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Investigational Medicinal Products for the Inner Ear: Review of Clinical Trial Characteristics in ClinicalTrials.gov

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Abstract

Background The previous 30 years have provided information on the mechanisms of cell death in the inner ear after noise exposure, ototoxic drug injury, and during aging, and clinical trials have emerged for all of these acquired forms of hearing loss. Sudden hearing loss is less well understood, but restoration of hearing after sudden hearing loss is also a long-standing drug target, typically using steroids as an intervention but with other agents of interest as well.

Purpose The purpose of this review was to describe the state of the science regarding clinical testing of investigational medicinal products for the inner ear with respect to treatment or prevention of acquired hearing loss.

Data Collection and Analysis Comprehensive search and summary of clinical trials listed in the National Library of Medicine (www.ClinicalTrials.gov) database identified 61 clinical trials.

Results Study phase, status, intervention, and primary, secondary, and other outcomes are summarized for studies assessing prevention of noise-induced hearing loss, prevention of drug-induced hearing loss, treatment of stable sensorineural hearing loss, and treatment of sudden sensorineural hearing loss.

Conclusion This review provides a comprehensive summary of the state of the science with respect to investigational medicinal products for the inner ear evaluated in human clinical trials, and the current challenges for the field.

Keywords

- otoacoustic emissions
- clinical trial
- ototoxicity
- noise induced hearing loss
- investigational medicinal product
- sensorineural hearing loss

Interests in otopathology underlying noise-induced hearing loss (NIHL), drug-induced hearing loss (DIHL), and age-related hearing loss (ARHL) are longstanding, dating back to at least the 1950's (for historic review, see [1–3]). Much of this literature shows outer hair cell (OHC) loss to be commonly associated with NIHL, DIHL, and ARHL. With advances in microscopy, molecular biology, and biochemistry, understanding of acquired hearing loss accelerated over the past 30 years, resulting in detailed insights into the cellular and molecular events associated with acquired hearing loss.[4] More recent reports have shown synapses between the inner hair cells (IHCs) and their auditory nerve fiber (ANF) targets to be highly vulnerable after noise-induced temporary threshold shift (TTS), with slow degeneration of the ANF population subsequent to synapse loss.[5] These findings have stimulated interest in functional deficits associated with specific synaptic and/or hair-cell based otopathologies.[6–8]

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The increasing understanding of mechanisms of NIHL, DIHL, and ARHL, has also driven expansive pre-clinical efforts to identify potential medicinal products for the inner ear, including otoprotective agents (delivered prior to injury/before the onset of hearing loss) and therapeutic treatments (delivered post injury/after the onset of hearing loss). Successful identification of possible medicinal products for the inner ear in animal models has supported the development and conduct of human clinical trials. There are multiple review papers, described next, that capture the systematic transition from work in animals to work in humans as the state of the science has progressed.

For those with interests in the role of oxidative stress and other biochemical events in acquired hearing loss, reviews from a variety of laboratories provide unique approaches and diverse insights into NIHL and DIHL prevention. Henderson et al.,[9] for example, provides a highly readable tutorial on the roles of oxidative stress and caspase activation in noise-induced apoptosis. Le Prell et al.[10] provides comprehensive technical description of the cascade of biochemical reactions leading to cell death including not only oxidative stress but also the activation of other biochemical events leading to cell death, and includes discussion of the constriction of the cochlear blood supply (vasoconstriction) occurring as a result of oxidative stress. Abi-Hachem et al.[11] expand on earlier reviews by noting overlapping protection for a variety of agents against NIHL and DIHL, and providing detailed discussion of the cytokine pathway, in which tumor necrosis factor alpha (TNF-α) activates the mitogen-activated protein kinase/c-Jun N-terminal kinase (MAPK/JNK) signaling cascade and the nuclear factor kappa B (NFκB) signaling pathway, ultimately activating the caspase cascade and resulting in cell death. Poirrier et al.[12] is helpful in providing additional information about the animal models used in studies on NIHL and DIHL otoprotection and provides brief review of the role of oxidative stress in ARHL.

Oishi and Schacht[13] briefly summarized the animal literature and expanded on earlier reviews with concise identification of agents investigated in early human clinical trials. Information about the subset of agents entering clinical testing at that time (N-acetylcysteine (NAC), D-methionine, Ebselen, dietary micronutrients) was expanded in the review by Le Prell and Bao,[14] which provides detailed description of both the extent of noise-induced permanent threshold shift (PTS) in control animals and relative reductions in PTS in animals treated with specific otoprotective agents. Evolutions in the literature can be detected in the reviews by Le et al.[15] and Sha and Schacht,[16] which discuss not only antioxidants and the anti-inflammatory effects of corticosteroids, but also the potential that neurotrophic factors may restore the ribbon synapses connecting the IHCs to the ANFs.

Several recent reviews have focused on human clinical trials, and, more specifically, the trials listed on ClinicalTrials.gov; lists of clinical trial ID numbers can be found for both DIHL otoprotection[17] and NIHL otoprotection.[18] Not all clinical trials are listed in the largely U.S.-based ClinicalTrials.gov database. There are other national and international clinical trial registries, including for example the EU Clinical Trials Register (EU-CTR). Therefore, the review by Schilder et al.[19] is particularly important as it provides a comprehensive summary of all drugs under commercial development for auditory indications regardless of what phase of development they were in at the time of the review. That review identifies 43 biotechnology and pharmaceutical companies developing a variety of agents with diverse mechanisms of action, with some agents in pre-clinical testing (i.e., under investigation in animal models) and others being tested in humans for either safety or efficacy.

Also worth note is the recent review of ARHL mechanisms and possible pharmacotherapies including antioxidants, anti-inflammatories, caspase inhibitors, and neurotrophins.[20] Insights into the quality of the various reports on human otoprotection can be obtained from the systematic review by Gupta et al.,[21] which conformed with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Gupta et al.[21] concluded that meta-analysis is not currently possible given the heterogeneity in methodologies and agents of interest, a finding that parallels earlier discussion of NIHL otoprotection research, with Le Prell and Miller[22] noting the challenges comparing relative efficacy of different agents tested in animal models based on the variation across study protocols.

Recent reviews expand on the variation across study protocols, with detailed discussions of NIHL otoprotection research paradigms in mice,[23] rats,[24,25] guinea pigs,[26] and chinchillas,[27,28] using impulse noise,[29] octave band noise,[30] or blast.[31] The variation observed in the design of preclinical studies is paralleled by variation in the design of human clinical trials. A variety of review papers highlight the diverse clinical trial paradigms used in NIHL otoprotection that have emerged over time, with widely varying participant noise exposure[32] and diverse study outcomes to be considered.[33–36] The problem of NIHL and difficulties accessing populations in which human NIHL otoprotection or treatment can be both reliably and ethically investigated has been a topic of recent discussion for Service members,[37] musicians and other performing artists,[38] and workers exposed to occupational noise.[39,40]

Within human DIHL research, recent detailed reviews have addressed clinical trials listed in ClinicalTrials.gov[17,41] and strategies for measuring DIHL.[42] Significant ototoxic change (SOC) is defined by the American Speech-Language-Hearing Association (ASHA) and the American Academy of Audiology (AAA) as ≥ 20 dB shift at any one test frequency, ≥ 10 dB shift at any two consecutive test frequencies, or loss of response at 3 consecutive frequencies where a response was obtained at baseline.[43,44] However, there are multiple other strategies for grading ototoxicity including for example Common Terminology Criteria for Adverse Events (CTCAE) published by the National Cancer Center, the TUNE grading scale, and the Brock, Chang, and International Society of Pediatric Oncology (SIOP) grading scales which are more commonly used for pediatric patients.[41,45,46]

Despite the numerous reviews and discussions of investigational medicinal products for the inner ear (i.e., studies seeking evidence that a drug will prevent or treat NIHL, DIHL,

or ARHL), there is a major gap in the literature with no systematic summary of clinical trial characteristics across these auditory indications. The lack of data with respect to the primary, secondary, and other outcomes in human clinical trials evaluating investigational medicinal products for the inner ear is concerning as it is difficult to compare the potential efficacy of different agents when primary outcomes vary from trial to trial and secondary outcomes are even more diverse. The discussion by Vetter and Mascha[47] is focused on anesthesiology rather than audiology, but their warnings regarding the importance of outcome selection within clinical trials applies across disciplines.

In the United States (U.S.), clinical trials are conducted under the oversight of the U.S. Food and Drug Administration (FDA). Within the FDA, the Center for Drug Evaluation and Research (CDER) oversees drug developers' plans for manufacturing and testing new drugs via the Investigational New Drug (IND) application process. As part of this process, investigators describe the study outcomes selected to determine safety and efficacy of the drug that is under investigation. The IND and its review are confidential, as is CDER's later review of completed reports to evaluate collected data, assess relative benefits and risks, and make decisions regarding labeling based on the clinical significance of the observed health benefits. Despite the confidentiality of the submissions to the FDA, studies meeting specific criteria related to U.S. data collection and/or U.S. drug manufacturing are required to be publicly disclosed via listing in the ClinicalTrials.gov database, per 42 CFR Part 11.

In addition to the rules for listing of clinical trials, 42 CFR Part 11 provides rules regarding the reporting of clinical trials. Results are generally required to be submitted no later than 1 year after the study's primary completion date. However, there are several exceptions to this rule including delays allowed under certain conditions (such as seeking approval, licensing, or clearance of a new use for the drug, biological, or device product). Failure to report results can result in pursuit of civil monetary penalties by the FDA, and it is possible that current and future grant funds from the NIH may not be released if reporting requirements are not met. Rules, exceptions, and penalties are specified in 42 CFR Part 11. Requirements for registration have at least in part been driven by concern that studies that are neither listed on a clinical trial repository nor published in the peer-reviewed literature could in effect be "hidden" from the scientific community with negative or other results not publicly disclosed. The International Committee of Medical Journal Editors (ICMJE) therefore recommends that journal editors require registration of clinical trials in a public trial registry at or before the time of first patient enrollment as a condition of consideration for publication and many journals are complying with this guidance.[48,49]

While all studies allowed to proceed under the FDA's IND process must be listed in the ClinicalTrials.gov database, not all studies listed on ClinicalTrials.gov are conducted under an IND. As per the disclaimer on the ClinicalTrials.gov website, "ClinicalTrials.gov, a resource provided by the U.S. National Library of Medicine (NLM), is a registry and results information database of clinical research studies sponsored or funded by a broad range of public and private organizations around the world. Not all studies listed on ClinicalTrials.gov are funded by the National Institutes of Health (NIH) or other agencies of the U.S. Federal Government. Not all listed studies are regulated and/or reviewed by the U.S. Food and Drug Administration or other governmental entities. Information on ClinicalTrials.gov is provided by study sponsors and investigators, and they are responsible for ensuring that the studies follow all applicable laws and regulations," (https://clinicaltrials.gov/ct2/about-site/disclaimer).

