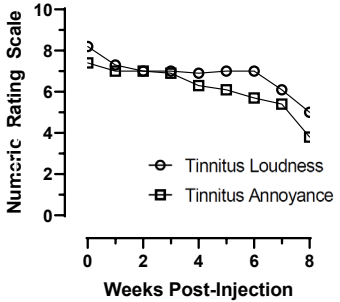




PGIC @ Day 57: Very Much Improved

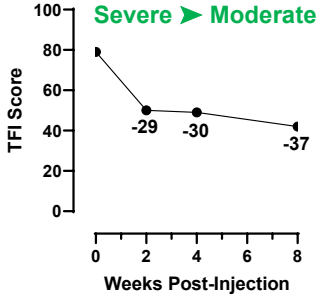
OTO-313: 2

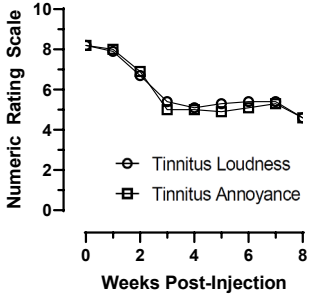




PGIC @ Day 57: Very Much Improved

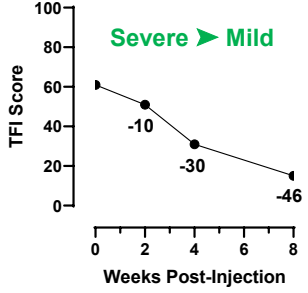
OTO-313: 3

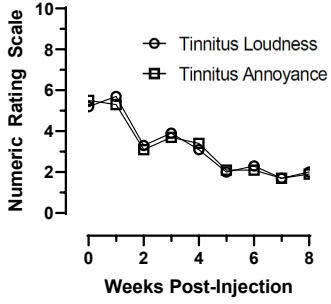




PGIC @ Day 57: Much Improved

OTO-313: 4



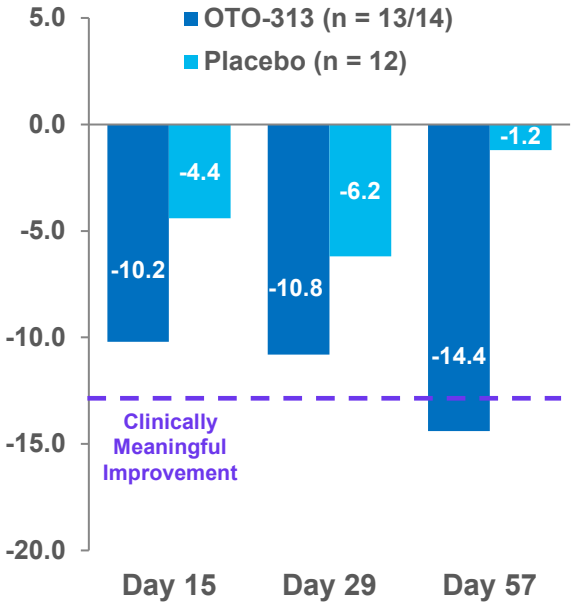


PGIC @ Day 57: Minimally Improved

Note: correlation coefficient between improvement in TFI and improvement in tinnitus loudness and annoyance levels as well as PGIC ≥ 0.8 (considered “very strong” relationship)

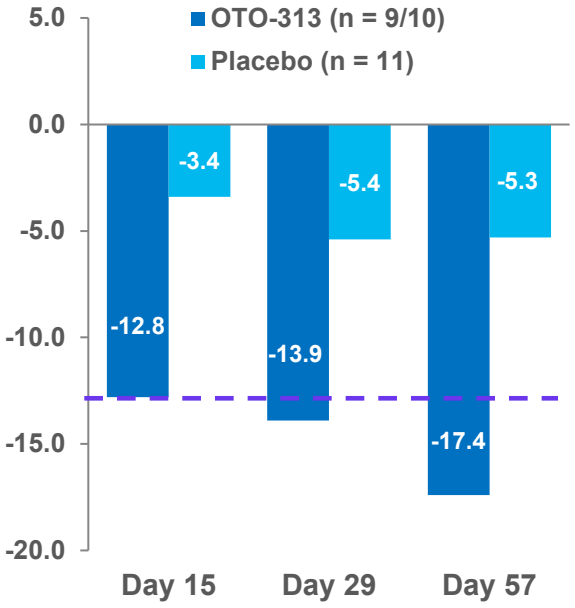
Subset Analyses Support Phase 2 Study Design

TFI Change for Patients with Baseline TFI of 40-100



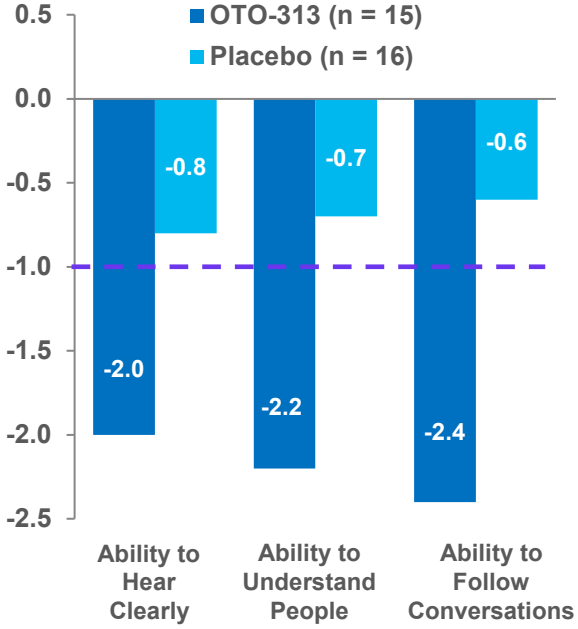
Entry criteria: TFI score ≥ 25

TFI Change for Patients with Tinnitus Duration of 3-6 Months



Entry criteria: tinnitus onset ≤ 6 months

Change in TFI Auditory Subscale Questions at Day 57

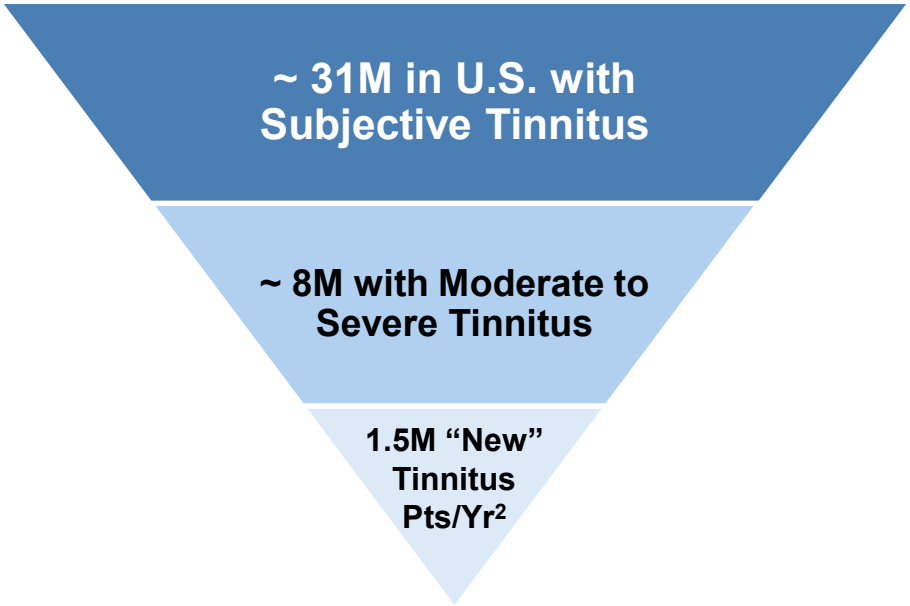


Initiating OTO-313 Phase 2 Trial 1Q21, Results mid-2022

- Targeting enrollment of 140 patients with unilateral tinnitus of at least moderate severity
- Single IT injection of OTO-313 or placebo
- Endpoints consistent with positive POC trial: responder analysis based on TFI with assessment of tinnitus loudness, tinnitus annoyance and PGIC
- Refining enrollment criteria to enrich and expand patient population
  - Excluding patients with severe hearing loss (less likely to respond to treatment)
  - Increasing the minimum TFI level (improve ability to demonstrate treatment benefit)
  - Increasing time from tinnitus onset up to 12 months (from 6 months)
- Efficacy assessment at Month 1 and 2 (same as POC trial) with additional 2 months of follow-up to evaluate durability of treatment effect

Large, Untapped Market Opportunity for OTO-313

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; high disease burden supports favorable pricing
- > $1B U.S. total market opportunity[1]

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

Hearing Loss is a Large and Growing Problem Worldwide

4th Leading Cause of Disability Globally[1]

Most prevalent neurologic health issue:

> 360M PEOPLE

have disabling hearing loss[2]

Common causes include:

AGING, NOISE, OTOTOXIC DRUGS AND GENETICS

Leads to Social Isolation, lower QOL,

AND HIGHER RATES OF DEMENTIA AND DEPRESSION

NO EFFECTIVE TREATMENTS

and no approved drugs for hearing loss

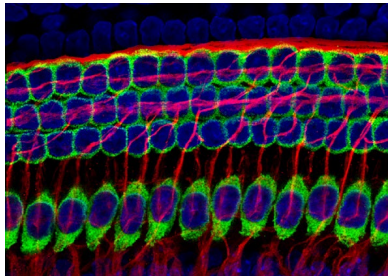
High economic burden:

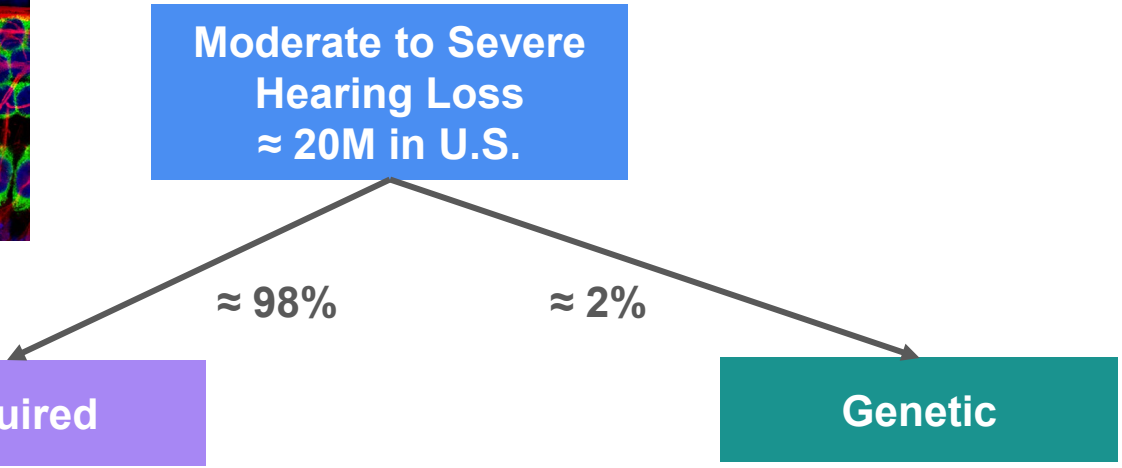
MEDICAL COSTS + IMPACT

of lower work productivity

[1]Wilson, et al. Lancet. (2017); [2]World Health Organization, Global Estimates on Prevalence of Hearing Loss, (2012)

Programs Address Broad Hearing Loss Populations



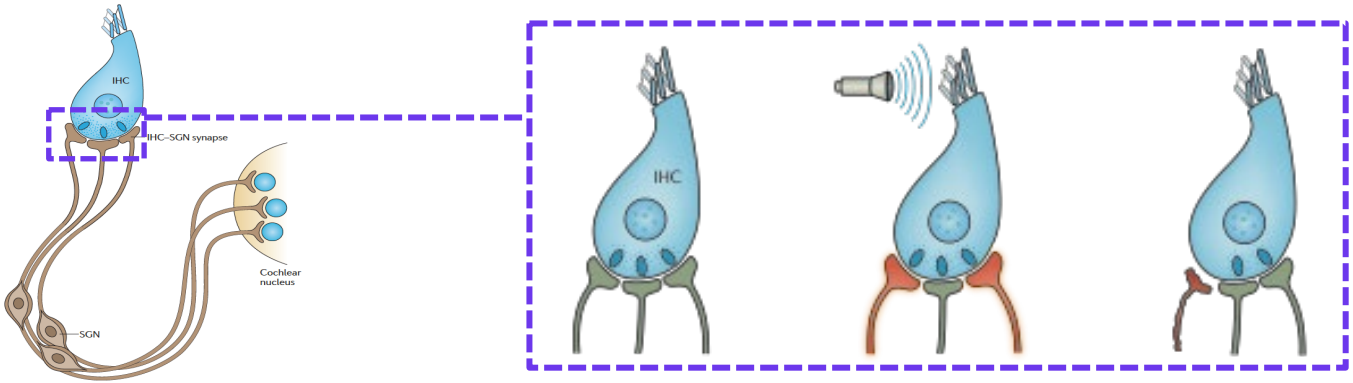


- OTO-413: restoration of cochlear synapses
- OTO-510: otoprotection for CIHL
- OTO-6XX: hair cell repair and regeneration

- OTO-825: gene therapy for GJB2

Patient population estimate and proportion Acquired vs. Genetic from Clearview Healthcare Partners analysis

Cochlear Synaptopathy is Common Hearing Loss Pathology



Example: noise-induced damage leads to loss of cochlear synapses

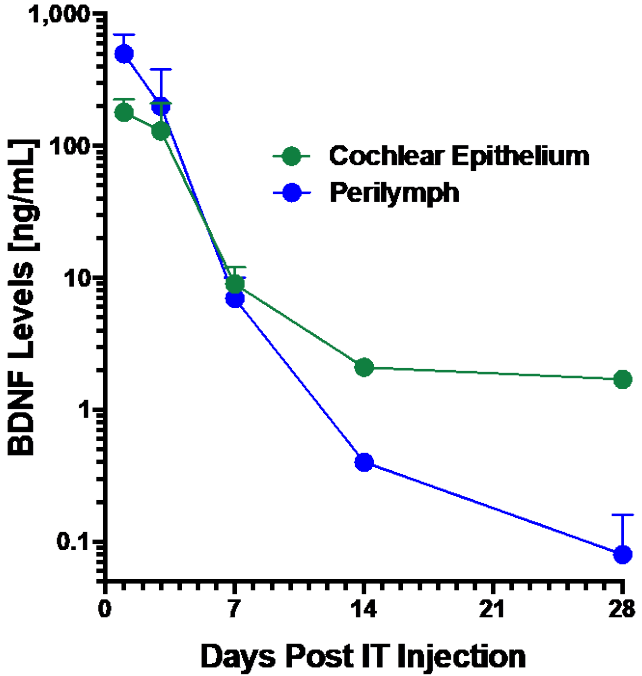
- Cochlear synaptopathy is loss of connection between inner hair cells and auditory nerve fibers
- Caused by noise exposure, aging, ototoxic chemicals or combination of these factors
- Evidence suggests that cochlear synaptopathy occurs earlier than hair cell loss[1]
- Patients report speech-in-noise hearing difficulty – **problem hearing in real-world setting**

Figure from Moser and Starr, Nature Reviews: Neurology (2016); IHC = inner hair cells; SGN = spiral ganglion neurons
[1]Kujawa and Liberman, J Neurosci 2009

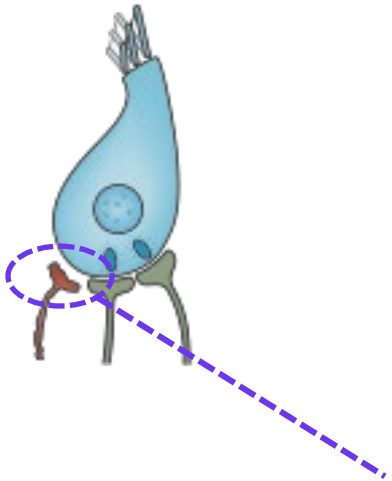
OTO-413: Sustained-Exposure Formulation of BDNF

- Brain-derived neurotrophic factor (BDNF) is an endogenous protein with potent neurotrophic effects on spiral ganglion neurons (auditory nerve fibers)
- OTO-413 is a sustained-exposure formulation of BDNF that provides several weeks of drug exposure from single intratympanic (IT) injection
- Preclinical data support the development of OTO-413 for treating cochlear synaptopathy

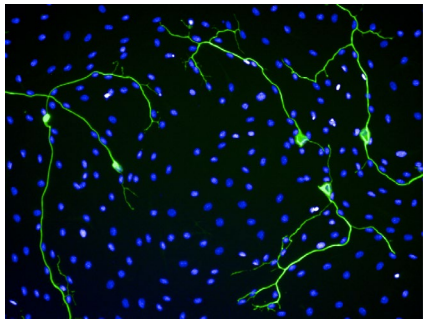
Preclinical PK for OTO-413



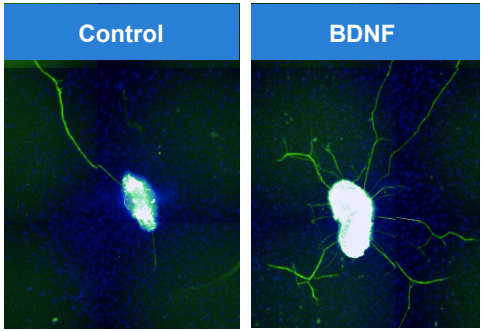
Therapeutic Effects of BDNF in the Cochlea



Promotes SGN Survival



Increases SGN Neurite Outgrowth



Reconnects SGNs with Hair Cells after Synaptopathy

OTO-413 Phase 1/2 Clinical Trial Design

Phase 1/2 Ascending Dose Safety and Exploratory Efficacy Study

Screening & Baseline Testing

Single IT injection: OTO-413 or placebo

Three Month Follow-up with Testing at Day 15, 29, 57 and 85

- All subjects had speech-in-noise (SIN) hearing difficulty (self-reported and by testing)
- Most subjects also had at least moderate hearing loss in quiet setting
- Randomized, controlled trial with 3:1 randomization to OTO-413 or placebo
- Primary objective: assess safety of OTO-413 across four ascending dose cohorts
- Secondary objective: evaluate therapeutic activity of OTO-413 for multiple exploratory endpoints with emphasis on clinically-validated SIN tests

OTO-413 Phase 1/2 Ascending Dose Trial Subject Disposition

Cohort 1 (0.01 mg)	Cohort 2 (0.03 mg)	Cohort 3 (0.10 mg)	Cohort 4 (0.30 mg)
• 6 OTO-413 • 2 Placebo	• 6 OTO-413 • 2 Placebo	• 6 OTO-413 • 2 Placebo	• 11 OTO-413 • 4 Placebo

Safety Evaluation
- 29 OTO-413
- 10 Placebo

- Sub-therapeutic dose
- Start-up and technical challenges with large battery of tests

Top-Line Assessment of Therapeutic Activity

- **OTO-413: 9 evaluable subjects from high dose cohort**
  (1 subject with no Day 57 visit and 1 early term not related to AE)
- **Placebo: 8 subjects pooled from Cohort 2, 3 and 4**

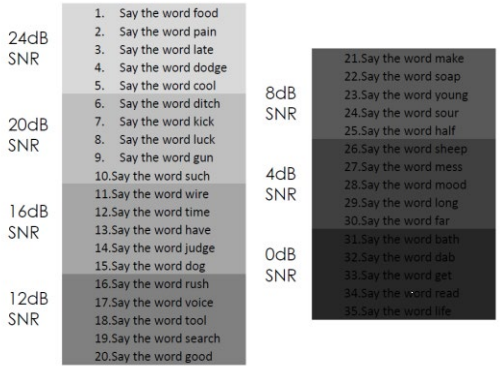
Review of Speech-in-Noise (SIN) Tests

Digits-in-Noise Test (DIN)

- 3 spoken numbers presented at varying sound intensities
- 23 digit-triplets (e.g., 9-2-5)
- Continuous, synchronous background noise at fixed level

Words-in-Noise Test (WIN)

- Word recognition test with multi-talker babble as background
- 35 words (5 words each at 7 varying signal-to-noise ratios)



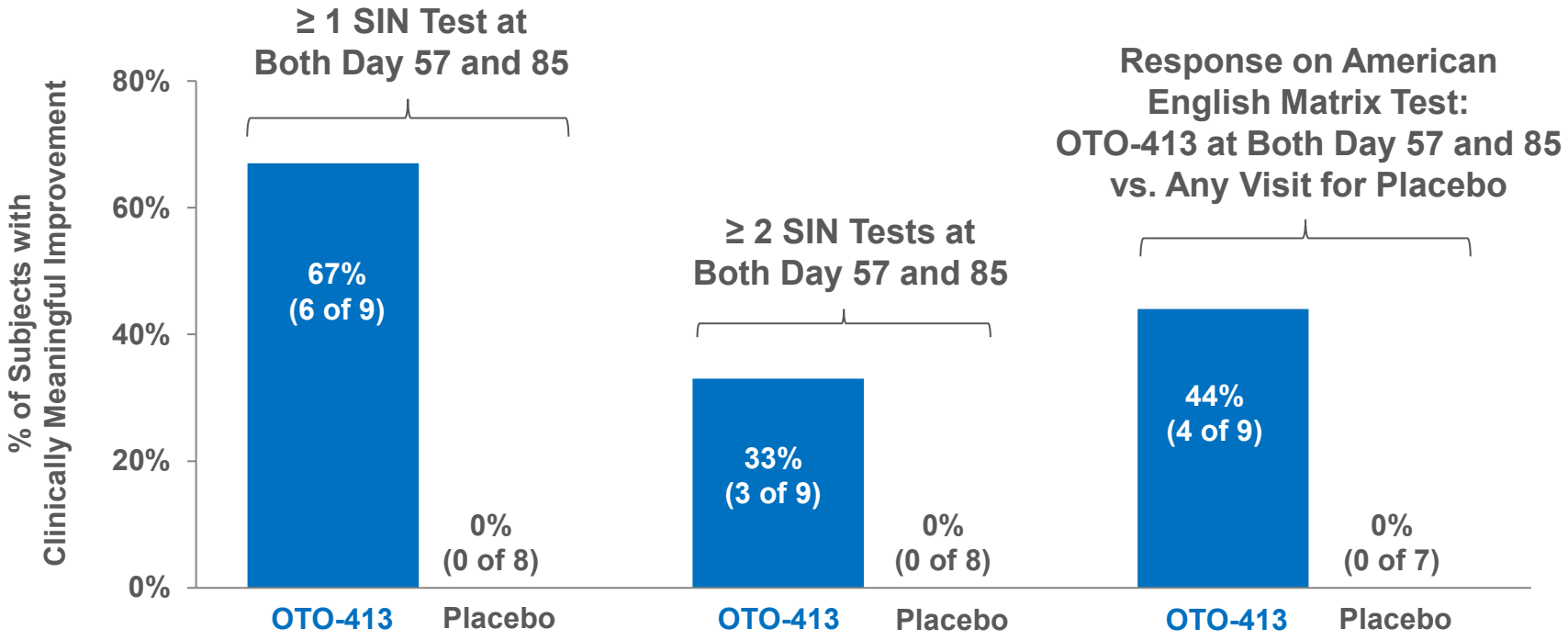
American English Matrix Test

- 20 five-word sentences
- Fixed background noise
- Test uses grammatically correct but unpredictable sentences to minimize learning effect
- Example: “Rachel wants for pretty chairs”

SIN tests conducted at screening, baseline (pre-dose), Day 15, 29, 57 and 85

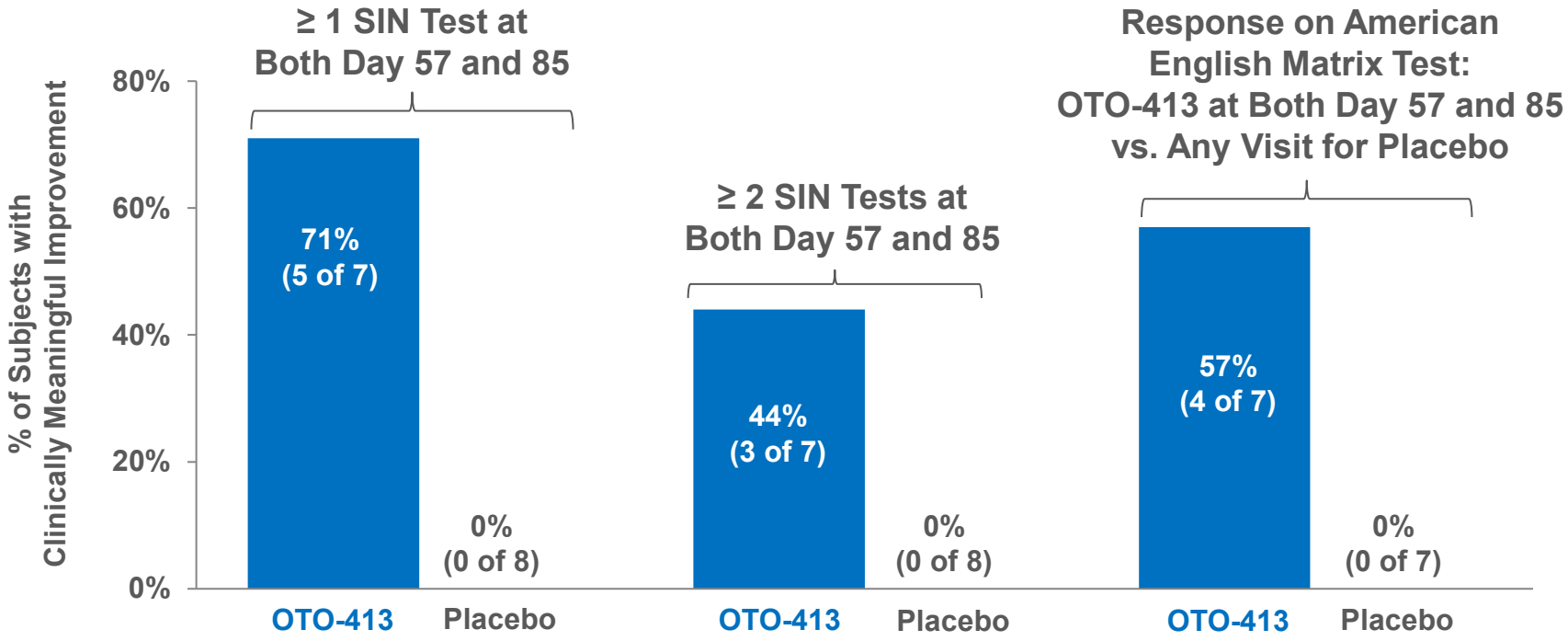
Figure from Cowen & Company Equity Research

OTO-413 Efficacy Signal Demonstrated on Responder Analysis



Notes: SIN = speech-in-noise test; one OTO-413 subject did not complete Day 57 visit but had clinically meaningful improvement at Day 85 for two SIN tests; one placebo subject did not complete Matrix test

Response for Subset with Moderate-to-Severe Hearing Loss

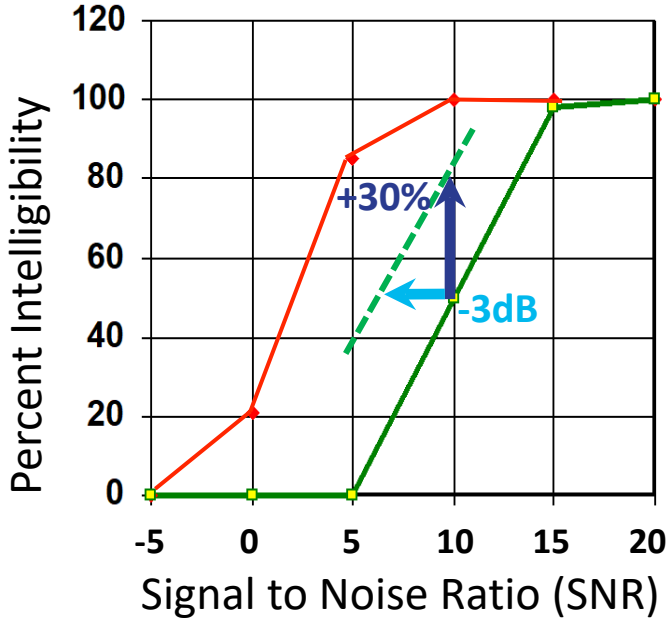


Notes: SIN = speech-in-noise test; one OTO-413 subject did not complete Day 57 visit but had clinically meaningful improvement at Day 85 for two SIN tests; one placebo subject did not complete Matrix test

SIN Test Improvement in Context of “Real-World” Hearing

Small Improvement in SIN Test Can Mean Significant Improvement in Speech Intelligibility

Ability to Understand Someone in Noisy Setting



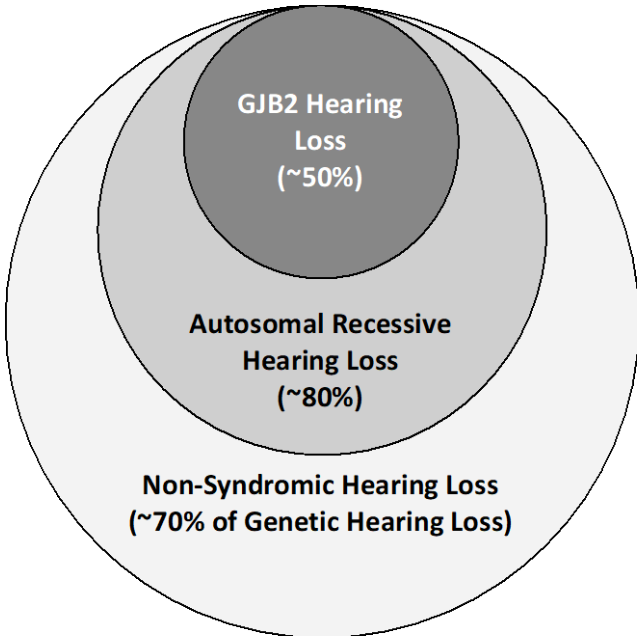
Measured by SIN tests

Positive Results Support Continued OTO-413 Development

- OTO-413 was well-tolerated across all dose cohorts
- OTO-413 therapeutic activity demonstrated by subjects achieving a clinically meaningful improvement from baseline across multiple speech-in-noise tests at consecutive timepoints (Days 57 and 85)
- No response observed in placebo subjects using these stringent criteria
- Plan to enroll additional hearing loss patients in expansion study to help prepare for Phase 2
  - Begin enrollment in 2Q21 with results expected mid-2022
  - Evaluate reduced number of endpoints focusing on speech-in-noise tests including American English Matrix, Words-in-Noise and Digits-in-Noise tests

Mutations in the Gap Junction Beta-2 (GJB2) gene are the most common cause of congenital hearing loss

- In developed countries, about 1 out of 500 children are born with or develop hearing loss prior to language development (”prelingual”)
- Genetic mutations are the most common cause of prelingual hearing loss
- GJB2 accounts for ~30% of congenital hearing loss cases
- Patients with GJB2 mutations often have severe-to-profound hearing loss in both ears
- Typically identified by newborn screening that is routine in US and EU



Reference: Shearer et al, “Hereditary Hearing Loss and Deafness Overview” (2017)

GJB2 gene encodes gap junction protein Connexin 26 that is involved in ion channel homeostasis

- Connexin 26 is expressed in non-sensory cell types within the cochlea
- Mutations in GJB2 gene impair gap junctions that control potassium homeostasis leading to hair cell dysfunction and hearing loss
- Goal: otic delivery of GJB2 therapy to achieve high local concentration of gene (low systemic exposure) to restore functional gap junctions and hearing

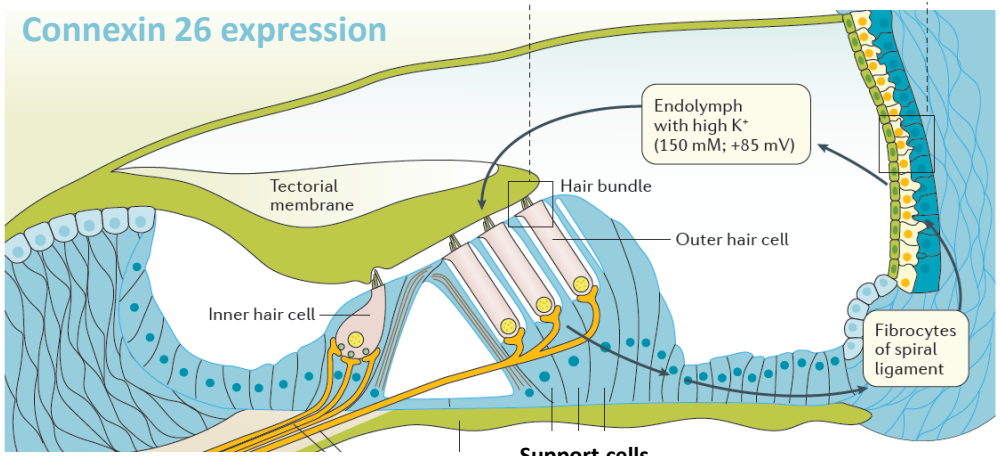
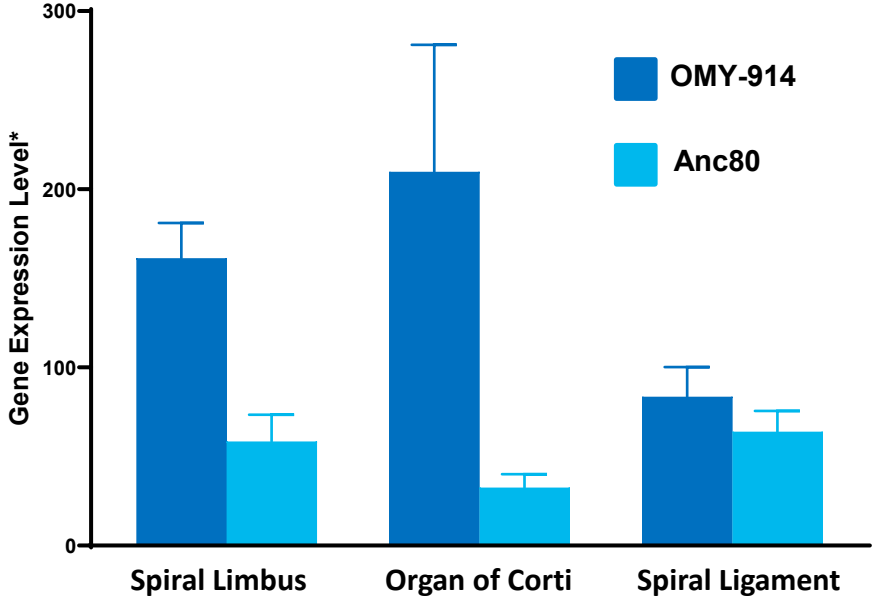


Figure reference: Korver et al, Nature Reviews Disease Primers (2017)

OTO-825: GJB2 Product Candidate for Development

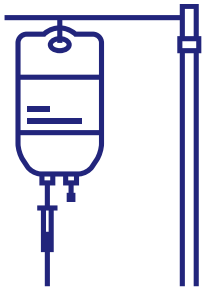
- Strategic collaboration with AGTC
- Novel and proprietary AAV capsids demonstrate high levels of expression in cochlear support cells, the target cells for GJB2 gene therapy
- Tropism and expression level superior to reference otic capsid
- Gene expression for at least 12 weeks following single injection in NHP study
- No signs of cellular toxicity
- Advancing OTO-825 into IND enabling studies

AAV-Mediated Expression in Cochlea



*GFP expression level compared to reference capsid in cochlear explant model

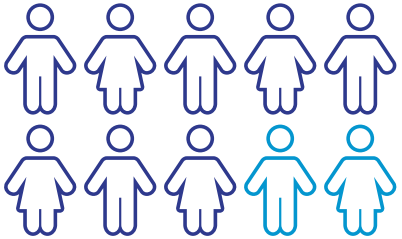
Need for Cisplatin-Induced Hearing Loss (CIHL) Protection



~ 500K

patients treated with platinum-based cancer chemotherapies each year in U.S. including

~ 5K CHILDREN



> 80% OF CHILDREN

treated with platinum agents experience hearing loss[1]

