OTONOMY®

Targeted Medicines for the Ear

OTO-413 Phase 2a Top-Line Results

April 20, 2022

Forward-Looking Statements

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Summary of Phase 2a Clinical Trial Results

- Clinical signal again demonstrated for OTO-413 vs. placebo for multiple endpoints based on responder analysis at Day 57 and Day 85 (supporting prior Phase 1/2 results)
- Clinically-meaningful improvement demonstrated for OTO-413 across range of hearing levels – supports continued targeting of broad hearing loss population
- Study provides important learnings regarding target patient profile, speech-in-noise test performance, and study conduct considerations for future trials
- Treatment with OTO-413 was well tolerated
- Enrollment in higher dose cohorts is ongoing with results expected for 2H22
- These results support continued development of OTO-413 for hearing loss including planning for initiation of a Phase 2 dose-ranging efficacy trial by the end of 2022

OTO-413 Targets the Major Complaint of Hearing Loss Patients: Difficulty Hearing in Noisy Setting

> 50M in U.S. Self-Report Problem Hearing in Background Noise[1]

- Breakthrough research over last decade identified cochlear synaptopathy (CS) as underlying cause of hearing loss
- CS is loss of connection between inner hair cells and auditory nerve fibers
- Evidence suggests that CS occurs earlier than hair cell loss due to noise exposure and aging
- Patients with CS report speech-in-noise hearing loss (functional hearing in real-world setting)
- Neurotrophins are potential treatment approach
- OTO-413 is sustained exposure formulation of brain-derived neurotrophic factor (BDNF)

[1]Mahboubi et al., JAMA Otolaryngol Head Neck Surg (2017)

Overview of OTO-413 Phase 2a Trial

Randomized, double-blinded, placebo-controlled efficacy cohort of OTO-413 given as a single intratympanic injection in subjects with hearing loss

2:1 randomization to
OTO-413 (0.3 mg) or placebo

Screening & Baseline	3-month Follow-up: hearing tests at Day 15, 29, 57 and 85

- 33 patients with self-reported speech-in-noise (SIN) hearing loss confirmed by testing
- Same primary endpoint used in Phase 1/2 trial: responder analysis based on clinically meaningful improvement in SIN hearing tests at both Day 57 and Day 85
- SIN hearing tests include DIN, WIN and American English Matrix
- Patients completed Patient Global Impression of Change (PGIC) question at each visit
- Not powered for statistical significance – purpose of study was to evaluate treatment benefit of OTO-413 in second, independent study and provide additional data on SIN tests

DIN = Digits-in-Noise; WIN = Words-in-Noise

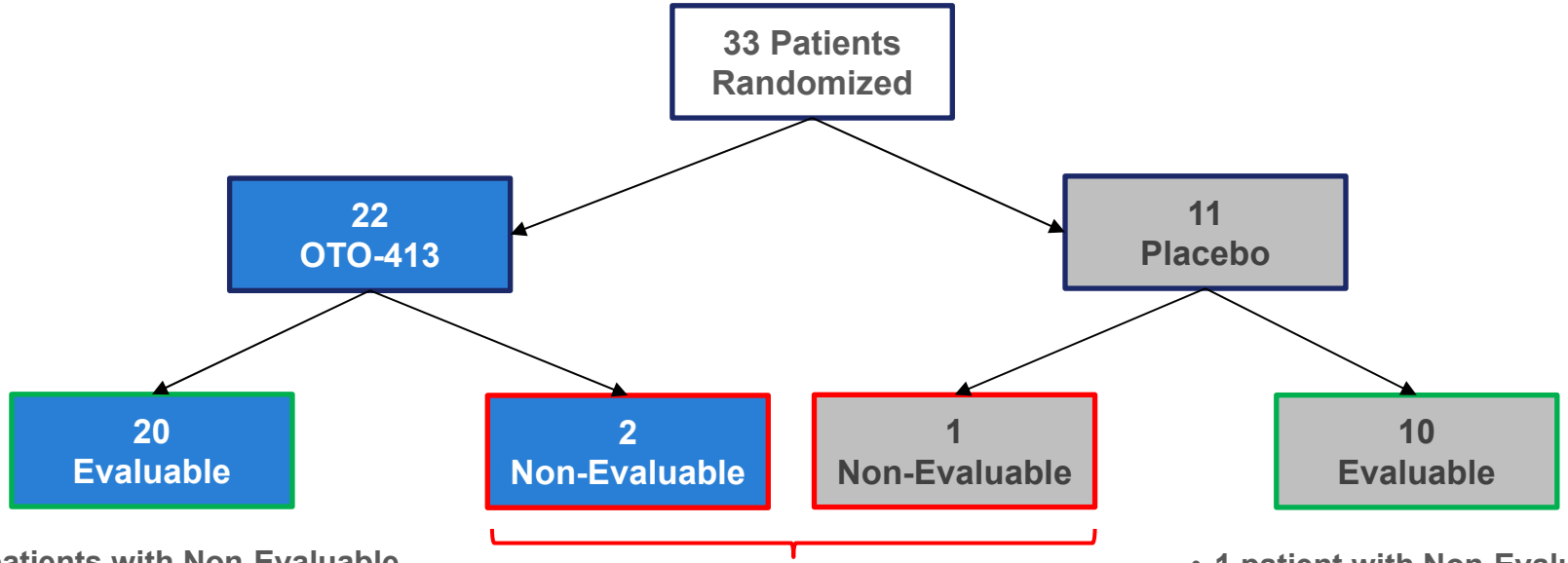
Balanced Baseline Characteristics and Demographics

	OTO-413 (N=22)	Placebo (N=11)
Male – n (%) Female – n (%)	10 (45.5) 12 (54.5)	5 (45.5) 6 (54.5)
Age in years, mean (SD)	50.2 (12.2)	47.5 (12.9)
Low Frequency PTA, mean (SD)	37.1 dB (16.3)	34.2 dB (16.5)
High Frequency PTA, mean (SD)	61.4 dB (19.6)	55.6 dB (16.4)
Digits-in-Noise SRT, mean (SD)	-4.6 dB (4.0)	-4.7 dB (6.0)
Words-in-Noise SRT, mean (SD)	15.0 (6.5)	15.5 (5.5)
American English Matrix SRT, mean (SD)	-4.2 (4.4)	-3.1 (4.2)

- DIN and WIN baseline results are slightly worse in Phase 2a compared to Phase 1/2 cohort
- Phase 2a low frequency PTA is worse than Phase 1/2, while high frequency PTA is comparable

Low Frequency PTA = Pure Tone Average at 1000, 2000, and 4000 Hz; High Frequency PTA = Pure Tone Average at 8000, 10000, and 12500 Hz; SRT = Speech Recognition Threshold in dB signal-to-noise ratio

Summary of Phase 2a Patient Disposition



- 5 patients with Non-Evaluable WIN test*
- 1 patient missing Day 57 and 1 patient missing Day 85; LOCF used for assessing response

Non-evaluable based on assessment of patient profile by blinded reviewer (atypical audiogram, confounding comorbidities, ability to perform tests)

- 1 patient with Non-Evaluable WIN test*
- 1 patient missing Day 85; LOCF used for assessing response

*Non-evaluable WIN test determined by blinded reviewer based on variability between screening and baseline tests; LOCF = last observation carried forward

Efficacy Endpoints Assessed in Phase 2a Clinical Trial

Digits-in-Noise Test (DIN)

- Used as screening test for patient eligibility in clinical trial
- 3 numbers spoken in presence of background noise (e.g., 9-2-5)
- Adaptive algorithm to identify SRT
- 3 dB improvement required for CMI (same as Phase 1/2)

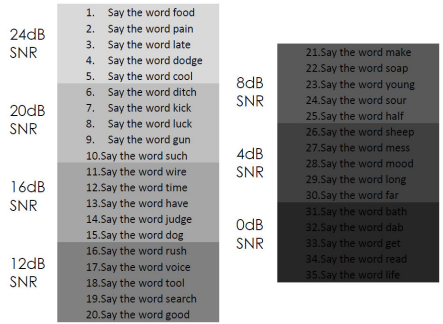
Words-in-Noise Test (WIN)

- Standard test in hearing loss refs
- 5 words presented at each of 7 fixed signal-to-noise ratios
- Test provides SRT and speech intelligibility curve
- 4 dB improvement required for CMI (increase from 2 dB in Phase 1/2)

American English Matrix Test

- Common test in Europe but not US
- 20 five-word sentences
- Adaptive algorithm to identify SRT
- 2 dB improvement required for CMI (same as Phase 1/2)

Each test determines a Speech Recognition Threshold (SRT) = signal-to-noise ratio where subject gets 50% correct



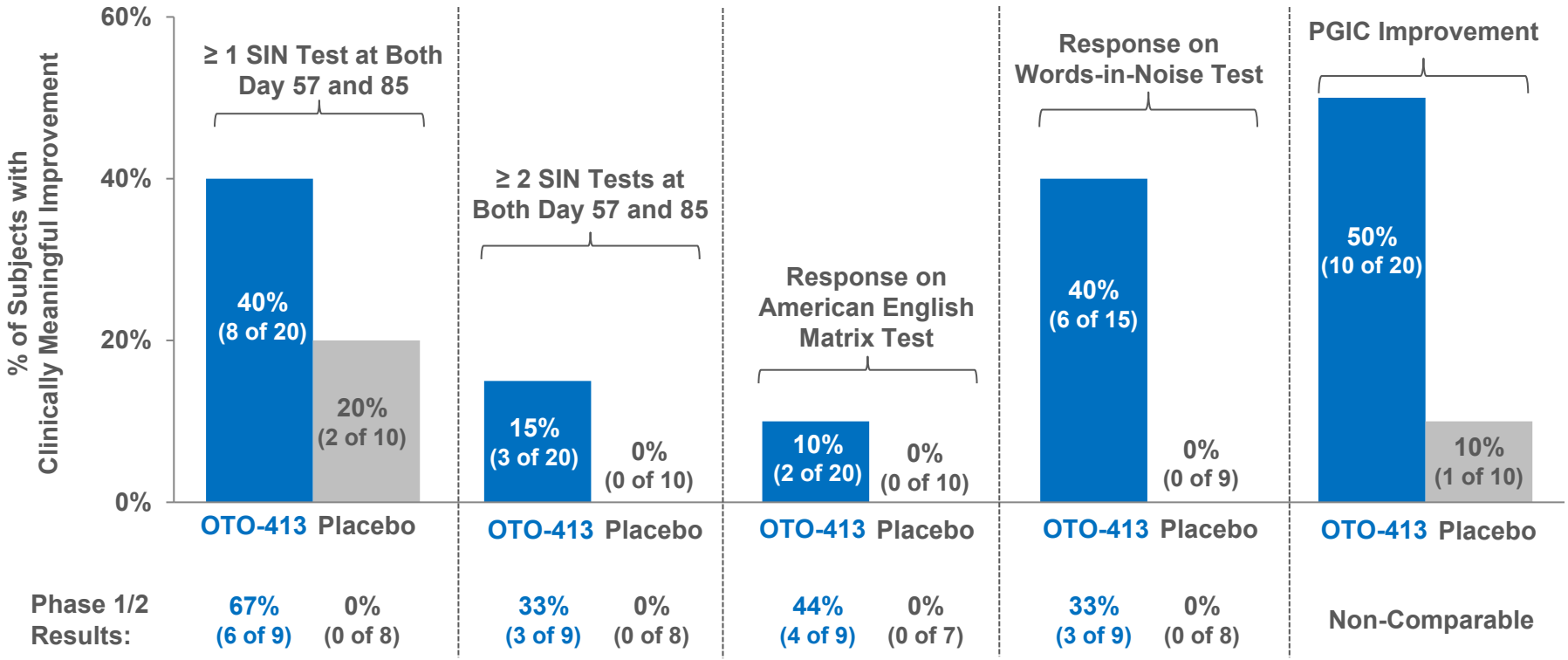
Patient Global Impression of Change (PGIC)

- Single question answered by patient at each follow-up visit
- "Since the beginning of the clinical study, how would you rate your ability to hear in a noisy environment?"

CMI = clinically meaningful improvement estimated to be ≥ 20% increase in speech intelligibility

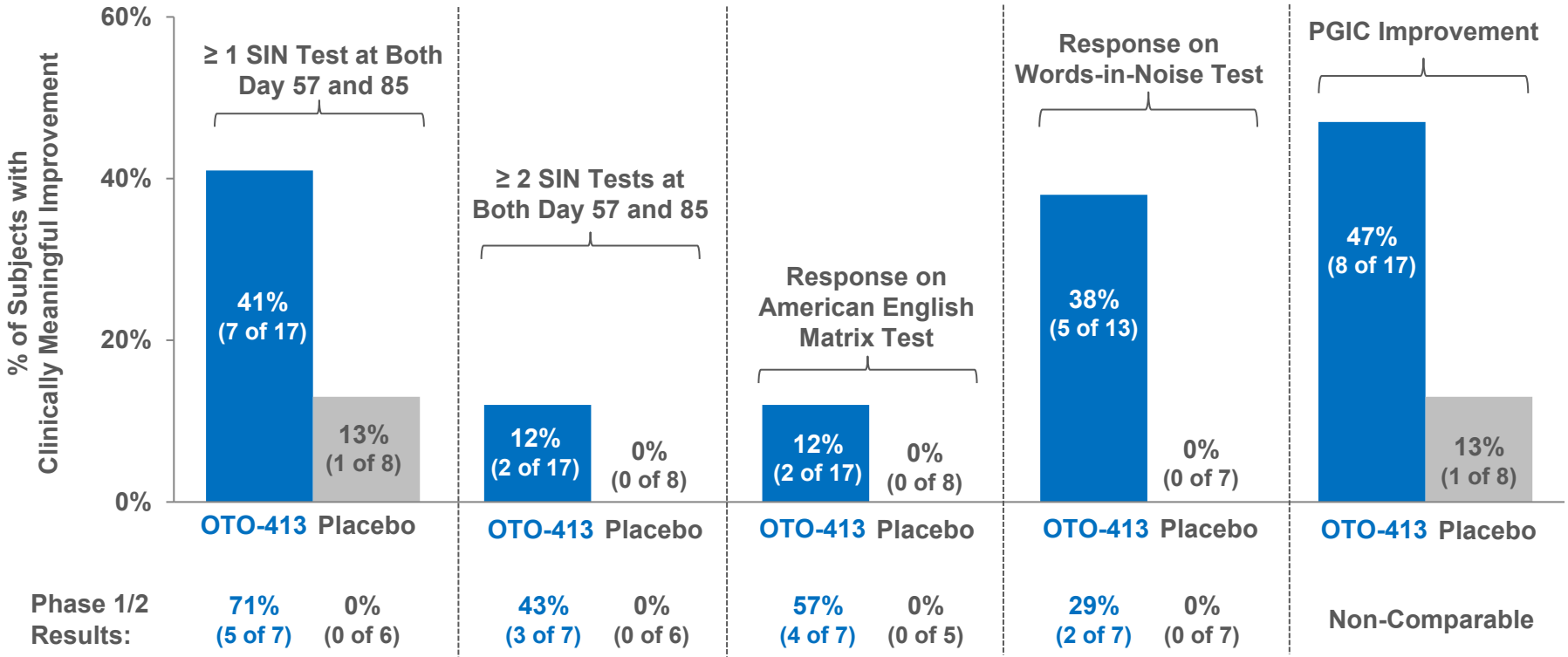
OTO-413 Efficacy Signal Demonstrated on Responder Analysis

(Responder = clinically meaningful improvement at both Day 57 and Day 85)



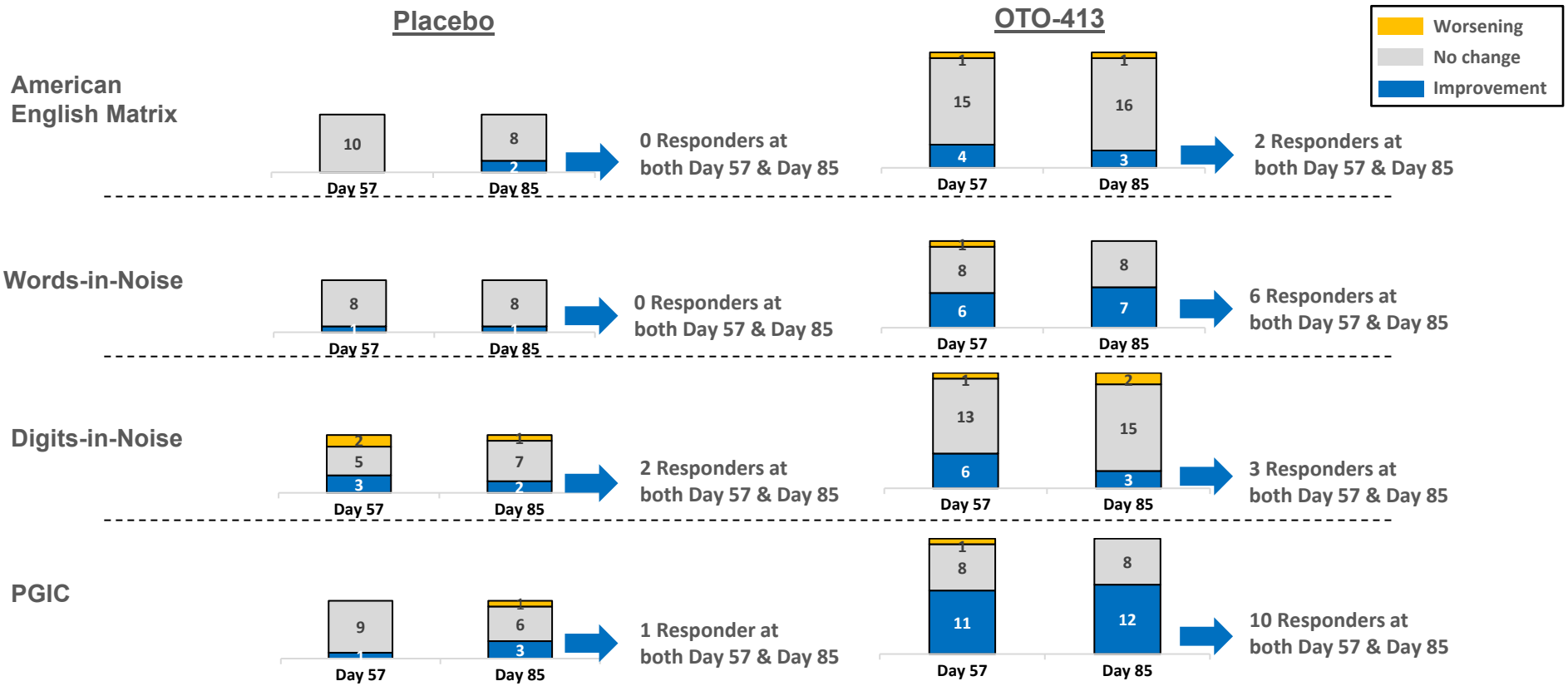
Notes: SIN = speech-in-noise test; PGIC = Patient Global Impression of Change; 5 OTO-413 patients and 1 Placebo patient did not have evaluable Words-in-Noise test

Response for Subset with Moderate-to-Severe Hearing Loss



Notes: SIN = speech-in-noise test; PGIC = Patient Global Impression of Change; 4 OTO-413 patients and 1 Placebo patient did not have evaluable Words-in-Noise test

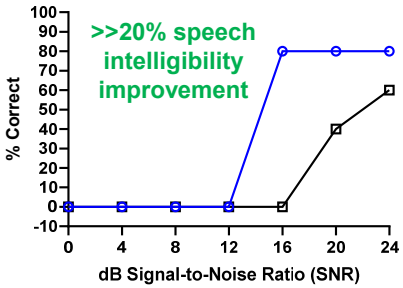
OTO-413 Clinical Signal Observed



Notes: Responder requires clinically meaningful improvement at both Day 57 and Day 85; PGIC = Patient Global Impression of Change; 5 OTO-413 patients and 1 Placebo patient did not have evaluable Words-in-Noise test

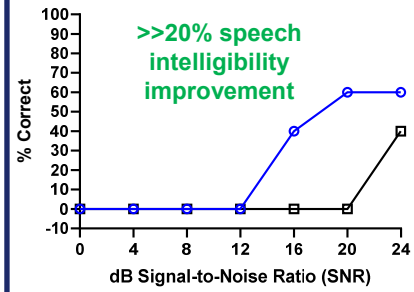
Improvement in Speech Intelligibility for OTO-413 Responders Based on Words-in-Noise Test (with reference to other endpoints)

OTO-413: #1 (mild high frequency hearing loss)



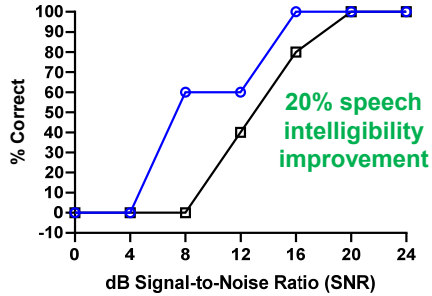
Day 57: CMI for WIN & DIN
Day 85: CMI for WIN & DIN
Patient counted as Responder for multiple SIN tests

OTO-413: #2 (moderate high frequency hearing loss)



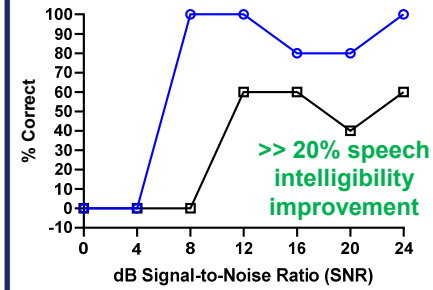
Day 57: CMI for WIN
Day 85: CMI for WIN
Patient counted as Responder for single SIN test

OTO-413: #3 (moderate high frequency hearing loss)



Day 57: CMI for WIN; PGIC
Day 85: CMI for WIN & AEMT; PGIC
Patient counted as Responder for single SIN test and PGIC

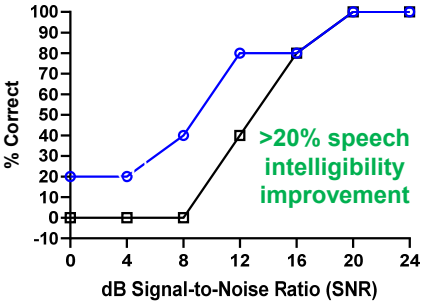
OTO-413: #4 (mod. severe high frequency hearing loss)



Day 57: CMI for WIN & DIN; PGIC
Day 85: CMI for WIN & DIN; PGIC
Patient counted as Responder for multiple SIN tests and PGIC

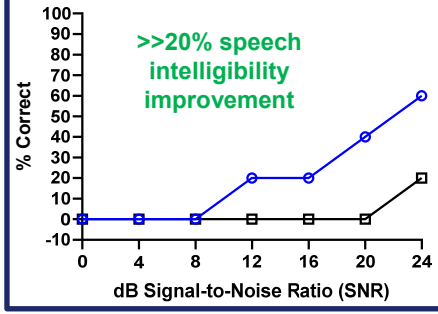
Improvement in Speech Intelligibility for OTO-413 Responders Based on Words-in-Noise Test (with reference to other endpoints)

OTO-413: #5 (severe high frequency hearing loss)



Day 57: CMI for WIN & AEMT
Day 85: CMI for WIN
Patient counted as Responder for single SIN test

OTO-413: #6 (moderate high frequency hearing loss)



Day 57: CMI for WIN, DIN, & AEMT
Day 85: CMI for WIN & AEMT
Patient counted as Responder for multiple SIN tests

Treatment with OTO-413 was Well-Tolerated

- Safety assessment included 22 subjects treated with OTO-413 and 11 with placebo
- 32% of OTO-413 vs. 46% of placebo subjects reported an adverse event (AE)
- No serious adverse events and no discontinued patients due to an AE
- OTO-413 AE severity was mild 4/22 (18%) or moderate 2/22 (9%)
  - Most ear-related AEs occurred on same day as injection or immediately following
  - Single severe AE (food poisoning) not related to OTO-413

Enrolling Patients in OTO-413 Higher Dose Evaluation

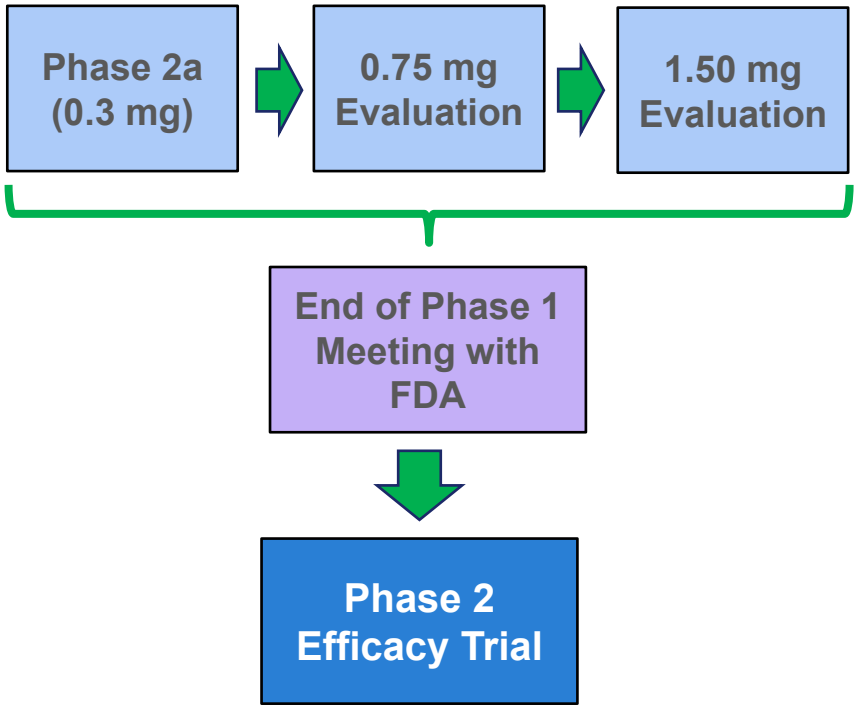
Randomized, double-blinded, placebo-controlled higher dose cohorts of OTO-413 given as a single intratympanic injection in subjects with hearing loss

Screening & Baseline	3-month Follow-up: hearing tests at Day 15, 29, 57 and 85

2:1 randomization to OTO-413 or placebo (0.75 mg or 1.50 mg)

- Expect increased C_{max} and longer duration of drug exposure based on preclinical PK studies
- Same enrollment criteria and clinical trial design used in Phase 2a study
- Each dose cohort expected to enroll approximately 12 patients with 2:1 randomization
- Started with 0.75 mg and escalated to 1.50 mg (5x dose used in Phase 2a trial)
- Expect top-line results 2H22, with results to be used to finalize Phase 2 plans

Expected Next Steps for OTO-413 Program



- Higher dosing cohorts provide additional placebo-controlled efficacy readouts
- Also expand data set for assessing SIN tests
- Considering review of results and SIN tests with FDA in EOP1 meeting
- Plan to initiate full dose-ranging Phase 2 efficacy trial by end of 2022
  - May evaluate 2 doses plus placebo
  - Incorporate “learnings” from Phase 2a and higher dose cohorts

Key Take-Aways from OTO-413 Phase 2a Results

- Phase 2a provides a second independent, placebo-controlled trial demonstrating the treatment benefit of OTO-413 vs. placebo
- Results support continued targeting of a broad hearing loss population
- KOLs are encouraged with the level of speech intelligibility improvements observed in OTO-413 responders
- Potential for broadening or increasing level of treatment response with higher dosing
- Phase 2a and ongoing evaluations provide important learnings for our next trial
- OTO-413 clinical signal supports initiation of a full dose-ranging Phase 2 efficacy trial by the end of 2022

Upcoming Milestones

Expected Timing	Program Milestone
✓	OTO-413 Phase 2a Top-line Results
Mid-2022	OTO-313 Phase 2 Top-line Results
2H22	OTO-313 Higher & Bilateral Dosing Safety Results
2H22	OTO-413 Higher Dose Evaluation Results
End of 2022	Initiate OTO-413 Phase 2 Efficacy Trial
1H23	Initiate OTO-313 Phase 3 Program
1H23	IND Filing for OTO-825