PROHEAR Study Synopsis

Sponsor:	**Name of IMP:**	**Active Ingredient:** Kv7.4 agonist
Acousia Therapeutics GmbH	ACOU085	**Indication:** Prevention of ototoxic hearing loss induced by cis-Pt
EUCT Number: 2023-503696-15-00		

Trial Title:

Phase IIa ***r***andomized, d***o***uble-blind, and placebo-controlled multicenter split body trial to determine safety, tolerability, and efficacy of repeated doses of ACOU085 for the prevention of ***hear***ing loss in testicular cancer patients receiving cisplatin

Trial Sites:

Multicenter trial in Germany planning to include up to 14 trial sites

Trial Duration:	**Trial Phase:** IIa
First patient first visit planned for QI 2024 Last patient last visit planned for QI-QII 2025	

Trial Objectives:

Primary Objective is to investigate the potential of ACOU085 for prevention of hearing loss after ototoxic damage induced by cis-Pt in testicular cancer (TCa) patients using an intraindividual comparison of functional hearing parameters.

Secondary Objectives are to assess the efficacy, safety, and tolerability profile of ACOU085 following three administrations (local transtympanic injections) in cis-Pt treated TCa patients.

Trial Design and Collective:

Randomized, double-blind, placebo-controlled, multicenter phase IIa clinical trial in adult male TCa patients with the risk to suffer from sensorineural hearing loss (SNHL) due to cisplatin therapy within a chemotherapeutic regimen of testicular cancer. Patients will have an indication for a cisplatin-containing chemotherapy according to current guidelines and trial site tumor board recommendations. The trial is designed to show efficacy, safety, and tolerability of ACOU085 administered into the middle ear using 3 transtympanic injections per ear prior to 3 planned and corresponding 3-week chemotherapeutic cycles.

The intraindividual control will be done by placebo injection into the respective contralateral middle ear.

Trial Course and Measures:

Nine weeks of observation with 4 trial visits (V1: Enrolment/Trial Start/Cycle 1; V2: Start of Cycle 2; V3: Start of Cycle 3; V4: End of Cycle 3) followed by a 3-month Follow-up Period ending with an End of Trial Visit (EOT; V5). The visits will include the incidence and severity of local and systemic adverse events, injection site/local reactions of both ears, vital signs, physical examination, ECG, and laboratory tests as well as facial nerve, auditory, and vestibular function. Hearing measurements such as high frequency pure tone audiometry (PTA), speech audiometry in quiet and noise, and otoacoustic emissions will have an intra-individual control by providing the comparison between verum- and placebo-treated ear.
Each patient will receive the first dose of IMP/Placebo prior to the initial chemotherapy cycle 1 (Day 1). Two further IMP/Placebo injections will be given, each prior to Cycle 2 (Day 22) and to Cycle 3 (Day 43). Thus, each TCa patient will receive three 3-week chemotherapeutic cycles preceded by 3 IMP/Placebo injections per ear. After the last IMP/Placebo injection at V3 (Day 43) a 3-week (V4; Day 64) and a further 12-week follow-up visit (V5, Day 150) will be done. A chemotherapeutic cycle can be a BEP-regimen with Bleomycin 30 U/week, Etoposide 100 mg/m^2/day for 5 days, and Cisplatin 20 mg/m^2/day for 5 days or other clinically adequate combinations always containing 20 mg/m^2/day Cisplatin.

Test Product (IMP):

Investigational Medicinal Product (IMP) will be ACOU085 as a thermoreversible hydrogel for local transtympanic injection provided by Acousia Therapeutics GmbH, Germany in ready-to-use sterile 1 mL glass vials. An injection requires standard syringes using long injection needles (for transtympanic injection 20G short bevel cannulas with a length of 75 mm are recommended). Concentration and volume for transtympanic injection (300 µL of a 2% ACOU085 hydrogel) was derived from results of a previous first-in-man dose escalation phase 1b study in patients with age-related SNHL (Acousia Study 01).

Placebo Treatment:

The placebo injection solution consists of a verum-free thermoreversible hydrogel for local trans-tympanic injection also provided by Acousia Therapeutics GmbH in ready-to-use sterile 1 mL glass vials

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Dose and Mode of Administration of IMP/Placebo:

Dosage:	300 µL thermoreversible 2% hydrogel of trial medication
Administration:	local transtympanic injection into both middle ears
Duration of treatment:	three transtympanic injections in each ear during at least 9 weeks always prior to a 3-week chemotherapeutic cis-Pt-containing cycle regimen

Number of Patients (planned):

A total number of 40 TCa-patients will be randomized and treated with IMP/Placebo and chemotherapy to finally achieve about 16 patients with ototoxicity for evaluation.

Randomization and Blinding:

When all in- and exclusion criteria apply and a written informed consent is available a patient will be randomly allocated to the trial treatment intra-individually as follows: per patient ACOU085 at right or left ear and Placebo at right or left ear according to the randomization list for the two treatment regimens (ie, ACOU085 left and Placebo right, or ACOU085 right and Placebo left; design of a split body trial).

This list will be generated block-wise for all 40 patients to be randomized implementing a randomization ratio of 1:1. Random numbers will be assigned to all patients enrolled in ascending order according to the chronological sequence of randomization. As the trial is double-blind and randomized it is important that each patient receives the treatment regimen labelled with a pertinent random number. Blinding will be secured by using a matching placebo solution for transtympanic injection identical in color, shape, and viscosity to the ACOU085 verum solution.

Diagnosis and Inclusion Criteria:

- Confirmed diagnosis of testicular cancer with indication for a cis-Pt-containing chemotherapeutic regimen according to current treatment guidelines and site-specific tumor board recommendations
- Male adult patients at an age between 18 and 45 years
- Planned cis-Pt treatment with a cumulative dose of ≥300 mg/m^2 which has to be administered in three chemotherapeutic cycles
- Normal or not clinically relevant otoscopic findings in both ears
- Normal hearing at both ears according to current WHO criteria for air-conduction 4PTA (0.5/1/2/4 kHz; 0 to 19 dB HL; average of audiometric thresholds at 0.5/1/2/4 kHz) at baseline
- Normal hearing at both ears according to ASHA criteria with a hearing threshold at any frequency (0.25 to 12 kHz) not exceeding 20 dB and a 4PTA (0.5/1/2/4 kHz) showing ≤15 dB HL at baseline
- Normal distortion product oto-acoustic emissions (DPOAE) present in both ears at baseline
- Patient shows normal results at trial start (V1) concerning heart rate (50 to 90 bpm), blood pressure (according to commonly accepted ranges), ECG (no pathological findings), and laboratory parameters (ie, liver and renal function values not clinically significant)
- Male patients and their female partner(s) must agree to use 2 forms of contraception (one of which must be a barrier method) during 6 months after trial start (V1)
- Patient is cooperative, able to understand all aspects of the trial, and able to speak German comparable to native speakers as per the investigator's discretion
- Patient has signed an approved informed consent form indicating that he understands the purpose of and procedures required for the trial, will follow the trial-specific measures, and is willing to participate in the trial

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Exclusion Criteria:

- Suspected or diagnosed genetic predisposition to hearing loss (incl. DFNA2 rel. to KCNQ4)
- History of middle ear pathology or surgery, otitis externa, chronic otitis media, or recent acute otitis media (within ≤3 months)
- History of otologic surgery (excluding myringotomy tubes or simple tympanoplasty)
- Meniere‘s disease or secondary endolymphatic hydrops, auto immune hearing loss, inner ear pathology, fluctuating hearing loss, perilymph fistula, cochlear baro-trauma, radiation-induced hearing loss, retro-cochlear lesion, severe tympanosclerosis, atrophic tympanic membrane
- Hearing loss of >45 dB averaged at 6 and 8 kHz in either ear
- Sudden hearing loss or conductive hearing loss >10 dB at two frequencies in either ear
- Asymmetry in hearing thresholds between left and right ear ≥20 dB at any single frequency or ≥10 dB at any 3 consecutive frequencies ≤ 8 kHz
- Intake of any ototoxic drugs other than the intended cis-Pt-containing chemotherapeutic drug regimen prior to start of the trial and during the trial period
- Previous radiation exposure >35 Gray to complete or parts of the cochlea
- Severe concomitant diseases such as heart failure (NYHA II-IV), COPD, bronchial asthma, ongoing malignancies other than testicular cancer, auto-immune or chronic-inflammatory diseases, endocrinological diseases, advanced hepatic or renal failure, and primary complaint of tinnitus
- Planned consumption of medications, herbal preparations, and specific food ingredients to treat hearing problems and/or tinnitus during the trial period
- Hypersensitivity against any primary or secondary ingredient of IMP/Placebo medication
- Male patients with female partners who are pregnant or planning to become pregnant during 6 months after trial start (V1)
- Use of any other investigational medicinal product (IMP) within five times the half-life of that IMP/relevant metabolites or one month (whichever is longer) prior to screening and planned use during the trial or up to 30 days after trial completion
- Patient has any dependent relationship or employment status with respect to the trial site, the sponsor, the investigator, or any supervisor

Previous and Concomitant Therapy:

Intake of any ototoxic drug other than the intended cis-Pt-containing chemotherapeutic drug regimen is not allowed prior to trial start and during the trial period. Patients will also be instructed to refrain from consumption of medication, herbal remedies, and specific food ingredients to treat hearing loss and/or tinnitus prior to trial start and during the trial course. To enable the transtympanic injections of ACOU085/Placebo, local anesthetics for use in the outer ear canal are recommended (ie, cotton pad with 1% Lidocaine). If more than the 3 planned chemotherapeutic cycles are conducted during the trial period until V5 (no preceding transtympanic injections for the additional cycles), this will be documented under concomitant therapy.

Usually the cisplatin-regimen is limited to 3 cycles and will be finished by the final study visit for all patients. Thus, no further otoprotective therapy is needed after trial termination. Nevertheless, all patients will continue to receive full standard of care treatment for the cisplatin chemotherapeutic regimen.

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Criteria for Evaluation:

Primary Parameter

- Proportion of patients showing a difference of ≥10 dB between both ears in at least two frequencies for air conduction in PTA focused on high (4, 6, 8 kHz) and extended high frequencies (10, 12, 14, 16 kHz) between baseline (V1; prior to first initiation of cis-Pt-containing chemotherapy) and end of chemotherapeutic cycle 3 (V4; Day 64).

Secondary Parameters

Efficacy

Protection for single audiometric variables (ie, intra-individual differences between both ears) including pure tone and speech audiometry in quiet and noise as well as otoacoustic emissions (DPOAEs) in terms of verum- vs. placebo-treated ear between V1 (baseline) and V2/V3/V4/V5, as defined in the following:

- Proportion of patients showing a difference of ≥10% between both ears for speech reception thresholds (SRT) in quiet for the Freiburger numbers and/or the Oldenburger sentence tests
- Proportion of patients showing a difference of ≥10% between both ears for speech discrimination in quiet at 50 and/or 65 dB SPL for the Freiburger monosyllable speech test
- Proportion of patients showing a difference of ≥1.5 dB SNR between both ears for speech discrimination in noise for the Oldenburger sentence test (fixed noise at 65 dB SPL)
- Proportion of patients showing a difference of ≥10 dB between both ears across all (0.25 to 12 kHz) and high frequencies (4 to 12 kHz) for the geometric mean of air conduction hearing thresholds
- Proportion of patients showing a difference of ≥5 dB between both ears for otoacoustic emissions

Safety and Tolerability

- Changes from baseline (differences in time and between both ears) in terms of facial nerve function (H. Brackmann/Stennert Index), cochlear function (tinnitus level/intensity and tympanometry/stapedius reflex), and vestibular function (nystagmus test and dizziness handicap inventory)
- Changes from baseline for vital signs, physical examinations, ECGs, and laboratory parameters
- Incidence, severity, and relationship of adverse events including injection site or local reactions at both ears during the trial course

Statistical Methods:

A hypothesis-based statistical sample size estimation was not performed. A patient collective of 40 patients randomized is regarded as sufficient to evaluate efficacy as well as local and systemic safety.

All patients enrolled and randomized and having received at least one transtympanic injection of IMP/Placebo will be evaluable for safety, tolerability, and efficacy. The different hearing tests for both ears after baseline assessment will be analyzed regarding changes in these measurements, separately for the verum- and the placebo-treated ear. Efficacy analyses will focus on intraindividual comparisons between baseline and post-treatment measurements of both ears and will be solely exploratory for all trial endpoints. