Investigational medicines for the inner ear: clinical trial design considerations

Colleen G. Le Prell, Ph.D.
Emilie and Phil Schepps Professor of Hearing Science
Chair, Department of Speech, Language, and Hearing
School of Behavioral and Brain Sciences
University of Texas at Dallas

Disclosures

Co-inventor on patents owned by the University of Michigan

Paid consultant on issues related to clinical trial design

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- 3M, Inc.
- Q30, Inc.
- MaxSound, Inc.
- Sound Pharmaceuticals, Inc.
- Edison Pharmaceuticals, Inc.

- Emilie and Phil Schepps Distinguished Professorship in Hearing Science
While many OTC dietary supplements are available online/in stores, there are NO products approved by the FDA for NIHL, DIHL, or SNHL prevention or hearing restoration at this time.

OTC dietary supplements marketed with an FDA disclaimer do not have to be studied for safety or efficacy.

Overview

- **Introduction**
- **Auditory measures**
  - Outcome, endpoint, and indication definitions
  - Objective and subjective test options
    - Systematic review of tests used in previous clinical trials
    - Hearing-in-noise test endpoints
- **Possible participant populations for hearing loss prevention/hearing restoration studies**
  - NIHL, DIHL, and SNHL indications require different populations
- **Types of investigational medicines of interest for hearing loss prevention and hearing restoration**
Development of Inner Ear Medicines: The Good News

- Extensive documentation of both *in vitro* and *in vivo* protection of hair cells and hearing sensitivity using various otoprotective drugs (antioxidant and other agents) to prevent various noise injuries as well as ototoxic drug insults
- Comparing effectiveness of agents across pre-clinical drug studies complicated by use of differences in species, treatment onset time, and duration of therapy, as well as use of different exposures with different injury severity
- This is active clinical trial space as evident from both PubMed searches and clinicaltrials.gov trial listings
- There are now more than 40 companies developing drugs for potential prevention of acquired hearing loss and/or hearing disorders (NIHL, DIHL, ARHL) as well as biologics for hair cell regeneration

The Not-So-Good News About Pre-Clinical Research

- Preclinical research has relied on multiple species
  - Guinea pigs, rats, chinchillas, mice
- With injury models that often fail to replicate the real-world condition
  - Noise exposures that induce profound pathology over hours, not years
  - Drug insults that induce profound pathology over days, not months or years
- With varying degrees of injuries for different species x drug combinations
  - How to compare prevention of 20 dB loss versus reduction of large (50-70 dB) loss?
- Using multiple treatment paradigms
  - Onset of treatment may be pre-injury (prevention) or post-injury (rescue, regeneration); duration of treatment varies, and very few dose response curves investigated for any drugs of interest
  - Difficult, if not impossible, to draw conclusions on relative pre-clinical efficacy
How drugs are tested in humans

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>First test of new treatment to see if it is safe</td>
<td>Preliminary test of safe agents to see if benefit is provided</td>
</tr>
</tbody>
</table>
| **Goals** | - is treatment safe  
- how to deliver (pills, shot)  
- determine dose-related side effects in healthy volunteers | - does treatment “work”  
- do new side effects emerge when patients are treated | - is new treatment better than, equivalent to, or poorer than standard of care |
| **Sample Size** | Typically 20-30 | Often 100 or more | Typically several hundred to several thousand |
| **What to Expect** | Physical exams and multiple laboratory tests | Physical exams and multiple laboratory tests; may be open-label or may be masked | Physical exams and blood tests; randomization, placebo control, double masking |


Slow and expensive process

- 10+ years
- Greater than $100M cost across all years of this process
  - Animal studies (toxicology, safety, Pk, ADME, and efficacy)
  - Manufacturing processes
  - Validated chemical assays
  - Human Phase 1
  - Human Phase 2 – 2 smaller studies required (~50-100 subjects)
  - Human Phase 3- 600-1000 subjects, multi-site; typically must be repeated
  - New Drug Application then filed with requested health claims
- Successful drugs must cover company investments in failed drugs – estimated to be $1B cost per success achieved


Most drugs do not survive this process

- Failure at Phase I: clinical safety issue or a Pk/Pd/ADME issue (doesn’t get to right target, doesn’t act at right receptor, etc.)
- Failure at Phase II or III: clinical safety or efficacy issue, commercial issues
- Commercial issues can include high bureaucracy, low flexibility, mergers and acquisitions, cash flow, cost-benefit ratio, fear of failure, etc.

“Failures could be linked to incomplete understanding of the human diseases and mechanisms investigated, lack of correlation of animal models to human diseases, poor biomarkers and surrogate endpoints, selection of non-optimal drug molecules (pharmacokinetics/pharmacodynamics profile, off-target effects, among others), idiosyncratic drug toxicity and poor clinical trials design.”


Facilitating Success: DoD HCE Open-Access Resources

• Special Topics in Clinical Monitoring; In: International Journal of Audiology 57(Suppl. 4), 2018.
Overview

• Introduction

• Auditory measures
  • Outcome, endpoint, and indication definitions
  • Objective and subjective test options
    • Systematic review of tests used in previous clinical trials
    • Hearing-in-noise test endpoints
  • Possible participant populations for hearing loss prevention/hearing restoration studies
    • NIHL, DIHL, and SNHL indications require different populations
  • Types of investigational medicines of interest for hearing loss prevention and hearing restoration

Key Definitions

• Outcome: measured variable
  • e.g., audiometric threshold, DPOAE amplitude

• Endpoint: analyzed parameter (e.g., change from baseline)
  • Primary endpoint – typically will be the most important outcome; addresses whether a new treatment prevents disease, or is better at preventing disease than the standard therapy
  • Secondary endpoint – other relevant questions to be answered by study; can build on primary endpoint with mechanistic insights (e.g., a drug for osteoporosis with fractures as the primary endpoint could include improved bone density as a secondary endpoint)

• Indication: use of a drug for treating a particular disease (e.g., use of a drug for NIHL prevention or ARHL treatment)
  • Multiple endpoints may be used to evaluate clinical benefit when (1) there are several important aspects of a disease or several ways to assess an important aspect, (2) there is no consensus about which one will best serve the study purposes, and (3) an effect on any one will be sufficient as evidence of effectiveness to support 501 approval.
Majority of Clinical Tests provide quantitative data – generate a numeric score that can be monitored for change

- Tympanometry – status of tympanic membrane; how well it moves
- Acoustic Reflex – measures stapedius muscle contraction in response to loud sound
  - Threshold – how loud sound must be to elicit response
  - Amplitude of response – strength of neural signal
- Audiogram
  - Pure-tone air-conduction thresholds
  - Speech reception threshold (SRT): correlates well with PTA512
- Word recognition – identification of words in quiet
- Hearing-in-Noise – identification of words in noise background (babble, speech-shaped noise, etc.)
- Otoacoustic Emissions – reflects health of outer hair cells, assuming normal conduction
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)
- Electrococleography (eCochG)/Auditory brainstem response (ABR) – reflects health of afferent neural pathway, assuming normal conduction and intact outer hair cells
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)

Quantitative tests can be objective or subjective

**Objective (Does not require patient participation)**

- Tympanometry
  - Pressure, admittance, volume
- Otoacoustic emissions
  - Threshold, amplitude
- Sound-evoked cochlear potentials (ABR, eCochG)
  - Threshold, amplitude, latency
- Central auditory processing (MLR, LLR)
  - Present/absent, amplitude, latency

**Subjective (Patient report)**

- Audiogram
  - Threshold (tones, words)
- Hearing-in-noise
  - WIN, QuickSin, HINT, BKB-SIN
- Tinnitus matching
  - Pitch, level
- Tinnitus surveys
  - Tinnitus Functional Index (TFI)
  - Tinnitus Handicap Inventory (THI)
- Hearing surveys
  - SSQ/SSQ12
  - Hearing Handicap Inventory (HHI-A, HHI-E)
  - Hearing Screening Inventory (HSI)
- Patient reported outcomes
  - Patient Global Impression of Change
Challenges in Matching Endpoints to Indications

- **Clinical Benefit**: A therapeutic intervention may be said to confer clinical benefit if it *prolongs life, improves function, and/or improves the way a patient feels*
  - Changes in OAE amplitude or ABR amplitude may be earliest outcomes of disease or injury process; however, if there are no measurable perceptual deficits associated with those changes, clinical benefit and medical indication may be difficult, to establish making them more appropriate secondary endpoints.
  - Changes in audiogram are the most common outcome but the specific endpoint definition for clinically significant changes in the audiogram vary significantly.
  - Hearing-in-noise is receiving increased discussion.
  - Systematic review strategy used to identify common endpoints.