Despite the limitation that the ClinicalTrials.gov database is not limited to studies completed under the oversight of the FDA, ClinicalTrials.gov is the best search tool currently available as there is no database listing only the trials reviewed by the FDA. None of the reviews identified in the comments above have systematically summarized study phase, status, population, outcomes, etc., within or across indications (NIHL, DIHL, ARHL, etc.). A systematic search of ClinicalTrials.gov listings was therefore performed to obtain current and complete information about clinical trials evaluating investigational medicinal products for the inner ear.

Methods

Clinical trials evaluating NIHL otoprotection were identified using search terms including "noise-induced hearing loss", "NIHL," "permanent threshold shift," "noise induced auditory threshold shift," "temporary threshold shift," and "temporary auditory threshold shift." The search process was started December 29, 2020 with final terms searched on February 21, 2021. For each of the returned results within ClinicalTrials.gov, the study record was opened and reviewed to determine if it met the inclusion criteria (use of an investigational medicinal product for prevention of NIHL). Studies that did not include an investigational medicinal product and/or did not evaluate NIHL prevention were excluded from further review. For those studies that met the inclusion criteria, Study ID (the ClinicalTrials.gov record number), study phase (as listed in the study record) and study status (as listed in the study record) were entered into ►**Table 1**. Age, hearing, health-related inclusion criteria, information about sound exposure and information about the investigational medicinal product were extracted from the ClinicalTrials.gov records and entered into ►**Table 1**. Finally, primary, secondary, and other outcomes were entered. Within ClinicalTrials.gov, the study sponsor specifies the category for each outcome. Subsequent to the database search, the search results captured in ►**Table 1** were cross-checked against the lists of studies identified in previous reviews[18,32] to assure that no previously identified listings had been missed.

Clinical trials evaluating DIHL otoprotection were searched on February 16, 2021 using the search terms "ototoxicity," "ototoxic hearing loss," and "otoprotection," as well as the combination term "cancer and hearing loss." For each of the returned results within ClinicalTrials.gov, the

Table 1 Noise-induced hearing loss (NIHL) otoprotection

Study ID Study phase; study status	Inclusion criteria Sound exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[50] NCT00552786 2 Completed; has results	25–65 yo, male Worker in steel industry Daily workplace noise exposure	N-acetylcysteine (NAC, 600 mg, twice daily for two wks)	Average threshold shift at 3, 4, and 6 kHz immediately post-work shift on 14th day of dosing	Average DPOAE threshold change at 3, 4, and 6 kHz immediately post-work shift on 14th day of dosing	N/A
[51] NCT00808470 2 Completed; has results	18–31 yo Type A tympanogram ≤25 dB HL, 0.25–8 kHz Air-bone gaps ≤10 dB Asymmetry ≤ 15 dB 4hr pre-recorded music delivered by insert earphones	Vitamin C (500 mg), magnesium (315 mg), vitamin E (267 mg), β carotene (18 mg); 6 chewable tablets once daily for 4 days	Average threshold shift at 4 kHz in both ears 15 min post music	1. Threshold shift at individual frequencies from 0.25 to 8 kHz 15 min post music 2. Tinnitus Presence (Yes/No)	1. DPOAE amplitude change 15 min post music and at later times 2. Threshold shift at individual frequencies from 0.25 to 8 kHz 1 hr 15 min post music and at later times
[52] NCT01444846 2 Completed, results submitted	18–31 yo Type A tympanogram ≤25 dB HL, 0.25–8 kHz Air-bone gaps ≤10 dB Asymmetry ≤ 15 dB Heart rate, blood pressure, respirations, temperature) within normal limits upon medical examination 4 hr pre-recorded music delivered by insert earphones	Ebselen (SPI-1005 capsule, 200, 400, or 600 mg, twice daily for 4 days)	Post-sound exposure pure tone audiometry compared with baseline testing to determine group mean level hearing threshold shift	N/A	N/A
[53] NCT02257983 2 Completed; no results posted	18–30 yo Healthy adults Normal audiology exam 4 hr sound exposure	Vincerinone™ (EPI-743, capsule, 400 mg orally t.i.d. for 9 days)	Pure tone audiometry	Time to recovery following acute noise exposure	N/A
[54] NCT02903355 3 Terminated; no results posted	21–45 yo Normal tympanometry PTA512 ≤40 dB HL Air-bone gaps ≤10 dB Drill Sergeant instructor trainees during and 22 days after their 11-day weapons training	D-methionine (oral liquid suspension, once daily for 18 days)	1. Change in pure-tone thresholds measured by absolute change and frequency of STS at day 15–16 2. Change in pure-tone thresholds measured by absolute change and frequency of STS at day 22	1. Change in tinnitus loudness/annoyance at day 15–16 2. Change in tinnitus loudness/annoyance at day 22 3. Tympanometric change	N/A
[55] NCT02779192 2 Not yet recruiting	18–50 yo existing NIHL history of occupational or recreational noise exposure exposure to calibrated sound challenge	Ebselen (SPI-1005 capsule, 200 or 400 mg, twice daily for 7 days)	Reduction in incidence of STS post-exposure	Improvement on post-exposure word recognition score, using Words in Noise (WIN) test	Adverse events due to study drug
[57] NCT02049073 1 Withdrawn	18–30 yo Good to excellent health Normal hearing 4 hr of pre-recorded music delivered by insert earphones	Zonisamide (pill, 100 or 200 mg either as single dose or once daily for 2 wks)	Pure tone hearing thresholds (particularly 2, 3, 4, and 6 kHz) 15-min post-exposure	1. DPOAE 2. Tinnitus (THI) 3. Pure tone hearing thresholds 75-, 135-, and 195-min post-exposure	Recovery of hearing one-wk post-exposure
[57] NCT02049073 2 Withdrawn	18–30 yo Good to excellent health Normal hearing 4 hr pre-recorded music delivered by insert earphones	Methylprednisolone (pill, 32 mg or 64 mg single dose)	Pure tone hearing thresholds (particularly 2, 3, 4, and 6 kHz) 15-min post-exposure	1. DPOAE 2. Tinnitus (THI) 3. Pure tone hearing thresholds 75-, 135-, and 195-min post-exposure	Recovery of hearing one-wk post-exposure

(*Continued*)

Table 1 (*Continued*)

Study ID Study phase; study status	Inclusion criteria Sound exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[56] NCT01727492 N/A Unknown	18–25 yo Temporary tinnitus after noise exposure Leisure noise above 100 dB for at least 30 min	600 mg N-acetylcysteine and 200 mg Magnesium (taken 1hr prior to leisure noise)	Protection against noise-induced tinnitus, defined as 50% reduction in loudness rating	Tinnitus duration	high frequency audiometry, speech-in-noise testing and otoacoustic emissions; other outcomes measured in limited subset of participants

Abbreviations: dB, decibel; dB HL, decibels hearing level; DPOAE, distortion product otoacoustic emission; hr, hour; kHz, kilohertz; mg, milligram; min, minutes; N/A, not available; NAC, N-acetylcysteine; PTA512; pure-tone threshold average at 0.5, 1, and 2 kHz; STS, Significant Threshold Shift; THI, Tinnitus Handicap Inventory; t.i.d., "ter in die," three times daily; WIN, Words-in-Noise; wk, week; yo, years old

study record was opened and reviewed to determine if it met the inclusion criteria (use of an investigational medicinal product for prevention of DIHL). Studies that did not include an investigational medicinal product and/or did not evaluate DIHL prevention were excluded from further review. For those studies that met the inclusion criteria, Study ID (the ClinicalTrials.gov record number), study phase (as listed in the study record) and study status (as listed in the study record) were entered into ►**Table 2**. Age, hearing, and health-related inclusion criteria and information about planned therapy with chemotherapeutics or aminoglycoside antibiotics were extracted from the ClinicalTrials.gov records and entered into ►**Table 2**. Information about the investigational medicinal product and primary, secondary, and other outcomes were entered into ►**Table 2**. Subsequent to the database search, the search results were cross-checked against the lists of studies identified in previous reviews[17,41] to assure that no previously identified listings had been missed.

Clinical trials evaluating drug benefits in patients with sensorineural hearing loss (SNHL) were searched on February 21, 2021 using the search terms "sensorineural hearing loss," "age-related hearing loss," "presbycusis," and "hearing in noise." While ARHL is of particular interest with respect to the large population that could benefit from potential prevention or treatment strategies, search terms were deliberately broad to capture not only ARHL but other SNHL studies that may share common otopathologies including sensory cell (OHC, IHC) loss, synaptic loss, and ANF degeneration. For each of the returned results within ClinicalTrials.gov, the study record was opened and reviewed to determine if it met the inclusion criteria (use of an investigational medicinal product for treatment or prevention of SNHL). Studies that did not include an investigational medicinal product and/or did not evaluate treatment or prevention of SNHL were excluded from further review. For those studies that met the inclusion criteria, Study ID (the ClinicalTrials.gov record number), study phase (as listed in the study record) and study status (as listed in the study record) were entered into either ►**Table 3** or ►**Table 4**. ►**Table 3** includes studies investigating treatment of patients with chronic (stable) SNHL whereas ►**Table 4** includes studies investigating treatment of acute (sudden) SNHL with the goal of reducing or preventing permanent SNHL. Age, hearing, and health-related inclusion criteria were extracted from the ClinicalTrials.gov records and entered into ►**Table 3** or **4** as appropriate for each record. Information about the investigational medicinal product and primary, secondary, and other outcomes were also entered. Because the original records were reported as posted, labels for sudden hearing loss, sudden sensorineural hearing loss (SSHL or SSNHL), and idiopathic sudden sensorineural hearing loss (ISSNHL) may appear to be used inconsistently in the data tables. Rather than revise study terminology for consistency within the data table, the study information has been reported as entered in ClinicalTrials.gov.

Taken together, the information that was extracted from all clinical trial records identified through the above search

Table 2 Drug-induced hearing loss (DIHL) otoprotection

Study ID; Study phase; study Status	Inclusion criteria Ototoxic drug exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[63] NCT00716976 3 Completed, has results	1–18 yo Newly diagnosed with germ cell tumor, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy Planning to receive chemotherapy including cumulative cisplatin dose $\geq$ 200 mg/m^2 with individual cisplatin doses to be infused over $\leq$ 6 hr	Sodium thiosulfate (16 g/m^2 or 533 mg/kg for patients administered cisplatin on a per kg basis due to young age or small body; administered over 15 min beginning 6 hr after completion of each cisplatin infusion	Rate of ASHA SOC	1. Change in hearing at 0.5, 1, 2, 4, and 8 kHz 4 wks post cisplatin 2. Event free survival 4 yrs post enrollment 3. Overall survival 4 yrs post enrollment 4. Hearing loss 4 wks post cisplatin in genetic mutation subgroups	N/A
[61] NCT00477607 2 Completed; has results	$\geq$18 yo Diagnosis of cancer Able to provide reliable behavioral threshold Treatment with cisplatin	Alpha-lipoic acid (1200 mg once/daily)	Rate of ASHA SOC	1. Maximum malondialdehyde (MDA) level increase 2. Maximum cumulative dose of cisplatin	N/A
[66] NCT01848457 2 Completed, has results	$\leq$ 30 yo Histological diagnosis of high-grade osteosarcoma Extremity or central axis primary tumor; localized or metastatic Hearing level threshold $\leq$25 dB at all frequencies in both ears Cisplatin and high-dose methotrexate	Pantoprazole (0.3 mg/kg i.v. as a loading dose followed by 1.3 mg/kg i.v. concurrent with cisplatin)	Change in urinary biomarkers of acute kidney injury	1. Change in tumor volume 2. Validating urinary biomarkers 3. Tissue microarray 4. Bone specific alkaline phosphatase 5. Nutritional status 6. Patient reported outcome survey 7. Average hearing level over the range of 4 to 8 kHz	N/A
[65] NCT01372904 2 Completed, has results	$\geq$18 yo Neoplastic disease Treatment protocol includes cumulative cisplatin dose of at least 300 mg	Dexamethasone Phosphate (0.7 ml of 10 mg/ml solution delivered into middle ear via trans-tympanic injected)	Pure tone, speech, and impedance audiometry, and DPOAE testing	N/A	N/A
[62] NCT00652132 3 Completed, no results posted	1 mo - 18 yo Histologically confirmed newly diagnosed hepatoblastoma Patients receive cisplatin i.v. over 6 hr on day 1 then every 2 wks for 4 courses	Sodium thiosulfate (administered i.v. over 15 min beginning 6 hr after completion of each cisplatin infusion)	Hearing loss rated using Brock grading scale (end of trial treatment or 3.5 yrs, whichever is later)	1. Response to preoperative chemotherapy 2. Complete resection 3. Complete remission 4. Event-free survival 5. Overall survival 6. Adverse drug reactions graded using CTCAE v 3.0 7. Long-term renal clearance 8. Feasibility of central audiology review (end of trial treatment or 3.5 yrs, whichever is later)	N/A
[69] NCT01271088 2/3 Completed, no results posted	18–65 yo End-stage renal disease Continuous ambulatory peritoneal dialysis Treatment with vancomycin and/or amikacin for peritonitis	NAC (600 mg, twice daily)	Rate of ASHA SOC	N/A	N/A
[64] NCT01139281 2 Completed, no results posted	$\geq$18 yo Beginning treatment with cisplatin	Ginkgo Biloba Extract (GBE761, 120 mg twice daily)	DPOAE mean amplitude and SNR values at frequencies from 1 to 8 kHz	N/A	N/A

(*Continued*)

Table 2 (*Continued*)

Study ID; Study phase; study Status	Inclusion criteria Ototoxic drug exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[60] NCT00003269 2 Completed; no results posted	19–80 yo Confirmed diagnosis of advanced head and neck cancer or advanced lung cancer Undergoing treatment with cisplatin, cyclophosphamide, and etoposide	Amifostine, i.v.	Duration of neutropenia	1. Incidence of nephrotoxicity 2. Incidence of ototoxicity	N/A
[68] NCT01131468 2 Completed, no results posted	18–70 yo End-stage renal disease Continuous ambulatory peritoneal dialysis Treatment with vancomycin and/or amikacin for peritonitis	NAC (600 mg, twice daily)	Purpose of study is to measure prevention of hearing loss; primary outcome not specified	N/A	N/A
[67] NCT03400709 N/A Completed, no results posted	≥18 yo Diagnosed with head and neck squamous cell carcinoma Chemoradiotherapy including Cisplatin	NAC (oral, before, during, and after cisplatin)	1. HFPTA (6–16 kHz) at baseline 2. HFPTA up to 4th wk of chemo-radiotherapy 3. HFPTA at study completion	N/A	N/A
[74] NCT04226456 4 Recruiting	≥18 yo Patients with a neoplastic disease to be treated with cisplatin, 70 to 100 mg/m^2 i.v. for 3 to 7 cycles, with or without radiotherapy	NAC (injection of 10% solution via trans-tympanic injection in both ears)	Ototoxicity 6 mo after last injection, as defined by CTCAE 5.0	1. Ototoxicity 6 mo after last injection, as defined by Tune grading scale 2. Hearing quality of life 3. Tinnitus Handicap Index (THI)	
[73] NCT04541355 2 Recruiting	≥18 yo Histologically or cytologically confirmed locoregionally advanced squamous cell carcinomas of mucosal surfaces of head and neck Concurrent chemoradiation with cisplatin	Sodium thiosulfate (i.v. delivered over 1–2 hr 4–5 hrs post cisplatin)	Number of patients who successfully complete planned treatment	1. Frequency of treatment related adverse events 2. Incidence of high-grade ototoxicity (change ≥2 grades on CTCAE v 5.0)	N/A
[75] NCT00075387 2 Recruiting	18–75 yo Histologically confirmed high-grade glioma Patients receive cyclophosphamide, etoposide phosphate and carboplatin intra-arterially over 10 minute; treatment repeats every 4 wks for up to 12 courses	Sodium thiosulfate (i.v. over 15 min at 4 and 8 hr after carboplatin)	Rate of platelet toxicities	1. Number of dose reductions and transfusions 2. Tumor response 3. Time to response 4. Time to disease progression 5. Granulocyte count 6. Erythrocyte counts 7. Change in hearing at 4 and 8 kHz, and from 9 to 16 kHz, including time to ASHA SOC 8. Quality of life	N/A
[72] NCT04291209 1/2 Recruiting	≥18 yo Advanced stage head and neck cancer High dose systemic cisplatin (100mg/m^2) with concurrent radiation therapy as part of their curative intent treatment	NAC (intra-tympanic)	1. Determination of safe and tolerable dose range for intra-tympanic NAC 2. Rate of hearing loss, defined as 10 dB shift at 3-contiguous frequencies	Hearing discrimination, subjective tinnitus, otoacoustic emission, speech spatial and quality of hearing	N/A
[76] NCT00983398 1/2 Recruiting	18–45 yo Histologically confirmed CNS embryonal tumor or germ cell tumor Regimen including mannitol IA over 30 sec, melphalan IA over 10 min, carboplatin IA	Sodium thiosulfate i.v. over 15 min at 4 and 8 hr after carboplatin	1. Maximum tolerated dose 2. Response rate	1. Progression free survival 2. Overall survival rate 3. Change in neurocognitive assessment score 4. Ototoxicity up to 30 days post	N/A

Table 2 (*Continued*)

Study ID; Study phase; study Status	Inclusion criteria Ototoxic drug exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
	over 10 min; repeated every 4–6 wks up to 12 cycles			treatment graded using CTCAE 4.0	
[71] NCT04262336 1 Recruiting	≥18 yo Ability to communicate Treatment for cancer with i.v. cisplatin once every 21 or 28 days Plan to receive a minimum cumulative dose of cisplatin of ≥ 280 mg/m^2 over at least three cycles	Sodium thiosulfate (DB-020, 12% or 25%, delivered via intra-tympanic injection)	Number of patients with treatment-emergent adverse events and/or abnormal changes from baseline in clinical laboratory abnormalities and/or vital signs and/or ECG assessments	1. Incidence of ASHA SOC 28 days after last dose 2. Change in threshold at frequencies from 0.25 to 16 kHz 3. Change in Tinnitus Functional Index (TFI) 4. Change in DPOAE amplitude from 1–4 kHz 5. Change on Words-in-Noise (WIN) test score 6. Change in Hearing Handicap Inventory for Adults (HHIA) 7. Plasma concentration of DB-020 prior to cisplatin 8. Maximum observed cisplatin plasma concentration (Cmax) 9. Area under the cisplatin plasma concentration-time curve (AUC 0-inf) 10. Time to reach maximum observed cisplatin plasma concentration (tmax) 11. Half-life (t1/2) of cisplatin plasma concentrations	N/A
[70] NCT02094625 1 Recruiting	1–21 yo New diagnosis of a localized malignancy Planned treatment course to include at least two cycles of cisplatin Total cumulative dose of planned cisplatin must be >200 mg/m^2 (or 6.67 mg/kg equivalent for infants requiring weight-based dosing)	NAC (225, 300, or 450 mg/kg i.v., administered over ∼60 min starting 4 hr after completion of cisplatin chemotherapy)	NAC target serum level immediately after first NAC dose	1. Adverse events during NAC infusion 2. NAC serum level pre-cisplatin, post-cisplatin, and 4 hr post NAC 3. Hearing assessment up to 40 wks from start of cisplatin 4. Renal toxicity 5. Response of tumor to treatment 6. Effect of genotype on hearing loss and otoprotection (glutathione polymorphisms) 7. Glutathione serum levels pre-cisplatin, post-cisplatin, immed post NAC, and 4 hr post NAC	N/A
[77] NCT02819856 2 Enrolling by invitation	≥18 yo Ability to perform behavioral tests Cystic fibrosis patients about to receive IV tobramycin for acute pulmonary exacerbation	Ebselen (SPI-1005 capsule, 200, 400, or 600 mg, twice daily for 21 days)	1. Number of participants with sensorineural hearing loss 2. DPOAE threshold shift in extended high frequency range 3. Change in WIN score 4. Changes in TFI 5. Vertigo symptom scale 6. Lung function	1. Pharmacogenomics (gene expression for Nrf2, glutathione peroxidase-1, hemeoxygenase-1, and thioredoxin class of redox proteins) 2. Pharmacodynamics (level of glutathione, cysteine, and cystine)	N/A

(*Continued*)

Table 2 (*Continued*)

