OTONOMY®

Targeted Medicines for the Ear

OTO-413 Phase 1/2 Top-Line Results

December 17, 2020

Forward-Looking Statements

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Broadest Pipeline Targeting Large Market Opportunities

Total Market Potential by Condition:

~39 M in U.S.

Vertigo ~11 M

OTIVIDEX®: successful Phase 3 trial completed, additional Phase 3 trial ongoing; enrollment completed, results in 1Q21; with positive results, expect to submit NDA in 3Q21

Tinnitus ~7.8 M

OTO-313: positive top-line Phase 1/2 trial results; advancing to full Phase 2 development

Hearing Loss ~20.5 M

OTO-413: positive top-line results in Phase 1/2 trial

Preclinical Programs:

- **OTO-510 for cisplatin-induced hearing loss**
- **OTO-6XX for severe hearing loss**
- **GJB2 gene Tx program for congenital hearing loss**

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

Positive Top-Line Clinical Trial Results for OTO-413

- OTO-413 is first therapeutic to be evaluated for treatment of hearing loss due to cochlear synaptopathy
- OTO-413 was well-tolerated across all dose cohorts
- Therapeutic activity for OTO-413 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 patients using these stringent criteria
- Results support continued clinical development of OTO-413 for hearing loss

Hearing Loss is a Large and Growing Problem Worldwide

Hearing Loss is 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

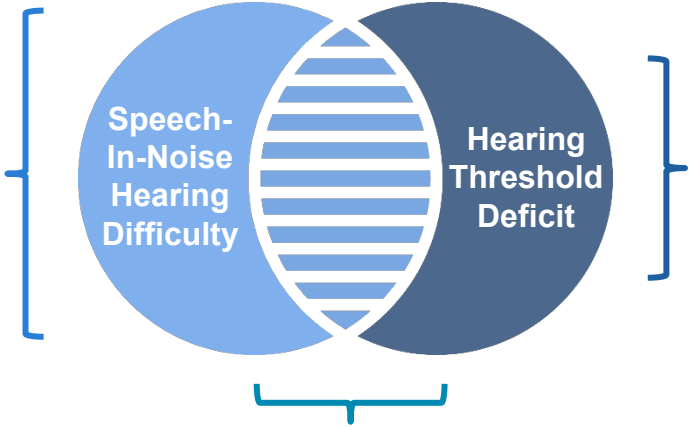
[1]Wilson, et al. Lancet. (2017); [2]World Health Organization, Global Estimates on Prevalence of Hearing Loss, (2012)

OTO-413 Targets a Broad Hearing Loss Population

Cochlear Synaptopathy

- Problem hearing in presence of background noise
- Normal standard hearing test, may have high frequency loss
- **U.S. prevalence[1] ≈ 9M**

Illustrative



Hair Cell Pathology

- Hearing loss detected in standard test (hear tones in quiet setting)

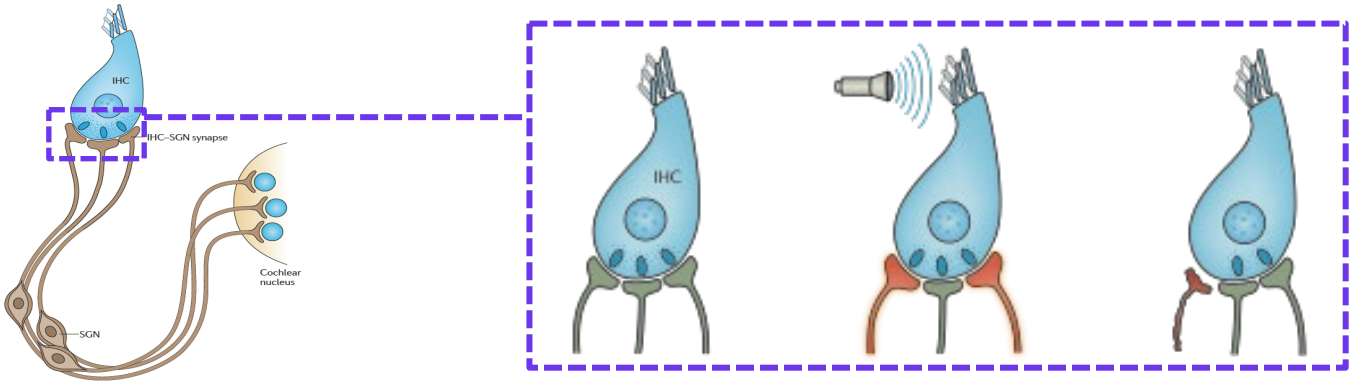
OTO-413 Target Patient Population

Mixed Pathology

- Speech-in-noise hearing difficulty & hearing threshold deficit
- **Significant proportion of 42M in U.S. with hearing threshold deficit[2-5]**

[1]Tremblay et al., Ear Hear, 2015; [2]Hoffman et al., JAMA Otolaryngol HNS, 2017; [3]Nash et al., Arch Otolaryngol HNS, 2011
[4]Morton et al., N Engl J Med, 2006; [5]Brooke et al., JAMA Otolaryngol HNS, 2017; Analysis by ClearView Healthcare Partners

Description of Cochlear Synaptopathy



Noise-induced damage leads to loss of cochlear synapses

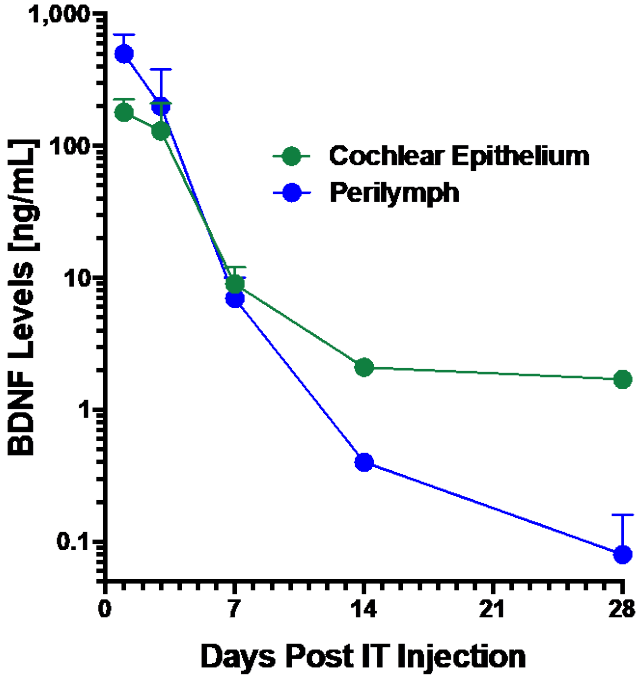
- Cochlear synaptopathy is loss of connection between inner hair cells and auditory nerve fibers
- Caused by noise exposure, aging, ototoxic chemicals or combination of these factors
- Evidence suggests that cochlear synaptopathy may occur earlier than hair cell loss
- Patients report speech-in-noise hearing difficulty; may also have high frequency hearing loss

Figure from Moser and Starr, Nature Reviews: Neurology (2016); IHC = inner hair cells; SGN = spiral ganglion neurons

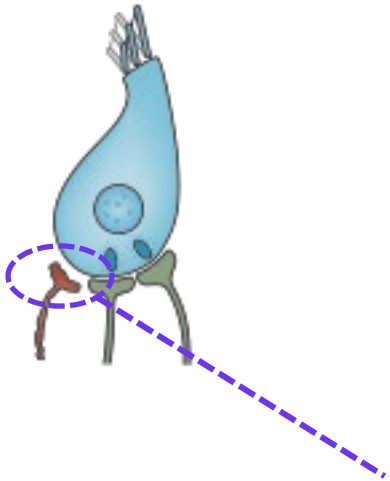
OTO-413: Sustained-Exposure Formulation of BDNF

- 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

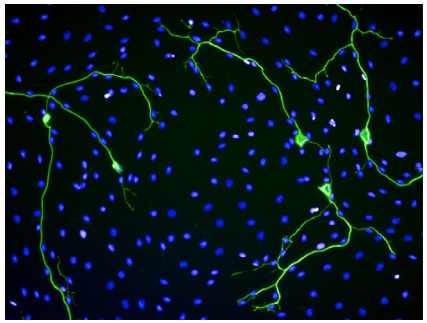
Preclinical PK for OTO-413



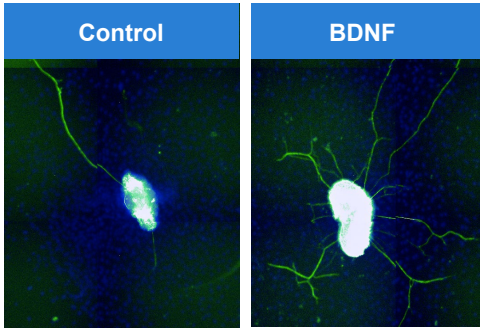
Therapeutic Effects of BDNF in the Cochlea