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ClinicalTrials.gov

- All clinical trials funded by NIH must be listed.
- 42 CFR 11.22 requirements broadly include registration for any U.S. clinical trial with one or more arms that (i) is interventional, (ii) is other than Phase 1, and/or (iii) studies an FDA-regulated drug product.
- The criteria for U.S. clinical trials further include (i) having at least one clinical trial location within the U.S. or one of its territories, (ii) product manufacturing in and export from the U.S. or one of its territories for study in another country, and/or (iii) the clinical trial has an FDA IND Number.
- Thus, all efficacy-based U.S. clinical trials submitted to FDA for review through IND (investigational new drug application) process and any clinical trial using drugs manufactured in the U.S. must be listed.
- Not every trial listed on ClinicalTrials.gov is overseen by FDA but there is no publicly available list of clinical trials making this website the best available proxy for drugs in development for possible future U.S. FDA approval.
### Endpoint measures in 61 hearing loss prevention/hearing restoration clinical trials posted on ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Primary, Secondary, or Other Endpoint</th>
<th>NIHL (n = 9)</th>
<th>DIHL (n = 30)</th>
<th>SNHL (n = 13)</th>
<th>SSNHL (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold Shift</td>
<td>7; 78%</td>
<td>14; 47%</td>
<td>8; 62%</td>
<td>9; 100%</td>
</tr>
<tr>
<td>Rate of ASHA SOC</td>
<td>0</td>
<td>6; 20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rate of CTCAE</td>
<td>0</td>
<td>3; 10%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rate of Brock</td>
<td>0</td>
<td>1; 3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rate of Boston SIOP</td>
<td>0</td>
<td>1; 3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other STS Rate</td>
<td>1; 11%</td>
<td>8; 27%</td>
<td>1; 8%</td>
<td>0</td>
</tr>
<tr>
<td>DPOAE Shift</td>
<td>5; 56%</td>
<td>10; 33%</td>
<td>1; 8%</td>
<td>0</td>
</tr>
<tr>
<td>EHF Threshold shift</td>
<td>1; 11%</td>
<td>5; 17%</td>
<td>2; 15%</td>
<td>0</td>
</tr>
<tr>
<td>Word Recognition Change</td>
<td>0</td>
<td>2; 7%</td>
<td>6; 46%</td>
<td>4; 44%</td>
</tr>
<tr>
<td>Hearing in Noise Change</td>
<td>2; 22%</td>
<td>2; 7%</td>
<td>5; 38%</td>
<td>0</td>
</tr>
<tr>
<td>Change in Tinnitus</td>
<td>5; 56%</td>
<td>7; 23%</td>
<td>5; 38%</td>
<td>1; 11%</td>
</tr>
<tr>
<td>Change in Hearing Status</td>
<td>0</td>
<td>6; 20%</td>
<td>2; 15%</td>
<td>1; 11%</td>
</tr>
<tr>
<td>ABR Shift</td>
<td>0</td>
<td>0</td>
<td>2; 15%</td>
<td>0</td>
</tr>
</tbody>
</table>


### Various definitions for pure-tone threshold shift across trials

<table>
<thead>
<tr>
<th></th>
<th>NIHL</th>
<th>DIHL</th>
<th>SNHL</th>
<th>SSNHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 kHz</td>
<td>HFPTA, 6-16 kHz</td>
<td>Average of 2 and 4 kHz</td>
<td>PTA 5124</td>
<td></td>
</tr>
<tr>
<td>2, 3, 4, or 6 kHz</td>
<td>Frequencies from 0.25 to 16 kHz</td>
<td>Change at 3 most affected frequencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA346</td>
<td>9, 10, 12.5 and 14 kHz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“group mean hearing level”</td>
<td>Degree or incidence of hearing loss using pure tone audiometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change in pure tone thresholds</td>
<td>Pure tone audiometry in conventional and high frequency ranges</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of ClinicalTrials.gov data

- Information available in ClinicalTrials.gov often lacked precision in the definition of outcome measures and endpoints
- Where detail was provided:
  - Audiogram was by far the most used outcome measure; however, study endpoints (definitions for threshold shift) varied widely within and across indications
  - DPOAEs were more common outcome measure in NIHL (56%) and DIHL (33%) trials than those for other indications (0-8%) – but with no consistent endpoint used
  - Hearing-in-noise was more common outcome measure in SNHL amelioration (33%) and NIHL prevention (22%) trials than those for other indications (0-8%) – but with no consistent endpoint used
- What about reports in scientific literature?

<table>
<thead>
<tr>
<th></th>
<th>PTS (pre-Tx) (n = 4 trials)</th>
<th>PTS (Post-tx) (n = 5 trials)</th>
<th>TTS (pre-tx) (n = 20 trials)</th>
<th>TTS (post-tx) (n = 2 trials)</th>
<th>Total (n = 31 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average threshold shift</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>17/20; 85%</td>
<td>2/2; 100%</td>
<td>22/31; 71%</td>
</tr>
<tr>
<td>Duration of threshold shift</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of ASHA SOC</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Other STS (unspecified)</td>
<td>1/4; 25%</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>2/31; 6%</td>
</tr>
<tr>
<td>Rate of threshold shift ≥ 25 dB</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of threshold shift ≥ 5, 15, or 25 dB</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of threshold shift ≥ 15 dB</td>
<td>0</td>
<td>1/5; 20%</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of threshold shift ≥ 10 dB</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>3/31; 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPOAE amplitude change</td>
<td>0</td>
<td>0</td>
<td>4/20; 20%</td>
<td>0</td>
<td>4/31; 13%</td>
</tr>
<tr>
<td>TEOAE amplitude change</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Word recognition change ≥15%</td>
<td>0</td>
<td>1/5; 20%</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
</tbody>
</table>