Agents, especially cisplatin, are

OTOTOXIC

CIHL impacts

SPEECH DEVELOPMENT, ACADEMIC PERFORMANCE, AND SOCIALIZATION

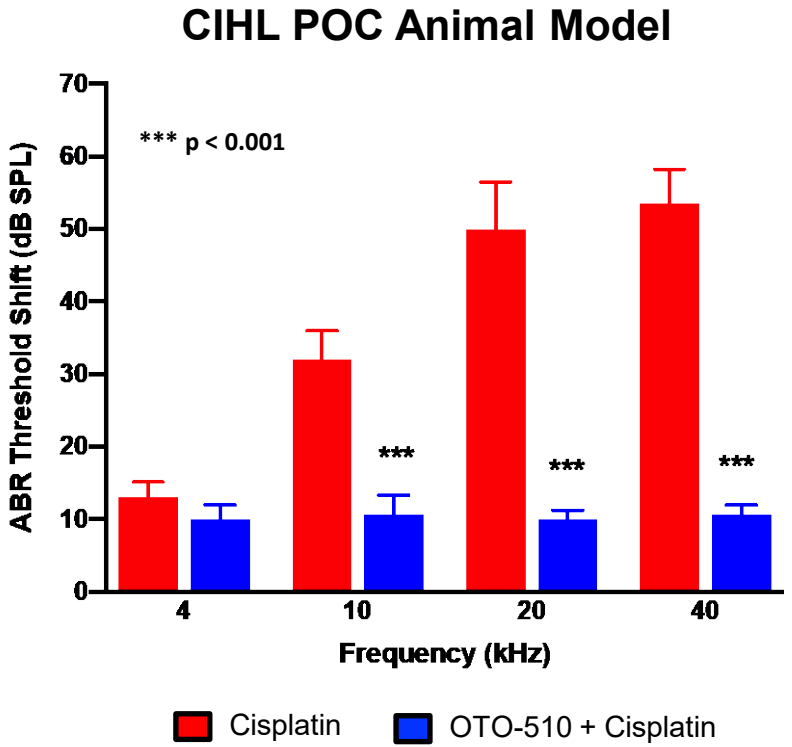
LIFE-LONG IMPACT

highlighted at recent patient symposium

[1]Landier, et al. Journal of Clinical Oncology. (2014)

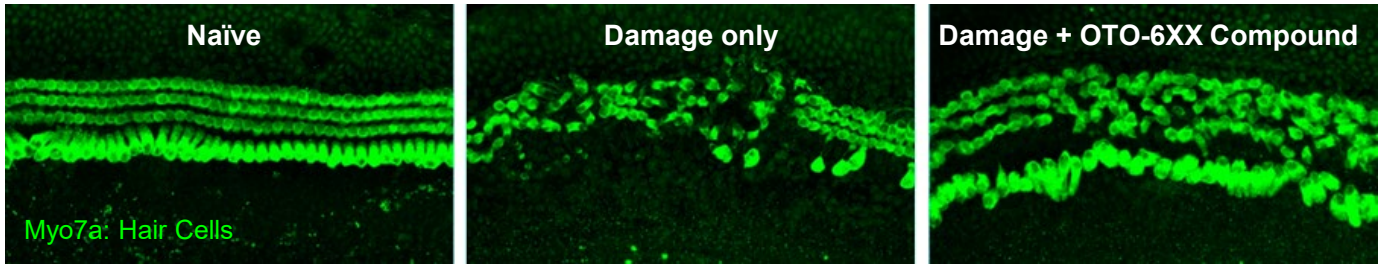
OTO-510 Initially Targeting Children Receiving Cisplatin

- Established clinical feasibility of conducting pediatric CIHL trial in pilot study using OTIVIDEX
- Identified new series of molecules with improved otoprotection in nonclinical studies
- Proof-of-concept demonstrated in CIHL animal model
- Preclinical development continuing for small molecule otoprotectant in sustained-exposure formulation



OTO-6XX: Hair Cell Repair and Regeneration

Hair cell regeneration model



Indication

- Multiple possible indications in which severe hearing loss is due to hair cell death
- May result from a variety of insults and significantly affects ability to communicate

Otonomy Program / Status

- Non-mammalian species able to regenerate hair cells; knowledge of pathways involved provides targets
- POC in hair cell regeneration model
- Research collaboration led to exclusive license of novel compound from Kyorin Pharma

Financial Update and Guidance

Operating Expenses[1]

- 4Q20 Results: Non-GAAP Op Exp = $8.5M and GAAP Op Exp = $10.1M
- 2020 Results: Non-GAAP Op Exp = $36.5M and GAAP Op Exp = $42.6M

Cash Runway

- Cash, cash equivalents and short-term investments as of December 31, 2020 totaled $86.3M
- Includes proceeds from financing completed in July 2020 with gross proceeds totaling $69.1M
- Long-term debt: $15M term loan with Oxford Finance; extended interest only period to end of 2021
- Current capital will fund operations through next clinical readouts for OTO-313 and OTO-413

[1]Primary adjustment from GAAP to Non-GAAP is stock-based compensation expense; reconciliation can be found on our web-site www.otonomy.com

Upcoming Milestones

Expected Timing	Program Milestone
1Q21	Initiate OTO-313 Phase 2 trial
2Q21	Initiate OTO-413 Expansion Study
Mid-2021	OTO-825 Program Update
Mid-2022	OTO-313 Phase 2 Results
Mid-2022	OTO-413 Expansion Study Results