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**

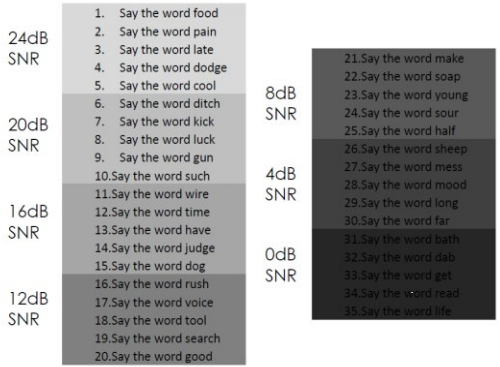
Review of Speech-in-Noise (SIN) Tests

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)



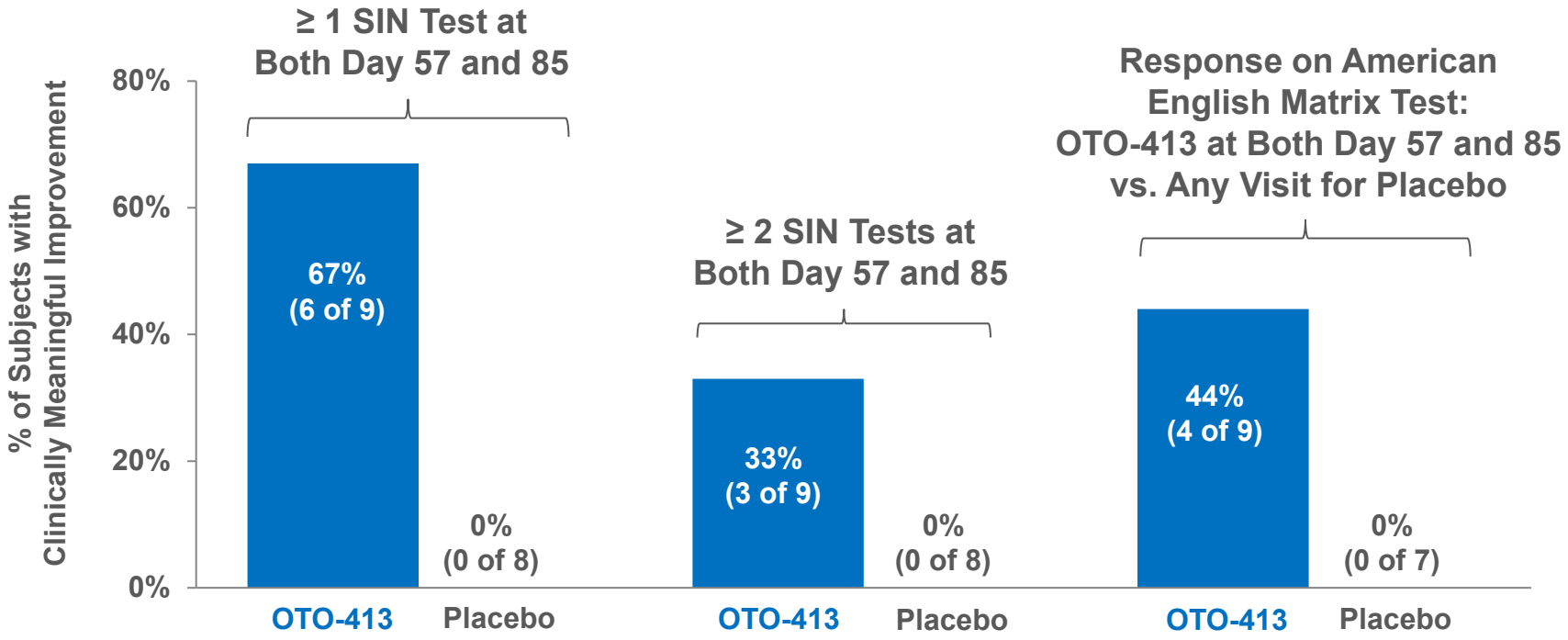
American English Matrix Test

- 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

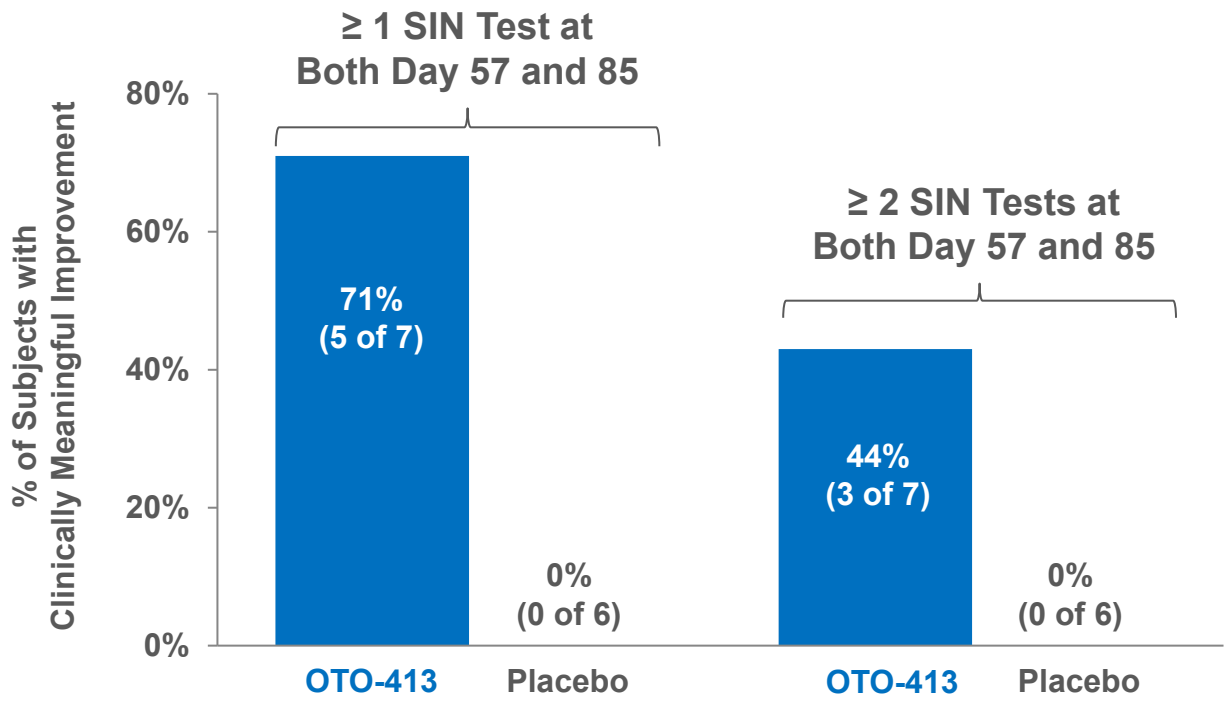
Figure from Cowen & Company Equity Research

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

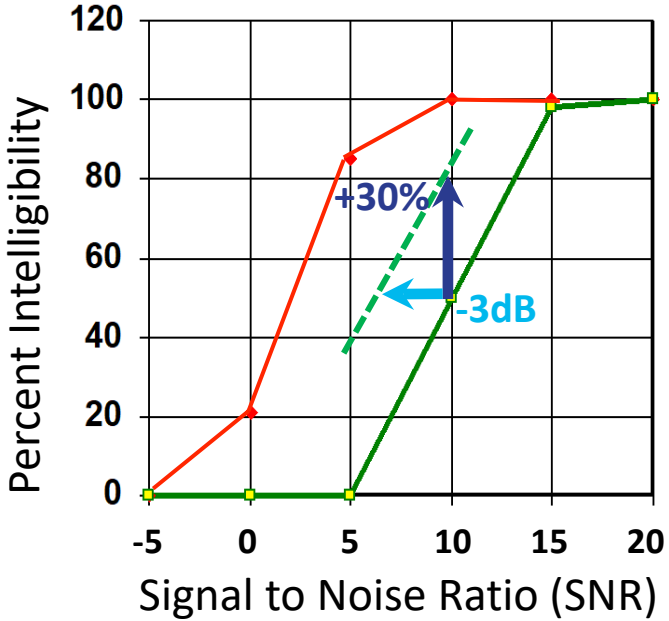


Notes: SIN = speech-in-noise test; one OTO-413 patient did not complete the Day 57 visit but had a clinically meaningful improvement at Day 85 for two SIN tests

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

OTO-413 Was Well-Tolerated Across All Dose Cohorts

- Safety assessment: 29 subjects treated with OTO-413 and 10 placebo
- 52% of OTO-413 vs. 70% of placebo subjects reported an adverse event (AE)
- No apparent impact of dose on AE incidence across OTO-413 cohorts
- No serious adverse events and no discontinued patients due to an AE
- OTO-413 AE severity was mild 28/37 (76%) or moderate 8/37 (22%)
  - Most ear-related AE's occurred on same day as injection or immediately following
  - Single severe AE (intermittent diarrhea) related to COVID-19 and not OTO-413

Positive Top-Line Clinical Trial Results for OTO-413

- 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
- Top-line results focus on high dose cohort and speech-in-noise endpoints, however activity also observed for other exploratory endpoints and doses
- OTO-413 was well-tolerated across all dose cohorts
- Results support continued clinical development of OTO-413 in patients with hearing loss

Review of OTIC's Multiple Clinical Trial Catalysts

Expected Timing	Program Milestone
✓	OTO-313 Phase 1/2 trial results
✓	OTO-413 Phase 1/2 trial results
1Q21	OTIVIDEX Phase 3 trial results
1Q21	Initiate OTO-313 Phase 2 trial