### Threshold-based secondary endpoint measures

<table>
<thead>
<tr>
<th></th>
<th>PTS pretreatment (n = 4 trials)</th>
<th>PTS post-treatment (n = 5 trials)</th>
<th>TTS pretreatment (n = 20 trials)</th>
<th>TTS post-treatment (n = 2 trials)</th>
<th>Total (n = 31 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Threshold Shift</td>
<td>1/4; 25%</td>
<td>1/5; 20%</td>
<td>8/20; 40%</td>
<td>0</td>
<td>10/31; 32%</td>
</tr>
<tr>
<td>Duration of Threshold Shift</td>
<td>0</td>
<td>0</td>
<td>3/20; 15%</td>
<td>0</td>
<td>3/31; 10%</td>
</tr>
<tr>
<td>Rate of ASHA SOC</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of OSHA/DOEHRSHC STS</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of NIOSH/DOEHRSHC Early Warning</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>0</td>
<td>0</td>
<td>3/31; 10%</td>
</tr>
<tr>
<td>Rate of Modified Navy STS</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Rate of threshold shift ≥ 10 dB</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Average EHF threshold shift</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>1/20; 5%</td>
<td>0</td>
<td>4/31; 13%</td>
</tr>
</tbody>
</table>


### DPOAE, ECochG, Hearing-in-noise as secondary outcome measures

<table>
<thead>
<tr>
<th></th>
<th>PTS pretreatment (n = 4 trials)</th>
<th>PTS post-treatment (n = 5 trials)</th>
<th>TTS pretreatment (n = 20 trials)</th>
<th>TTS post-treatment (n = 2 trials)</th>
<th>Total (n = 31 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPOAE amplitude shift</td>
<td>2/4; 50%</td>
<td>2/5; 40%</td>
<td>3/20; 15%</td>
<td>0</td>
<td>7/31; 23%</td>
</tr>
<tr>
<td>DPOAE threshold shift</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>DPOAE unspecified shift</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>TEOAE amplitude shift</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>1/1; 100%</td>
<td>2/31; 6%</td>
</tr>
<tr>
<td>CAP/ECochG amplitude shift</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>1/20; 5%</td>
<td>0</td>
<td>4/31; 13%</td>
</tr>
<tr>
<td>Change in Hearing-in-Noise</td>
<td>1/4; 25%</td>
<td>2/5; 40%</td>
<td>1/20; 5%</td>
<td>0</td>
<td>4/31; 13%</td>
</tr>
</tbody>
</table>

### Tinnitus secondary outcome measures

<table>
<thead>
<tr>
<th></th>
<th>PTS pretreatment (n = 4 trials)</th>
<th>PTS post-treatment (n = 5 trials)</th>
<th>TTS pretreatment (n = 20 trials)</th>
<th>TTS post-treatment (n = 2 trials)</th>
<th>Total (n = 31 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus Handicap Inventory</td>
<td>0</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Tinnitus incidence</td>
<td>0</td>
<td>0</td>
<td>3/20; 15%</td>
<td>0</td>
<td>3/31; 10%</td>
</tr>
<tr>
<td>Tinnitus loudness/annoyance</td>
<td>1/4; 25%</td>
<td>0</td>
<td>1/20; 5%</td>
<td>0</td>
<td>2/31; 6%</td>
</tr>
<tr>
<td>Tinnitus severity</td>
<td>1/4; 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
<tr>
<td>Tinnitus intensity</td>
<td>0</td>
<td>1/5; 20%</td>
<td>0</td>
<td>0</td>
<td>1/31; 3%</td>
</tr>
</tbody>
</table>


### Summary of NIHL study data

- Audiometric threshold shift was primary outcome in ~70% of studies, and secondary outcome in remaining 30%
  - Rate of STS was only rarely used - however, rate of NIOSH or OSHA STS are of high interest as “accepted” definitions of noise-injury
- Changes in objective outcomes only used as primary endpoint in about 15% of studies (OAEs), and secondary endpoint in about 30% of studies (OAEs in ~25%, ABR/eCochG in about 15%)
- Tinnitus measures not used as primary endpoint in NIHL prevention studies and appear as secondary endpoint in just 10% of studies
- Hearing-in-noise changes have not been used as primary endpoint in NIHL prevention studies and appear as secondary endpoint in just 13% of NIHL studies
Hearing in background noise

- Difficulties hearing-in-noise are one of most common complaints; can occur with or without hearing loss
- Out of 100,000 patient records reviewed at one clinic, 10% seen for hearing-in-noise complaints with no audiometric loss at testing (Parthasarathy et al., 2020)
- Some jobs critically rely on hearing-in-noise ability; important for social reasons as well
- No agreed-on gold standard test, but there are multiple standardized published tests
- Emerging literature shows hearing in noise deficits can occur with damage to OHCs or damage to synapses – deficits are NOT a diagnostic for synapse loss

For detailed reviews, see:

Multiple validated speech-in-noise tests are available

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Items</th>
<th>SNR range</th>
<th>Sentence Sound Levels</th>
<th>Target Voice</th>
<th>Noise/Babble Background/Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HINT</td>
<td>25 sentence lists, 10 sentences per list, 6 target words per sentence</td>
<td>SNR step size begins at 4-dB, and changes to 2-dB. Sentence level is manipulated up/down to determine lowest level at which all words are correctly repeated.</td>
<td>Sentence presentation level at either 90 dB SPL (PTA&lt;40 dB HL) or 100 dB SPL (PTA&gt;40 dB HL); level is increased in 4-dB steps until listener correctly repeats sentence</td>
<td>Male talker</td>
<td>Speech-spectrum noise fixed at 65-dBA (or 72-dBA)</td>
</tr>
<tr>
<td>BKB-SIN</td>
<td>18 pairs of lists, 10 words per list</td>
<td>Sentences presented at SNRs of +21, +18, +15, +12, +9, +6, +3, 0, -3, and -6 (3-dB decrements)</td>
<td>Sentence presentation level varies from 96 dB SPL (first 8 sentences) to 93 (9th sentence) and 90 dB SPL (10th sentence)</td>
<td>Male talker</td>
<td>Multi-talker babble with 4 voices (&quot;Auditech babble&quot;); Background babble increases by 3-dB per sentence</td>
</tr>
<tr>
<td>QuickSin</td>
<td>12 sentence lists, 6 sentences per list, 5 target words per sentence</td>
<td>SNR levels of 0 (hardest), +5, +10, +15; can also include +20 and +25 (easiest)*</td>
<td>70-dB HL sentence presentation level (100-dB SPL)</td>
<td>Female talker</td>
<td>4-talker babble; babble level increases from 75 dB SPL to 100 dB SPL to increase difficulty of task</td>
</tr>
<tr>
<td>WIN</td>
<td>2 word-lists, with 35 NU-6 words per list. Five words per SNR</td>
<td>SNR decreasing from 24 (easiest) to 0 (most difficult) in 4-dB decrements*</td>
<td>Word level varies from 104 dB SPL to 80 dB SPL to increase difficulty of task</td>
<td>Female talker</td>
<td>Multi-talker babble with 6 female voices, fixed at 80 dB SPL</td>
</tr>
</tbody>
</table>

* If no correct words are achieved within a level, then harder SNRs are not tested.
Tests are related to each other

Figures 2 and 3: Test named at top is test plotted on x-axis; test named in upper left corner is test plotted on y-axis. 24 listeners with normal hearing (circles) and 72 listeners with hearing loss (squares).


• All listeners do better on BKB-SIN and HINT than QuickSin or WIN.
  – BKB-SIN and HINT sentences provide more context than QuickSin sentences
  – WIN is word-based not sentence based; reduces role of memory, cognition, and linguistic context, with greater emphasis on acoustic cues
• QuickSin and WIN better than BKB-SIN and HINT for separating normal and hearing impaired listeners
• Wilson et al. recommend either the QuickSin or WIN for clinical use

Sound exposure results in temporary hearing-in-noise deficits the next day, at difficult SNRs (≤8 dB SNR) using WIN

• 28 participants attended recreational event they deemed loud
  • Level: 93.3±7.8 dBA (range 73.1–104.2 dBA)
  • Duration: 4.2±3.5 hrs (range 1.5–16.0 hrs)
• Average dose and TWA calculated using 29 CFR 1910.95 (OSHA)
  • 168.4±276% (range 3.5%–1,230.8%)
  • 87.8 dBA TWA±9.5 dBA (range 65.8–108.1 dBA TWA)
• Participants generally equally divided into groups with < 50% dose (4M, 5F), 50-100% dose (4M, 6F), and > 100% dose (3M, 6F)
• Among participants with >100% OSHA dose, hearing in noise deficits were observed at 0, 4, and 8 dB SNRs

Overview

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• Auditory measures
  • Outcome, endpoint, and indication definitions
  • Objective and subjective test options
    • Systematic review of tests used in previous clinical trials
    • Hearing-in-noise test endpoints
• Possible participant populations for hearing loss prevention/hearing restoration studies
  • NIHL, DIHL, and SNHL indications require different populations
• Types of investigational medicines of interest for hearing loss prevention and hearing restoration

Our NIHL clinical trial populations

• Completed: TTS after Weapons Training/Swedish Military

• Completed: Music Player TTS studies

• Completed: Music Player TTS studies

• Vincerinone, funded by Edison Pharmaceuticals. NCT02257983 conducted at University of Florida with Drs. Patrick Antonelli, Chris Spankovich, Ed Lobarinas, Scott Griffiths. Results masked by sponsor.

• Recruiting: PTS after Surgical Skull-Based Drilling Noise, Safety Officer Weapons Training
  • Zonisamide, funded by Department of Defense W81XWH-19-C-0054. NCT04768569 conducted at University of Washington in St. Louis with Drs. Craig Buchman, Jianxin Bao, Amanda Ortman; NCT04774250 conducted at University of Akron with Drs. Craig Buchman, Jianxin Bao, Kristine Sonstrom-Malowski
### Endpoint measures in our studies

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Swedish Soldiers</th>
<th>MP3 players, ACEMg</th>
<th>MP3 players, Ebselen</th>
<th>MP3 players, Vincerinone</th>
<th>Skull-based drilling</th>
<th>Safety Officers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Max shift at 3, 4, 6 kHz in either ear</td>
<td>Change in 4kHz threshold</td>
<td>Change in 4 kHz threshold</td>
<td>Change in 4kHz threshold</td>
<td>Proportion of patients with &gt;10 dB shift between 2-6 kHz</td>
<td>Proportion of officers with &gt;10 dB shift between 2-6 kHz</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td>Shift at each frequency</td>
<td>Shift at each frequency</td>
<td>Shift at 3, 4, 6 kHz</td>
<td>Shift at each frequency</td>
<td>Proportion of patients meeting NIOSH red flag</td>
<td>Proportion of officers meeting NIOSH red flag</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td>Shift at 0.5, 1, 2 kHz</td>
<td>Average shift from 0.25 to 8 kHz</td>
<td>Shift at 4, 6, 8 kHz</td>
<td>EHF threshold shift (10-14 kHz)</td>
<td>EHF threshold shift (10-14 kHz)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td>Shift at 3, 4, 6 kHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DPOAEs</strong></td>
<td>F2=2,3,4,6,8 kHz; L1=25-65 dB SPL</td>
<td>F2=2,3,4,6,8 kHz; L1=25-65 dB SPL</td>
<td>No</td>
<td>F2=2,3,4,6,8 kHz; L1=35,45,55 dB SPL</td>
<td>F2=1-6 kHz; L1=65 dB SPL</td>
<td>F2=1-6 kHz; L1=65 dB SPL</td>
</tr>
<tr>
<td><strong>Hearing-in-noise</strong></td>
<td>4k PMTF</td>
<td>No</td>
<td>No</td>
<td>WIN</td>
<td>WIN</td>
<td>WIN</td>
</tr>
<tr>
<td><strong>Tinnitus</strong></td>
<td>Incidence, loudness, bothersomeness</td>
<td>Incidence, loudness, bothersomeness</td>
<td>No</td>
<td>Incidence, loudness, bothersomeness</td>
<td>Tinnitus Functional Index (TFI)</td>
<td>Tinnitus Functional Index (TFI)</td>
</tr>
<tr>
<td><strong>ABR/eCochG</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>ABR</td>
<td>ABR</td>
<td></td>
</tr>
</tbody>
</table>

### Another PTS Population: U.S. Service Members

- **Camp Pendleton Marine Corps Base, STS after 16 days of basic training including weapons training**
  - “As part of routine weapons training, all subjects were uniformly exposed to various noises including impulse, steady-state noise, as well as simulated explosions. The most common noise exposure was M-16 rifle fire, with every trainee firing 325 rounds during the training.”
  - **Primary endpoint:** ASHA Significant Ototoxic Change - increase >20 dB at any test frequency or average increase >10 dB at any two consecutive test frequencies
  - **Secondary endpoint:** US Navy STS rate in trigger-hand ear (increase of >15 dB at any test frequency or average increase of >10 dB at any two consecutive test frequencies)

- **Fort Jackson Drill Sargent instructor training, STS after 11 days of weapons training with minimum of 500 rounds of M-16 weapon fire**
  - Rate of ASHA SOC, OSHA STS (average shift > 10 dB at 2, 3, and 4 kHz), and DoD Early warning (15 dB shift at 1, 2, 3, or 4 kHz in either ear) all reported

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Gene therapy across tissues

- Over 1800 human clinical trials in the 2013 review by Ginn et al. – no hearing loss trials reported
- 2017 review by Ahmed et al noted that there were no trials in the human inner ear yet
- Over 2600 human clinical trials in the 2018 review by Ginn et al. – hearing loss was included as part of “other diseases” – which comprised a combined 58 trials (2%) out of the >2600 trials reported