Study ID; Study phase; study Status	Inclusion criteria Ototoxic drug exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
			7. Plasma ebselen and major metabolites, trough levels		
[81] NCT02997189 2 Terminated (based on efficacy results from another study)	6 mo – 21 yo Diagnosed with neuroblastoma, hepatoblastoma, osteosarcoma or extracranial germ cell tumors and has not been previously treated with cisplatin or carboplatin $\leq$ 20 dB HL from 2–8 kHz in both ears Scheduled to receive a chemotherapy regimen that includes a cumulative cisplatin dose of $\geq$ 200 mg/m^2.	Dexamethasone (OTO-104, 12 mg dexamethasone delivered via intratympanic injection)	Feasibility assessed via questionnaire	1. SIOP-Boston Ototoxicity Scale 2. Safety assessed by adverse events 3. Local tolerability assessed by otoscopic examination	N/A
[79] NCT01369641 N/A Terminated, poor accrual	$\geq$18 yo Cisplatin in the dose range of 80–120mg/m^2	Sodium thiosulfate eardrops administered through the tympanic membrane via pressure equalization tubes	Degree or incidence of hearing loss using pure tone and speech audiometry, and DPOAE at 3, 6, and 12 wks, and every 6 mo thereafter for up to one yr	N/A	N/A
[80] NCT02281006 2 Terminated, poor accrual	$\geq$18 yo Newly-diagnosed locally-advanced (stage III or IV) squamous cell carcinoma of the mouth, oropharynx, hypopharynx, or larynx Scheduled to be treated with cisplatin 100 mg/m^2 3 times	Sodium thiosulfate gel (0.1 ml of Seacalphyx + Healon gel placed on round window via trans-tympanic injection)	Permanent threshold shift at 9, 10, 12.5 and 14 kHz, one mo post-cisplatin	1. DPOAE recordings 2. Permanent threshold shift at 9, 10, 12.5 and 14 kHz, one mo and one yr post-cisplatin 3. Adverse effects of trans-tympanic injection	N/A
[78] NCT00074165 2 Terminated, lack of accrual; results posted	18 mo - 75 yo Histologically or cytologically confirmed primary CNS lymphoma Receive rituximab i.v. on day 1; on days 2 and 3: carboplatin intra-arterially over 10 min, cyclophosphamide i.v. over 10 min, and etoposide or etoposide phosphate i.v. over 10 min in conjunction with blood-brain barrier disruption	High-dose sodium thiosulfate i.v. over 15 min administered 4 and 8 hr after carboplatin on days 2 and 3	Complete response to chemotherapy regimen at 2 yrs	1. Overall survival at 5 yrs 2. Progression-free survival at 5 yrs 3. Quality of life before treatment and every 3 mo 4. Ototoxicity assessed monthly during treatment 5. Complete blood count weekly during treatment	N/A
[84] NCT02382068 NA Withdrawn	$\geq$18 yo Planned cisplatin treatment >50 mg/m^2 every 3–4 wks up to 7 cycles maximum	Dexamethosone (intra-tympanic injection)	Pure tone audiometry in conventional and high frequency ranges up to 3 mo post cisplatin	1. DPOAE amplitude in conventional and high frequency ranges up to 3 mo post cisplatin 2. ASHA SOC up to 3 mo post cisplatin	N/A
[82] NCT01138137 1 Withdrawn	18–75 yo Histologically confirmed diagnosis of stage 3 or 4 epithelial ovarian or primary peritoneal carcinoma Paclitaxel IV, 135 mg/m^2 (day 1) and IP cisplatin 100 mg/m^2 (day 2), followed by	IV NAC (i.v., starting at 150 mg/kg) infused over 30 min, starting 60 min prior to each course of IP cisplatin with planned dose escalation for NAC	Determine the maximum tolerated dose and assess toxicity of NAC	1. Tumor response 2. Incidence and severity of nephrotoxicity 3. Incidence and severity of hearing loss 4. Incidence and severity of	NA

Table 2 (*Continued*)

Study ID; Study phase; study Status	Inclusion criteria Ototoxic drug exposure	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
	Taxol IP, 60 mg/m^2 (day 8) every 3 wks for 6 courses			peripheral and autonomic neuropathy	
[83] NCT00584155 1 Withdrawn	≥18 yo Patients with cancer to be treated with cisplatin Must be expected to receive a minimum of 3 rounds of chemotherapy with a minimum cisplatin dose of 70 mg/m^2	Lactated Ringer's Solution with 0.03% ofloxacin (one dropper full delivered in ear canal, at start of chemotherapy, 30 min post chemotherapy, and hourly for 4 hr after chemotherapy	Pre-treatment audiogram will be compared with the post treatment audiogram.	N/A	N/A
[85] NCT01451853 2 Unknown	18–70 yo Histologically confirmed hematologic malignancies and adult solid tumors Undergoing treatment with platinum chemotherapy (cisplatin, carboplatin)	Ebselen (SPI-1005 capsule, 200, 400, or 600 mg, twice daily for 3 days for each cycle of chemotherapy)	Number of participants with adverse events	1. Incidence and severity of hearing loss 2. Incidence and severity of tinnitus	N/A
[86] NCT02241876 4 Unknown	18–80 yo Head and neck cancer Undergoing anticancer treatment including three cycles of cisplatin (80 to 100 mg/m^2) plus radiotherapy	NAC [600 mg in 15 ml, administered once a day, during 7 days in each cycle (2 days before chemotherapy, on the day of chemotherapy, and 4 days after chemotherapy)]	1. Hematologic, nephro, and hepatotoxicity: 120 hr post-dose and 20 days post-dose 2. Gastrointestinal toxicity: 1 day and 120 hr post-dose 3. Ototoxic hearing loss: 1 day and 30 days post treatment 4. Nephrotoxicity: 1 day and 30 days post treatment	1. Quality of life: 1, 22, and 43 days post treatment 2. Cellular and plasma oxidative stress biomarkers: 120 hr and 20 days post-dose 3. Effectiveness of anticancer therapy: 1 and 30 days post-treatment	N/A
[88] NCT01108601 1/2 Unknown	≥15 yo Patients undergoing platinum-based chemotherapy	Lactated Ringer's Solution with 0.03% ciprofloxacin (four drops delivered into ear canal twice a day during chemotherapy	Pre-treatment audiogram will be compared with post- chemotherapy treatment audiogram for up to four yrs	DPOAEs	N/A
[89] NCT01285674 N/A Unknown	18–90 yo Patients who are candidates for cisplatin treatment	Methylprednisol (intra-tympanic injection of 0.5cc of 62.5mg/cc; one injection per ear before each of 3 cisplatin treatments)	Change in hearing assessed by behavioral hearing test and otoacoustic emissions, ~1 mo after first treatment	Appearance or worsening of tinnitus 1 mo post treatment	N/A
[87] NCT00578760 N/A Unknown	≥18 yo Normal otoscopic examination Undergoing cisplatin treatment for germ-cell, bladder, or head and neck malignancy	Aspirin (325 mg daily orally during course of chemotherapy)	Hearing loss after chemotherapy	Hearing loss and tinnitus questionnaires after cisplatin treatment	N/A
[90] NCT04132882 Compassion-ate Use Program Available	1 mo – 18 yo Standard-risk hepatoblastoma Receiving cisplatin	Sodium thiosulfate (i.v. 80 mg/ml)	Any clinical assessments, physical examinations, and dosage changes will be determined by the treating physician as per local standard medical practice; all serious adverse events and related non-serious adverse events will be reported	N/A	N/A

Abbreviations: ASHA SOC, Significant Ototoxic Change as defined by the American Speech-Language Hearing Association; AUC, area under the curve; Cmax, maximum observed plasma concentration; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; dB, decibel; dB HL, decibels hearing level; DPOAE, distortion product otoacoustic emission; ECG, electrocardiogram; g, gram; HFPTA; high-frequency pure-tone threshold average; hr, hour; i.v., intra-venous; kg, kilogram; kHz, kilohertz; month, mo; m^2, meter squared; MDA, malondialdehyde; mg, milligram; min, minutes; ml, milliliter; N/A, not available; NAC, N-acetylcysteine; Nrf2, nuclear factor erythroid 2-related factor 2; sec, second; SIOP, International Society of Pediatric Oncology; SNR, signal to noise ratio; t1/2, half-life of plasma concentration; TFI, Tinnitus Functional Index; Tmax, time to reach maximum plasma concentration; WIN, Words-in-Noise; wk, week; yo, years old.

process was systematically entered into data tables for categories including prevention of NIHL (►**Table 1**), prevention of DIHL (►**Table 2**), reduction in stable SNHL (►**Table 3**), and treatment for acute SSNHL (►**Table 4**). Studies that did not meet the eligibility criteria for inclusion in any of the above categories were excluded and are not discussed further in this report.

There was no effort to determine if completed studies were published within the peer-reviewed literature; however, if the ClinicalTrials.gov record included results, this was recorded as part of the study status. While the focus of this review is not the specific agents under evaluation, the interventions and their timing were extracted and provided in the data tables to allow comparisons of investigational medicinal products for the inner ear across the included indications of interest. Within each Table, completed trials with results are listed first, followed by completed trials that have not posted results, and then studies that are currently recruiting participants, terminated studies, studies that are not yet recruiting, studies that have been withdrawn, and studies with unknown status.

Results

NIHL Otoprotection

Nine clinical trials evaluating NIHL otoprotection were identified (see ►**Table 1**). The studies summarized in ►**Table 1** include four completed clinical trials evaluating TTS otoprotection,[50–53] one terminated clinical trial evaluating PTS otoprotection,[54] one not yet recruiting clinical trial evaluating TTS otoprotection,[55] one study with unknown status evaluating TTS otoprotection,[56] and two withdrawn clinical trials (both listed under[57]). Two of the completed trials have posted results,[50,51] one submitted results which have not yet been posted,[52] and one has not submitted results.[53] While the listings included one phase 3 clinical trial,[54] the majority of the clinical trials were Phase 2. One trial was identified as Phase 1[57] and one trial was defined as "Phase Not Applicable"[56].

Across NIHL otoprotection clinical trials, the audiogram served as the primary outcome with six studies using reduction in average threshold shift as the primary outcome ([50–53], both studies listed under [57]). In addition, one study assessed both reduction in average threshold shift and reduction in Significant Threshold Shift (STS) rate,[54] and one study assessed STS reduction.[55] STS was not explicitly defined in the two studies listing STS as a primary or co-primary outcome.[54,55] Only one study included hearing measures under "Other Outcomes," with the primary and secondary outcomes for that study being tinnitus loudness and tinnitus duration[56]; other outcomes included high frequency audiometry, speech-in-noise testing, and otoacoustic emissions, but audiometric testing within the conventional frequency range was not included as an outcome for that one study. Distortion product otoacoustic emissions (DPOAEs) were included as a secondary outcome in three studies ([50], both studies listed under [57]), and as an "other" outcome measure for a subset of participants in two studies.[51,56] Tinnitus measures including the rate at which tinnitus was reported and the loudness and annoyance of tinnitus were also included as secondary outcome measures ([51,54], both studies listed under [57]). Hearing-in-noise will serve as a secondary outcome in the not yet recruiting clinical trial,[55] and is planned for a subset of participants in the study with unknown status.[56] Two additional clinical trials were added to ClinicalTrials.gov after the above review and analysis were completed and they are not captured within ►**Table 1** or the above summary.[58,59] Neither of these newly added clinical trials are recruiting yet; both will examine PTS prevention.

DIHL Otoprotection

Thirty clinical trials evaluating DIHL otoprotection and one compassionate use protocol were identified (see ►**Table 2**). The studies summarized in ►**Table 2** include 10 completed clinical trials evaluating either prevention of cisplatin-induced[60–67] or amikacin-induced[68,69] hearing loss. Currently, five studies are recruiting participants receiving cisplatin,[70–74] two studies are recruiting participants receiving carboplatin,[75,76] and one study is recruiting participants receiving tobramycin using invited enrollment.[77] Four clinical trials were terminated either as a consequence of poor accrual[78–80] or based on the results of related studies[81] and three studies were withdrawn for reasons including lack of funding,[82] departure of the principal investigator from the study site,[83] or with no reason provided.[84] Five studies had unknown status.[85–89] As noted above, one compassionate use protocol is also included in ►**Table 2**.[90] A compassionate use protocol allows a patient with a serious or life-threatening disease to gain access to an investigational drug outside of clinical trials when there is no treatment available, the patient has not benefitted from approved treatments, or the patient is not eligible for enrollment in clinical trials.

Four of the completed DIHL otoprotection trials have posted results,[61,63,65,66] and six have not submitted results.[60,62,64,67–69] While the listings included two phase 3 clinical trials,[62,63] the majority of the clinical trials were Phase 1,[70,71,82,83] Phase 1/2,[72,76,88] Phase 2,[60,61,64–66,68,73,75,77,78,80,81,85] or Phase 2/3.[69] Two clinical trials were identified as Phase 4[74,86] and five clinical trials were identified as "Phase Not Applicable".[67,79,84,87,89]

The DIHL studies included some trials in which audiometric changes served as the primary outcome and some trials in which the primary outcomes were related to cisplatin or aminoglycoside antibiotic therapeutic outcomes (event free survival, overall survival) and protection against audiometric change was a secondary outcome (see ►**Table 2**). Event free survival refers to the length of time post-treatment that the patient remains free of symptoms; in the context of the studies in ►**Table 2**, event-free survival would specifically refer to the length of time post-chemotherapy that the patient remains free of cancer symptoms. Overall survival refers to the length of time that the patient remains alive after the start of treatment. In studies in which investigational medicinal products for the inner ear are combined with chemotherapeutics, inclusion of event-free survival and overall survival are used to assure the investigational

Table 3 Treatment of stable sensorineural hearing loss (SNHL)

Study ID Study phase; study Status	Inclusion criteria	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[105] NCT02345031 2 Completed, has results	50–89 yo English speaking Difficulty hearing in noisy environment No recent middle ear disease Not a professional musician Not a current or recent user of hearing aids	AUT00063 (enhances activity at voltage-gated potassium channels; 600 mg, orally, once a day, for 4 wks)	QuickSin	1. Adaptive test of temporal resolution 2. Safety and Tolerability 3. Pharmacokinetics	N/A
[102] NCT01267994 1/2 Completed, has results	13–75 yo Bilateral sensorineural hearing loss with active decline in hearing in one ear No audiometric improvement with 28–30 days oral prednisone or other corticosteroid Enrollment within 14 days of completion of corticosteroid therapy	Anakinra (interleukin-1 receptor antagonist, 100 mg by s.c. injection for 84 consecutive days)	Improvement in hearing threshold and durability of improvement to 180 days	Number of serious adverse events	N/A
[100] NCT01518920 1 Completed, no results posted	50–75 yo Current diagnosis of age-related sensorineural hearing loss in the range of 30–60 dB, averaged over 2 and 4 kHz in at least one ear Symmetric hearing loss Can read, speak and comprehend English	PF-04958242, (0.27 or 0.35 mg oral solution, two single doses)	Change in the average threshold at 2 and 4 kHz at 1-hr post dose	1. Change in the average threshold at 2 and 4 kHz at 5 hr post dose 2. Change in Speech Discrimination Score at 1- and 5 hr post dose 3. Change in Speech in Noise Score at 1- and 5 hr post dose 4. Change in Tinnitus Severity Ranking Scale at 1- and 5 hr post dose 5. Plasma concentration at 45 minute post dose and following endpoint assessments at 1- and 5 hr post dose	N/A
[97] NCT03616223 1/2 Completed, no results posted	18–65 yo Stable sensorineural hearing loss (no changes >10 dB at any frequency for >6 mos) Medical history consistent with hearing loss being caused by noise exposure or sudden sensorineural hearing loss	FX-322 (single intra-tympanic hydrogel injection; low dose or high dose)	Number of participants with treatment related adverse events, to day 15	Time concentration of FX-322 in plasma within the first 24 hrs	N/A
[99] NCT02951715 N/A Completed, no results posted	20–80 yo Bilateral NIHL audiogram 4 kHz > 25 dB HL 10 dB notch at 4 or 6 kHz	Zinc gluconate (Zinga 78 mg, 10 mg elemental zinc), two tablets twice per day (40 mg elemental Zinc per day)	1. THI 2. Serum Zinc level	1. Pure tone audiometry 2. Speech discrimination 3. DPOAE SNR ≥6 dB 4. Tinnitus pitch match 5. Tinnitus loudness match 6. Tinnitus loudness relative to threshold (dB SL)	N/A
[101] NCT04601909 1 Active, not recruiting	66–85 yo Documented medical history consistent with age-related sensorineural hearing loss Pure tone average of 26–70 dB at 0.5, 1, 2, and 4 kHz Ability to communicate well with the investigator	FX-322 (intra-tympanic hydrogel, single injection)	1. Treatment related adverse events to 3 months 2. Safety – otoscopy to 3 months 3. Safety-tympanometry to 3 months 4. Columbia Suicide Severity Rating Scale to 3 months	1. Word recognition in quiet (CNC word lists) to 3 mo 2. WIN/CNC word lists-in-noise to 3 mo 3. EHF audiometry to 3 mo 4. Tinnitus assessment to 3 mo	N/A
[98] NCT04120116 2 Active, not recruiting	18–65 yo Stable sensorineural hearing loss (no changes >10 dB at any one frequency or >5 dB at any two contiguous frequencies from most recent audiogram to study screening) Medical history consistent with hearing loss being caused by noise exposure or sudden	FX-322 (intra-tympanic hydrogel; one, two, or four doses of active agent within 4 wkly doses)	1. Word recognition in quiet (CNC word lists), to day 210 2. WIN/CNC word lists-in-noise to day 210 3. Standard pure tone audiometry, to day 210 4. Systemic Safety, to day 210	1. EHF pure tone audiometry, to day 210 2. TFI, to day 210 3. Hearing Handicap Inventory, to day 210 4. Hearing Screening Inventory, to day 210	N/A

(*Continued*)

Table 3 (*Continued*)

Study ID Study phase; study Status	Inclusion criteria	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
	sensorineural hearing loss Pure tone audiometry within 26–70 dB in the ear to be injected		5. Abnormalities during otoscopy, to day 210 6. Abnormal changes in tympanometry, to day 210		
[106] NCT04129775 1/2 Active, not recruiting	21–64 yo Audiometrically defined normal hearing or mild hearing loss Self-reported difficulty hearing in noise for at least 6 months Speech-in-noise hearing deficit in at least one ear	OTO-413 (single intratympanic injection of brain-derived neurotrophic factor)	1. Treatment-emergent adverse events from dosing through 12 wk post-dosing 2. Otoscopy, change from baseline through 12 wk post-dosing 3. Audiometry, clinically significant change from baseline through 12 wk post-dosing	N/A	1. Speech-in-noise at 2, 4, 8 and 12 wks post drug 2. Auditory brainstem response at 2, 4, 8 and 12 wks post drug 3. Patient global impression of change (change in overall hearing status from -3/very much worse to +3/very much improved)
[94] NCT04629664 1 Recruiting	18–65 yo Severe sensorineural hearing loss Pure tone threshold average of 71–90 dB HL at 0.5, 1, 2, and 4 kHz in the ear to be injected Ability to communicate well with the investigator	FX-322 (intra-tympanic hydrogel, single injection)	1. Systemic Safety 2. Safety – otoscopy to 3 mo 3. Safety-tympanometry to 3 mo 4. Columbia Suicide Severity Rating Scale	1. Word recognition in quiet to 3 mos 2. BKB-SIN to 3 mo 3. Standard pure tone audiometry to 3 mos 4. EHF pure tone audiometry to 3 mos 5. Tinnitus Functional Index (TFI) to 2 mos	N/A
[95] NCT04462198 1/2 Recruiting	18–75 yo Bilateral sensorineural hearing loss Normal tympanogram in the ear to be injected	PIPE-505 (single intra-tympanic injection)	Treatment-emergent adverse events from baseline to 3 mo follow-up	1. Pharmacokinetics – area under the curve 2. Pharmacokinetics – half life	1. Speech-in-noise at 1, 2, and 3 mo post drug 2. Audiogram at 1, 2, and 3 mo post drug 3. Auditory brainstem response at 1, 2, and 3 mo post drug
[96] NCT03101722 NA Enrolling by invitation	≥60 yo Mild-to-moderate sensorineural hearing loss (0.25 to 4 kHz pure tone average 26–70 dB HL), with subjective tinnitus, cognitive decline, or mild cognitive impairment Constant tinnitus >3 months THI score >10 Able to accomplish relevant tests	huperzine A (acetylcholinesterase inhibitor, dose of 0.1–0.2 mg/time, 2 times/day)	Change in threshold at 3, 6, and 12 mo	1. Global cognitive protection 2. Special cognitive domains (orientation to time, orientation to place, registration, attention and calculations, recall, language, repetition and complex commands) 3. Tinnitus suppression	Adverse events
[103] NCT01186185 1 Terminated (PI moved to another institution)	18–89 yo Idiopathic sudden sensorineural hearing loss within past 3 mo Failure to recover hearing with glucocorticoid treatment or inability to tolerate glucocorticoid	Fludrocortisone (mineralocorticoid, 0.2 mg by mouth daily for 30 days)	Pure-tone and speech audiometry measured at completion of treatment	N/A	N/A
[104] NCT02414152 1/2 Terminated (inability to secure funding)	18–75 yo Unilateral sudden sensorineural hearing loss; ≥30 dB at 3 contiguous frequencies evolving in ≤3 days, with PTA ≤25 dB in contralateral ear; Previous high-dose corticosteroid therapy for ≥7 days plus ≥7 day taper with <5 dB improvement; ≤30 days from discontinuation of steroid treatment	Anakinra (also known as Kineret, interleukin-1 receptor antagonist, 100 mg by s.c. injection for 28 consecutive days, with additional 28 day cycle possible based on clinical response)	Improvement in hearing threshold and durability of improvement to 120 days	N/A	N/A

Abbreviations: BKB-SIN, Bamford-Kowal-Bench Speech-in-Noise test; CNC, consonant-nucleus-consonant; dB, decibel; dB HL, decibels hearing level; dB SL, dB sensation level; DPOAE, distortion product otoacoustic emission; EHF, extended high frequency; hr, hour; i.v., intra-venous; kg, kilogram; kHz, kilohertz; mg, milligram; min, minutes; mo, month; N/A, not available; NIHL, noise-induced hearing loss; QuickSin, Quick Speech in Noise test; s.c., subcutaneous; SNR, signal to noise ratio; TFI, Tinnitus Functional Index; THI, Tinnitus Handicap Inventory; wk, week; yo, years old.

Table 4 Treatment of acute sudden sensorineural hearing loss (SSNHL)

Study ID Study phase; study Status	Inclusion criteria	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[120] NCT00097448 3 Completed, has results	≥18 yo Unilateral idiopathic sensorineural hearing loss developing within 72 hour and occurring within past 14 days Pure tone average at 0.5, 1, 2, and 4 kHz ≥ 50 dB HL in affected ear Affected ear ≥ 30 dB worse than contralateral ear in at least one of the four frequencies	Methylprednisolone (four intratympanic injections over 2 wks; control condition is 19 days oral prednisolone)	Change in pure tone average at 0.5, 1, 2, and 4 kHz	N/A	N/A
[117] NCT03331627 3 Completed, no results posted	≥18 yo Unilateral idiopathic sensorineural hearing loss or acute acoustic trauma in one or both ears within past 96 hour	STR001-IT intratympanic gel injection with or without additional 12 wks treatment via STR001-ER oral tablets	Absolute hearing improvement after 12 wks	Percent of patients with complete hearing recovery after 12 wks	N/A
[121] NCT00335920 3 Completed, no results posted	18–75 yo Unilateral idiopathic sudden sensorineural hearing loss developing within 72 hour at least 12 days ago but no more than 21 days ago; Thresholds at 0.5, 1, 2, 3, and 4 kHz must be ≥ 50 dB HL for three frequencies, ≥ 60 dB HL for two frequencies, or ≥ 70 dB HL for one frequency within this range, or SRT ≥70 dB, or speech discrimination score ≤ 30%	Dexamethasone (continuous two-week intratympanic application, delivered to round window niche)	Pure tone audiometric threshold	1. Word recognition 2. Tinnitus improvement 3. Adverse events	N/A
[115] NCT02561091 3 Completed, no results posted	18–65 yo Unilateral idiopathic sensorineural hearing loss developing within 72 hour prior to treatment Mean hearing threshold ≥60 dB HL at 3 contiguous frequencies with largest hearing loss (“PTA frequencies”) Mean hearing loss ≥ 40 dB averaged across the PTA frequencies compared with contralateral ear, previous audiogram, or ISO 7029;2000 norms	AM-111 (0.4 mg/ml or 0.8 mg/ml given as single intra-tympanic injection)	Change in pure-tone-average threshold at 3 most affected frequencies at day 28	N/A	N/A
[114] NCT00802425 2 Completed, no results posted	18–60 yo Unilateral acute sensorineural hearing loss within past 48 hour Mean hearing loss ≥30 dB at 3 contiguous frequencies compared with contralateral ear	AM-111 (low dose or high dose as single intra-tympanic injection)	Change in pure-tone-average threshold at 3 most affected frequencies between day 0 and day 7	Change in pure-tone-average threshold at 3 most affected frequencies between day 0 and days 3, 30, and 90	N/A
[119] NCT01621256 1/2 Completed, no results posted	18–70 yo Unilateral idiopathic sudden sensorineural hearing loss ≥30 dB Enrollment within 7 days after SSHL onset	Ancrod (also known as Viprinex; i.v. infusion on days 2, 4, 6)	Change in pure tone audiogram in the affected ear, at day 8	Change in speech recognition in the affected ear, at day 8	1. Patient assessment of change in hearing on days 8, 30, and 90 2. Change in fibrinogen concentration 3. Change in biomarkers

(*Continued*)

Table 4 (*Continued*)

Study ID Study phase; study Status	Inclusion criteria	Intervention	Primary outcomes	Secondary outcomes	Other outcomes
[118] NCT03603314 2/3 Recruiting	≥18 yo Sudden hearing loss onset within 96 hours of first study drug intake Unilateral idiopathic SSHL or unilateral/bilateral acute acoustic trauma leading to SSHL	SENS-401 (5 HT3 antagonist, 29 or 43.5 mg dose, oral tablets, twice daily, for 4 wks)	Change in pure tone audiometry PTA in affected ear from baseline to the end of treatment visit	N/A	N/A
[122] NCT03255473 2 Recruiting	18–80 yo Unilateral sudden sensorineural hearing loss (SSNHL) of 30 dB HL or greater over 3 continuous frequencies Participants report hearing loss occurred within 3 days Seen within six weeks of initial hearing loss Normal tympanometry	High-dose oral dexamethasone (control condition is standard of care, lower dose prednisolone)	Change in pure tone threshold at 1 wk, 1 month, and 3 months	1. Change in word recognition 2. Change in pure tone average threshold 3. Frequency analysis for categories of hearing improvement 4. Percent analysis for categories of hearing improvement	N/A
[116] NCT02809118 3 Terminated (based on efficacy results from another study)	≥18 yo Unilateral idiopathic sudden sensorineural hearing loss (ISSNHL) onset within 72 hour of study treatment Mean hearing threshold ≥60 dB HL at 3 contiguous frequencies with largest hearing loss ("PTA frequencies") Mean hearing loss ≥ 40 dB averaged across the PTA frequencies when compared with contralateral ear or preexisting audiogram collected within 2 years of the ISSNHL incident	AM-111 (0.4 or 0.8 mg/ml gel administered as a single intra-tympanic injection after topical anesthesia)	Change in pure-tone-average threshold at 3 most affected frequencies between day 0 and day 91	Change in word recognition score between day 0 and day 91	N/A

Abbreviations: dB, decibel; dB HL, decibels hearing level; hr, hour; ISSNHL, idiopathic sudden sensorineural hearing loss; i.v., intra-venous; kHz, kilohertz; mg, milligram; min, minutes; ml, milliliter; mo, month; N/A, not available; SSHL, sudden sensorineural hearing loss; SSNHL, sudden sensorineural hearing loss; wk, week; yo, years old.

product does not compromise the efficacy of the chemotherapeutic (see for example [91]).

In the subset of DIHL studies in which audiogram-based measures served as secondary outcomes, the audiogram-based measures were nonetheless the primary strategy for evaluating otoprotection. The audiogram based measures serving as either primary or secondary outcomes in DIHL otoprotection trials included rate of ASHA-defined significant ototoxic change (i.e., ASHA SOC),[61,63,69,84] average threshold shift in the conventional frequency range,[66,83] and average threshold shift in the extended high frequency range.[67,80] Other audiogram based measures included deficits assessed using CTCAE ototoxicity grade,[73,74,76] Brocks grading categories,[62] and the SIOP-Boston ototoxicity scale.[81] One (terminated) study used DPOAE amplitude as the sole primary outcome measure,[79] and several studies included DPOAE amplitude shifts as a secondary outcome measure.[64,71,80,84] A few studies listed multiple audiometric measures as the primary outcome, such as pure tone and speech audiometry in combination with DPOAE testing,[65,79] or a combination of testing at conventional and extended high frequencies.[75,84] Other metrics including tinnitus, vertigo, words-in-noise, and/or the Hearing Handicap Inventory (first described by [92,93]) were also included as secondary outcomes in some studies.[71,77] One less common primary outcome was a 10 dB shift at 3 contiguous frequencies.[72] Interestingly, there were a number of study listings in which the criteria for ototoxic change were not clearly defined.[60,68,70,78,82,85,86]

Stable SNHL Treatment

Eleven clinical trials evaluating drug benefits in patients with stable SNHL were identified (see ►**Table 3**). These studies included populations diagnosed with stable SNHL,[94–96] stable SNHL consistent with NIHL or previous (unresolved) SSNHL,[97,98] stable NIHL,[99] stable ARHL,[100,101] or SSNHL previously treated with but not responsive to steroids.[102–104] In addition to the two studies investigating treatment for ARHL,[100,101] two additional studies listed in ►**Table 3** specifically cited treatment of ARHL or presbycusis in the study title or the inclusion criteria for types of stable SNHL.[96,105] Thus, a total of four of the 13 studies listed within ►**Table 3** specifically cited treatment of ARHL or presbycusis. Two additional studies listed in ►**Table 3** recruited participants with difficulty hearing in noise.[105,106] These studies are included in ►**Table 3** given that difficulty hearing in noise is widely hypothesized to be a consequence of damage to OHCs, IHCs, IHC/ANF synapses, ANFs, or a combination of these otopathologies.[8,107]

Two of the completed stable SNHL trials have posted results,[102,105] and three have not submitted results.[97,99,100] The clinical trials were predominantly Phase 1[94,100,101,103] or Phase 1/2,[95,97,102,104,106] with two Phase 2 clinical trials[98,105] and two trials identified as "Phase Not Applicable".[96,99]

The audiogram was the primary auditory outcome in the majority of studies listed in ►**Table 3**. The Quick Speech in Noise (QuickSin) test (described by [108]) and the Words-in-Noise (WIN) test (described by [109,110]) served as primary outcomes in one study each.[98,105] The Bench-Kowal-Bamford Speech in Noise Test (BKB-SIN) (described by [111,112]) and the WIN served as a secondary outcomes in one investigation each.[94,101] One study using speech-in-noise as a secondary outcome[100] and two studies using speech-in-noise as an "other" outcome[95,106] did not provide enough information to determine which speech-in-noise test was used. DPOAE testing was only included in one of these clinical trials[99] whereas tinnitus tests were included in six clinical trials.[94,96,98–101] Extended high frequency hearing was included in three clinical trials,[94,98,101] and auditory brainstem response was measured in two clinical trials.[95,106] Finally, patient reported assessment of hearing was included in two clinical trials,[98,106] using tools such as the Hearing Handicap Inventory for Adults (HHIA),[92,93] Hearing Screening Inventory (HSI) (described by [113]), or Patient Global Impression of Change (change in overall hearing status, ranging from very much worse (-3) to very much improved (+3)).

Acute SSNHL Treatment

Nine clinical trials evaluating therapeutics for acute SSNHL are included in ►**Table 4**. Unlike the populations with stable SNHL listed in ►**Table 3**, the participants in studies listed in ►**Table 4** were required to have developed their hearing loss over a short period of time. On the low end, they were required to present for SSNHL treatment from as short as 48,[114] 72,[115,116] or 96[117,118] hours after the hearing loss occurred. On the high end, they were required to present for treatment within 7 days,[119] 14 days,[120] 12-21 days,[121] or six weeks[122] after the hearing loss occurred.