Investigational new drug applications (INDs) in gene therapy by year to US FDA

- First clinical trial of gene therapy, for a rare inherited form of immunodeficiency, began at NIH in 1990
- The first approved gene therapy in the US wasn’t until 2017 when FDA approved treatment of a rare form of congenital blindness caused by autosomal recessive mutations in the gene RPE65

Katherine A. High. 2020. Turning genes into medicines—what have we learned from gene therapy drug development in the past decade? Nature Communications, 11:5821; https://doi.org/10.1038/s41467-020-19507-0
Gene therapy is more advanced for the eye than the ear

- Pharmaceutical industry once neglected the eye (just like the ear) but now there are blockbuster drugs injected into the eye to prevent blindness from retinal diseases
- Gene therapy for the eye: retinal RPE65 gene therapy
  - Spark Therapeutics Luxturna https://luxturnahcp.com/id-appropriate-patients/rpe65-gene/
- Genentech Lucentis and Regeneron Eylea are vascular endothelial growth factor-A (VEGF-A) drugs injected into the retina for wet macular degeneration and diabetic retinopathy indications
- Multiple companies are in the process of developing gene therapies in which VEGF production is stimulated by delivering genes responsible for VEGF production
  - https://www.brightfocus.org/macular/article/gene-therapy-eye-dis
- Excellent overview of lessons learned from studies of the eye are available in Zhang et al. (2018)

Current barriers to gene therapy in the eye

- Each treatment can only fix a single gene
  - Retinal RPE65 gene therapy via Luxturna
  - Retinitis pigmentosa can be caused by 100 different mutations in the RHO gene, making it difficult to develop gene therapy for this disease
- Developing a gene therapy is expensive
  - It is not financially feasible to develop gene therapies for every mutation, especially for extremely rare mutations
  - One strategy in progress is to “silence” the RHO gene whether mutated or not and then use gene therapy to introduce a replacement copy that is immune to the RNA silencing
- Gene therapy is not cheap.
  “In the US, Luxturna costs a whopping $425,000. Per eye. That makes Luxturna one of the most expensive drugs in the world (along with other gene therapies such as Novartis’ Zolgensma or bluebird bio’s Zynteglo).”

https://www.labiotech.eu/features/gene-therapy-blindness-cure/
## Gene therapy/small-molecule regeneration therapy trials: Adults with severe SNHL

<table>
<thead>
<tr>
<th>Clinical Trial ID</th>
<th>Inclusion Criteria</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02132130</td>
<td>21-75 yrs; non-fluctuating severe-to-profound unilateral or bilateral HL</td>
<td>Adverse events, conventional audiometry, bone conduction audiometry</td>
<td>BAER, vestibular function (HIT, VEMP, SVV), speech recognition</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT03300687</td>
<td>18 or older; severe to profound SNHL of 80 dB HL or poorer at 500 Hz, meets criteria for CI; has chosen CI surgery</td>
<td>Adverse events (tinnitus, vertigo, perforation)</td>
<td>plasma pharmacokinetics over 24 and 72 hours; perilymph pharmacokinetics within 24 hours</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT04629664</td>
<td>18-65 yrs; acquired, non-genetic, severe sensorineural hearing loss; PTA5124 of 71-90 dB HL in ear to be injected</td>
<td>Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk</td>
<td>speech in quiet, speech in noise (BKB-SIN), conventional and high frequency audiometry, tinnitus (TFI)</td>
<td>Completed</td>
</tr>
</tbody>
</table>


## Gene therapy/small-molecule regeneration therapy trials: older populations

<table>
<thead>
<tr>
<th>Clinical Trial ID</th>
<th>Inclusion Criteria</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04462198</td>
<td>66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected</td>
<td>Treatment emergent adverse events</td>
<td>Pharmacokinetics; other outcomes include speech in noise, audiometry, auditory brainstem response</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT04601909</td>
<td>66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected</td>
<td>Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk (C-SSRS)</td>
<td>speech in quiet, speech in noise (WIN), conventional and high frequency audiometry, tinnitus (TFI)</td>
<td>Active, Not yet recruiting</td>
</tr>
</tbody>
</table>

### Gene therapy/small-molecule regeneration therapy trials: Adults with intact hearing

<table>
<thead>
<tr>
<th>Clinical Trial ID</th>
<th>Inclusion Criteria</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04120116</td>
<td>18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 26-70 dB HL in the injected ear</td>
<td>Speech in quiet, speech in noise (WIN), audiometry, CTCAE v5.0 adverse events, abnormal otoscopic changes; abnormal change in tympanometry</td>
<td>high frequency audiometry, tinnitus assessment (TFI), patient reported outcome measures (HHIA, HIS)</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT03616223</td>
<td>18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 better than 70 dB HL</td>
<td>Number of CTCAE v5.0 adverse events</td>
<td>drug concentration in plasma within first 24 hours</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT04129775</td>
<td>21-64 yrs; normal or up to moderately severe hearing impairment, self-reported difficulty hearing in noise for at least 6 months and a speech-in-noise deficit in at least one ear</td>
<td>Number of adverse events; abnormal otoscopic changes; abnormal change in audiometry</td>
<td>speech in noise, auditory brainstem response, and patient global impression of change</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT05086276</td>
<td>18-65 yrs; acquired, adult onset, SNHL (NIHL or sudden SNHL); PTA5124 of 35-85 dB HL in ear to be injected</td>
<td>Speech perception</td>
<td>standard and high frequency audiometry, tinnitus assessment, and multiple patient reported outcome measures</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT05061758</td>
<td>18-65 yrs; minimum of 6 months; stable hearing loss (&lt;80 dB HL) and stable word recognition test for approximately 6 months</td>
<td>Number of responders with at least 2 dB improvement in an adaptive sentence in noise test (international matrix test) compared to placebo</td>
<td>Not yet recruiting</td>
<td></td>
</tr>
</tbody>
</table>


### Summary of Populations

- **NIHL studies have included both TTS and PTS populations**
  - Studies in which noise is unavoidable are preferred for ethical (risk) reasons
  - Studies in which HPDs are required due to noise exposure have observed less than expected rate of NIHL
  - Occupational studies have focused on post-shift TTS however the overarching clinical need is prevention of PTS that develops over years of exposure
- **DIHL studies recruit participants who are required to receive cisplatin or aminoglycoside antibiotics for therapeutic indications**
  - Caution is required as otoprotective drugs have the potential to bind to and inactivate therapeutic agent of interest
  - Interest in DIHL prevention has seen significant shift from systemic treatment (pre-clinical) to middle ear delivery (clinical)
- **Gene therapy and small molecule regeneration therapies have emerged and populations enrolled in clinical trials are shifting to populations with less hearing loss as safety studies show hearing can be preserved from injection-related trauma**
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Commercial Activity

June 2018 search to identify companies working in the field of therapeutics for inner ear and central hearing disorders

43 companies with pre-clinical or clinical research programs identified
  • 24 in United States, 4 in France, 4 in Germany, 3 in Switzerland, 2 in the United Kingdom, 1 each in Japan, Israel, Sweden, Denmark, Belgium and the Netherlands

Otoprotection
  • 24 companies, 37 therapeutic programs
  • Ototoxicity, noise injury, aging, ISSNHL, CI insertion trauma
  • 20 programs preclinical, 4 Phase I programs, 5 Phase 2 programs (2 failed), 3 Phase 3 programs

Regeneration
  • 15 companies, 16 therapeutic programs
  • 13 programs pre-clinical, 2 Phase I programs, 1 Phase I/2 program

Tinnitus Reduction
  • 12 companies, 13 therapeutic programs
  • 8 programs preclinical, 2 Phase I programs, 1 Phase 2 (failed), 2 Phase 3 programs (failed)

Central Hearing Disorders
  • 1 company, 1 therapeutic program
    • Preclinical

Balance
  • 5 companies, 5 therapeutic programs
  • 2 programs preclinical, 1 Phase I programs, 1 Phase 2 programs, 1 Phase 3 programs

Investigational medicines have diverse mechanisms of action and are being assessed for diverse clinical indications

• Preclinical: Animal models
• Phase 1: Safety endpoints
• Phase 2: Safety and efficacy endpoints
• Phase 3: Large efficacy studies
• Phase 4: Post-marketing

• Exciting time for inner ear medicine development with multiple promising agents, growth in companies, and growth in investment

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• Exciting time for inner ear medicine development with multiple promising agents, growth in companies, and growth in investment

Summary

• Pre-clinical test paradigms highly variable; so are clinical trial protocols to date
  • Pure tone audiometry better reflects OHC loss than IHC loss or peripheral neuropathy
  • Hearing-in-noise ability not well predicted by audiometric PTA thresholds
  • OAEs assess integrity of OHCs; no agreed-on definitions of clinically significant change
  • ABRs of significant interest but uncertain value for human “hidden hearing loss”
  • Audibility (threshold) and clarity (identification) may be distinct and both are of significant clinical value
  • Self-reported hearing difficulty has no gold standard but patient-reported outcomes and global measures of function are of high interest to FDA

• As additional drugs enter and complete Phase II testing, standardization may emerge – FDA will play significant role as they review proposed endpoints as part of study approval

• Once a first inner ear medication is approved, there will be a benchmark for other drugs seeking to establish non-inferiority
Questions and Discussion