One completed trial has posted results,[120] and five have not submitted results.[114,115,117,119,121] While the listings are largely Phase 3 clinical trials,[115–117,120,121] Phase 1/2,[119] Phase 2,[114,122] and Phase 2/3 trials[118] were also noted. None of the clinical trials were identified as "Phase Not Applicable."

In all identified acute SSNHL trials, the audiogram served as the primary outcome, with changes in pure tone thresholds being the primary outcome. Word recognition in quiet was included in four clinical trials[116,119,121,122] and tinnitus measurement was included in one clinical trial.[121] DPOAEs, hearing-in-noise, and extended high frequency thresholds were not included as outcomes in any of these trials.

Study Demographics

Interestingly, DIHL prevention research was more common than NIHL, stable SNHL, or SSNHL research with respect to completed research. The total number of DIHL otoprotection trials ($n = 30$) listed in ClinicalTrials.gov is roughly equivalent to the combined total for NIHL otoprotection trials ($n = 9$), stable SNHL ($n = 13$) treatment trials, and acute SSNHL ($n = 9$) treatment trials (see ►**Table 5**). Limiting the analysis to completed trials, more DIHL otoprotection trials ($n = 10$) listed in ClinicalTrials.gov have been completed than for NIHL otoprotection ($n = 4$), stable SNHL ($n = 5$) treatment, or acute SSNHL ($n = 6$) treatment; taken together, there are approximately twice as many DIHL trials completed relative to any other indication (see ►**Table 5**). While DIHL otoprotection

Table 5 Comparison of clinical trial design, completion, and results submission rates across NIHL, DIHL, stable SNHL, and acute SSNHL studies

		NIHL ($n = 9$)	DIHL ($n = 30$)	SNHL ($n = 13$)	SSNHL ($n = 9$)
Study Phase	1 (and ½)	1; 11%	7; 23%	9; 69%	1; 11%
	2 (and ⅔)	6; 67%	14; 47%	2; 15%	3; 33%
	3	1;11%	2; 7%	0	5; 56%
	4	0	2; 7%	0	0
	NA	1; 11%	5; 17%	2; 15%	0
Study Status	Completed, with results	2; 22%	4; 13%	2; 15%	1; 11%
	Completed, no results	2; 22%	6; 20%	3; 23%	5; 56%
	Percent of completed studies with results posted	2/4 = 50%	4/10 = 40%	2/5 = 40%	1/6 = 17%
	Recruiting	0	8; 27%	3; 23%	2; 22%
	Terminated	1; 11%	4; 13%	2; 15%	1; 11%
	Not Yet Recruiting	1; 11%	0	3; 23%	0
	Withdrawn	2; 22%	3;10%	0	0
	Unknown	1; 11%	5; 17%	0	0
Inclusion as Primary, Secondary, or Other Outcome	Average Shift	7; 78%	14; 47%	8; 62%	9; 100%
	ASHA SOC	0	6; 20%	0	0
	CTCAE	0	3; 10%	0	0
	Brock	0	1; 3%	0	0
	Boston SIOP	0	1; 3%	0	0
	Tune	0	1; 3%	0	0
	Other STS	1; 11%	8; 27%	1; 8%	0
	DPOAE	5;56%	10; 33%	1; 8%	0
	EHF	1; 11%	5; 17%	2; 15%	0
	Word Recognition	0	2; 7%	6; 46%	4; 44%
	Hearing in Noise	2; 22%	2; 7%	5; 38%	0
	Tinnitus	5; 56%	7; 23%	5; 38%	1;11%
	Survey	0	6; 20%	2; 15%	1; 11%
	ABR	0	0	2; 15%	0
	Vertigo	0	1; 3%	0	0
Method of Drug Delivery	Oral	9; 100%	9; 30%	5; 38%	2; 22%
	Intra-tympanic/eardrop	0	11; 37%	6; 46%	6; 67%
	Intra-venous	0	10; 33%	0	1; 11%
	Sub-cutaneous	0	0	2; 15%	0

Abbreviations: ABR, Auditory Brainstem Response; ASHA SOC, significant ototoxic change as defined by the American Speech-Language-Hearing Association; CTCAE, Common Terminology Criteria for Adverse Events as defined by the National Cancer Institute; DPOAE, Distortion Product Otoacoustic Emission; DIHL, drug-induced hearing loss; EHF, Extended High Frequency; NIHL, noise-induced hearing loss; SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss; SSNHL, sudden sensorineural hearing loss; STS, Significant Threshold Shift.

trials (total and completed) are more numerous, DIHL, NIHL, and stable SNHL clinical trials are predominantly in Phase 1 or Phase 2 with 0-11% of trials being Phase 3 studies, whereas more than 50% (5/9) of the acute SSNHL trials are Phase 3 clinical trials.

Although DIHL studies are greater in number, they do not have higher success rates with respect to study completion. When the percent of completed clinical trials is expressed as a percent of the total listed trials, the current completion rate is around 40% for NIHL, DIHL, and stable SNHL trials, whereas almost 70% of the acute SSNHL trials have been completed (see ►**Table 5**). Of the completed studies, results have been submitted for 40-50% of NIHL, DIHL, and stable SNHL trials, whereas less than 20% of the completed acute SSNHL trials have

results available. Taken together, it appears there are lower study completion rates for NIHL, DIHL, and stable SNHL than for acute SSNHL, but of the studies that are completed, results are somewhat more likely to be posted within ClinicalTrials.gov for NIHL, DIHL, and stable SNHL than for acute SSNHL studies.

Summary of Audiometric Outcomes

To facilitate comparisons across therapeutic targets (NIHL, DIHL, stable SNHL, acute SSNHL), summary data integrating information within the four clinical trial categories are provided in ►**Table 5**. With respect to clinical outcomes, there were notable differences across the different types of trials. For example, inclusion of average threshold shift as an outcome measure ranged from 47 to 100% across clinical trial categories. The use of this measure was lowest in the DIHL otoprotection category, at 47%, with 20% of trials monitoring the rate of ASHA SOC and 10% monitoring the rate of CTCAE adverse hearing events. None of the NIHL, stable SNHL, or acute SSNHL trials reported ASHA SOC, CTCAE adverse hearing events, or any of the other categorical ototoxicity monitoring scales as clinical trial outcomes. DPOAEs were monitored in about 33% of the DIHL and 56% of the NIHL trials, but they were largely absent from stable SNHL and acute SSNHL clinical trials. Conversely, word recognition in quiet was monitored in 44-46% of the stable SNHL and acute SSNHL clinical trials but none of the NIHL trials and only 7% of the DIHL trials. Interestingly, while DIHL is often accompanied by comorbidities including tinnitus and balance disorders,[123] only 23% of DIHL clinical trials included tinnitus metrics whereas 56% of the NIHL otoprotection studies included tinnitus metrics.

Drug Delivery Methods

Differences across the method of drug delivery were also observed across trial categories, with fairly low (22-38%) rates of oral drug use in DIHL, stable SNHL, and acute SSNHL trials, but 100% oral administration in studies on NIHL prevention (see ►**Table 5**). Between 37 and 67% of DIHL, stable SNHL, and acute SSNHL trials used transtympanic drug administration, with relatively greater use in stable SNHL (46%) and acute SSNHL (67%) than DIHL (37%) trials. About 33% of the DIHL otoprotection studies administered the otoprotective agents intra-venously, presumably using i.v. lines already set up for the cisplatin or carboplatin infusions. None of the NIHL or stable SNHL trials used i.v. administration, and only one acute SSNHL trial used i.v. administration of the therapeutic agent. It is reasonable to infer that many of the individuals at risk for NIHL, such as Service members,[37,124] employees working in loud industries,[40] musicians and other performing artists,[38] and others who are exposed to loud recreational sound[125,126] would find an oral therapeutic easier to administer on a regular basis given recurring sound exposure, which may explain the bias towards oral therapeutics in NIHL otoprotection clinical trials.

Investigational Medicinal Products

Summary data for mechanism of drug administration is provided in ►**Table 6**. Review of ►**Table 6** shows that some drugs have been tested using multiple methods of delivery. N-acetylcysteine (NAC), for example, has been delivered orally in six clinical trials (two NIHL, four DIHL), via intra-tympanic injection in two clinical trials (DIHL), and via intra-venous infusion in two clinical trials (DIHL). Similarly, methylprednisolone has been delivered orally in one clinical trial (NIHL) and via intra-tympanic injection in two clinical trials (one DIHL, one acute SSNHL). Finally, sodium thiosulfate has been delivered via intra-tympanic injection in two clinical trials (DIHL) and via intra-venous (i.v.) infusion in seven clinical trials (DIHL). Other drugs have shown less variation in their method of administration and their application for different targets within human clinical trials.

Discussion

The purpose of this review was to describe the state of the science regarding clinical testing of investigational medicinal products for the inner ear with respect to treatment or prevention of acquired hearing loss. Comprehensive search of clinical trials listed in the ClinicalTrials.gov database identified approximately 60 clinical trials assessing treatment or prevention of NIHL, DIHL, stable SNHL (including ARHL), or acute SSNHL. Clinical trials specifically targeting ARHL were a small subset, with only four clinical trials specifically identifying ARHL or presbycusis within the study title or the inclusion criteria. The study phase, status, intervention, and primary, secondary, and other outcomes were summarized for each study meeting inclusion criteria (►**Tables 1–4**) with summary data provided across therapeutic indications in ►**Tables 5** and **6**. This review of completed and active clinical trials, as well as not yet active and discontinued trials, provides important insight into the state of the science.

It is encouraging to see active efforts to evaluate investigational medicinal products for the inner ear. As of the time of this review, a total of 13 clinical trials were actively recruiting participants and 4 were active but not yet recruiting. The majority of the trials actively recruiting were DIHL otoprotection studies (8/13, 62%) whereas the majority of the not yet recruiting trials (3/4, 75%) were stable SNHL treatment trials (see ►**Table 5**). Taken together, the most active clinical trial program appears to be DIHL otoprotection both with respect to the number of completed studies and the number of current studies but stable SNHL treatment studies are quickly emerging. This observed result is intriguing as NIHL otoprotection might be considered a potentially "easier" target than DIHL otoprotection because one does not need to worry about drug interactions that might occur if an otoprotective agent is delivered in parallel with and interacts with a drug (i.e., a chemotherapeutic or aminoglycoside antibiotic) with life-saving therapeutic benefits. As noted above, the inclusion of event-free survival and overall survival as the primary outcome in many clinicals investigating DIHL otoprotection in humans are done specifically because of this concern. On the other hand, participants in DIHL studies cannot avoid exposure to the ototoxin whereas participants in NIHL trials are often required to wear hearing

Table 6 Comparison of route of administration and specific drugs investigated across NIHL, DIHL, stable SNHL, and acute SSNHL studies

		NIHL ($n = 9$)	DIHL ($n = 30$)	SNHL ($n = 13$)	SSNHL ($n = 9$)
Oral Drug Administration	Alpha-Lipoic Acid		1		
	Aspirin		1		
	AUT00063			1	
	Dexamethasone				1
	D-methionine	1			
	Dietary Nutrient (ACEMg)	1			
	Fludrocortisone			1	
	EPI-743/Vincerinone	1			
	Ginkgo Biloba		1		
	Huperzine A			1	
	Methylprednisolone	1			
	N-acetylcysteine	2	4		
	PF-04958242			1	
	SENS-401				1
	SPI-1005/Ebselen	2	2		
	Zinc gluconate			1	
	Zonisamide	1			
	Total	**9; 100%**	**9; 30%**	**5; 38%**	**2; 22%**
Intra-tympanic Drug Injection	AM-111				3
	Dexamethasone		3		1
	FX-322			4	
	Methylprednisolone		1		1
	N-acetylcysteine		2		
	OTO-413/BDNF			1	
	PIPE-505			1	
	Sodium Thiosulfate		2		
	STR001-IT				1
	Total	**0**	**8; 27%**	**6; 46%**	**6; 67%**
Eardrop Administration	Lactated Ringers		2		
	Sodium Thiosulfate		1		
	Total	**0**	**3; 10%**	**0**	**0**
Intra-venous Drug Infusion	Amifostine		1		
	Ancrod/Viprinex				1
	N-acetylcysteine		2		
	Pantaprazole		1		
	Sodium Thiosulfate		7		
	Total	**0**	**10; 33%**	**0**	**1; 11%**
Subcutaneous Drug Injection	Anakinra/Kineret			2	
	Total	**0**	**0**	**2; 15%**	**0**

Abbreviations: ACEMg, Combination of β-carotene, vitamins C and E, and magnesium; DIHL, drug-induced hearing loss; NIHL, noise-induced hearing loss; SNHL, sensorineural hearing loss; SSNHL, sudden sensorineural hearing loss.

protection devices (HPDs: earplugs, earmuffs) as part of hearing conservation programs and HPDs will prevent NIHL if they are consistently and correctly used by the participants. None of the studies listed in ►**Table 1** provided specific information regarding sound exposure levels or HPD use even though this is an important factor to consider.

Significant efforts were made within this review to describe the various audiometric outcomes used across clinical trials with different therapeutic targets (NIHL, DIHL, stable SNHL (including ARHL), acute SSNHL), with noted variability both within and across clinical trials. Use of average threshold shift as an outcome measure (primary, secondary, or other) ranged from 47 to 100% across clinical trial categories. The use of this measure was lowest in the DIHL otoprotection category, at 47%. Instead of average threshold shift, DIHL studies very commonly used the rate of STS as primary, secondary, or other outcomes; 66% of the DIHL studies used rate of STS, with 20% of trials monitoring the rate of ASHA SOC (6/30), 10% monitoring the rate of CTCAE adverse hearing events (3/30), and 3% of trials each choosing Brock, Boston-SIOP, or Tune ototoxicity criteria. Given that both ASHA and AAA have published ototoxicity monitoring guidance based on the rate of STS,[43,44] it is appropriate that rate of STS be considered the primary outcome in DIHL studies although comparisons across studies would be facilitated by use of the same STS criteria across investigations.

In contrast to DIHL study listings, none of the NIHL, stable SNHL, or acute SSNHL trials reported ASHA SOC, CTCAE adverse hearing events, or any of the other categorical ototoxicity monitoring scales as clinical trial outcomes. As discussed in Le Prell et al.[39] one could envision the rate of OSHA STS (an average threshold shift of 10 dB or greater at 2, 3 and 4 kHz)[127] being monitored in occupational NIHL prevention studies. However, as discussed in that report, using the median age-corrected NIHL data from ISO-1999 data,[128] the median worker with 90 dBA time-weighted-average (TWA) exposure (90 dBA for 8 hrs or other exposure accruing 100% dose) would be predicted to develop an OSHA STS at approximately 20 years of exposure. Little additional STS growth would be predicted for the median worker over the next 20 years of occupational exposure given that NIHL is decelerating (accrues more quickly in early years, more slowly in later years) whereas ARHL is accelerating (accrues slowly in early years, more quickly in later years). This has tremendous implications for NIHL prevention study feasibility as it suggests that workers would need to be enrolled early in their occupational career and followed for extended periods of time to adequately power a clinical trial assessing prevention of OSHA STS in workers who wear HPDs that effectively reduce their exposure to 100% of the permissible exposure limit (90 dBA TWA). However, best practice is to attenuate exposure to less than 85 dBA TWA.[129] If exposure is effectively attenuated to 85 dBA TWA across the working career, the ISO-1999 data suggest that the median worker would develop 5 dB noise-induced PTS averaged at 2, 3, and 4 kHz after 40 years of exposure.[39] Because workers do not routinely achieve the expected level of protection from HDPs, it is possible that hearing loss would accrue more quickly and to a greater degree if workers were followed over time as part of a clinical trial. However, it is also possible that HPD use might improve due to the workers attention to their hearing as part of enrollment in the clinical trial. It is difficult to provide guidance on PTS prevention study designs given the emphasis on TTS prevention within the existing study listings and limited rate of PTS in the single Phase 3 study listed. Additional detailed discussion of the state of the science for NIHL otoprotection research based on both the peer-reviewed literature and studies listed in ClinicalTrials.gov can be found in Le Prell.[130]

Looking beyond the audiogram, DPOAEs were monitored in about 33% of the DIHL and 56% of the NIHL trials, but they were largely absent from stable SNHL and acute SSNHL clinical trials. In participants entering a clinical trial with significant hearing loss, as in many of the stable SNHL and acute SSNHL trials in ►**Tables 3** and **4**, DPOAEs likely have limited utility as they are expected to be compromised at enrollment and thus it is not surprising they were not included in the study test battery. In NIHL and DIHL prevention studies, the participants are likely to have hearing that is within normal limits at the time of enrollment and thus changes in DPOAEs can be monitored for insights into OHC loss prior to the development of threshold shift.

Conversely, word recognition in quiet was monitored in 44-46% of the stable SNHL and acute SSNHL clinical trials but none of the NIHL trials and only 7% of the DIHL trials. Given that hearing-in noise is compromised the day after recreational noise exposure even in the absence of TTS[131] and there is significant evidence of hearing-in-noise difficulties in groups of participants with significant noise exposure compared to control groups with less sound exposure,[132] one might predict hearing-in-noise measures would be commonly included in NIHL otoprotection research. Despite documented noise-induced deficits, hearing in noise is not commonly used in clinical trials assessing NIHL prevention. Patient complaints regarding hearing-in-noise difficulties were a topic of discussion at the recent Hearing Loss Association of America (HLAA) meeting on investigational medicines for the inner ear, titled, "Externally-led patient-focused drug development (PFDD) meeting for people and families living with sensorineural hearing loss" (https://www.hearingloss.org/hlaa-pfdd/). PFDD meetings are FDA-led public meetings through which patients and their families provide input to the FDA regarding their most significant symptoms, impact of the condition on daily life, and current approaches to treatment. It is possible that these patient commentaries will prompt greater attention to hearing in noise measurements when evaluating drug benefits.

Finally, while DIHL is often accompanied by comorbidities including tinnitus and balance disorders,[123] only 23% of DIHL clinical trials included tinnitus metrics whereas 56% of the NIHL otoprotection studies included tinnitus metrics. Where validated surveys have been used, the THI and TFI have been the two most frequently used surveys; however, in many cases the ClinicalTrials.gov listing did not specify a formal tinnitus survey. This is a known shortcoming of the ClinicalTrial.gov database. The instructions suggest but do not

require a detailed protocol. Therefore, while the outcomes are listed, how those outcomes will be collected is not always clear, limiting the ability to replicate clinical trial design using only the ClinicalTrials.gov listing. To know what equipment was used, what transducers were used, who collected the data, what the presentation levels for the speech materials were, the order of test administration, etc., one would need to wait for information to (hopefully) be provided within the peer-reviewed literature or communicate with the study contact listed on ClinicalTrials.gov in hopes they will share more information. Abrams et al.[133] provide comprehensive discussion of these issues and recommendations for increased transparency including through the advance (pre-study) publication of protocols.

In closing, the information captured in this review highlights the tremendous progress that has been made, with work transitioning from animal models to clinical trials, and reviews the studies that are described within ClinicalTrials.gov for four specific inner ear indications: NIHL, DIHL, stable SNHL, and acute SSNHL. The results summarized in this report should be interpreted carefully given that data are limited to the ClinicalTrials.gov records and thus the results do not broadly reflect international activity but rather are primarily a reflection of US research. However, given that drugs being developed for possible future approval in the US are typically developed through the IND process, and regulatory statutes state that clinical trials reviewed through the IND process must be listed on ClinicalTrials.gov, it seems reasonable to conclude that without a healthy pipeline of clinical trial listings in the ClinicalTrials.gov database, there will not be a healthy pipeline of drugs progressing through the FDA review process for possible future human use preventing or treating human acquired hearing loss. The information provided in this report provides insights into the audiometric outcomes that have been selected in clinical trials and which can be considered for use by those who are planning new clinical trials evaluating investigational medicinal products for the inner ear.

Summary and Conclusion

42 CFR Part 11 requires clinical trials initiated after September 27, 2007 to be listed in the ClinicalTrials.gov database if they meet certain criteria regarding collection of data at U.S. study sites or if the drugs being used in the clinical trial are manufactured in and exported from the U.S. The current search of this database for information on clinical trials evaluating investigational medicinal products for the inner ear therefore provides new insights into 1) variation in the clinical trial populations in which drug interventions are currently being evaluated or have been evaluated within the past 15 years, and 2) variation in clinical trial outcomes across NIHL and DIHL otoprotection trials as well as drug intervention studies for stable SNHL and acute SSNHL. Drugs evaluated for these different targets have varied across indications despite the shared otopathology underlying many of these clinical targets. While the audiogram has often served as a primary outcome, average threshold shift has been the predominant outcome in NIHL, SNHL, and SSNHL trials whereas the rate of STS has been the predominant outcome in DIHL trials. Secondary and other outcomes have varied with respect to use of DPOAEs, extended high frequency hearing, word recognition in quiet, hearing in noise, tinnitus, and use of quality of hearing/quality of life surveys to assess global patient outcomes. The current review provides increased transparency into the variation across study designs. Increased consistency in the selection of primary and secondary outcomes within indications would facilitate comparisons of efficacy across investigational medicinal products. Different test batteries are needed for different inner ear indications based on patient/participant hearing ability, expected progression of deficits over time, and treatment goals.

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Conflict of Interest
None declared.

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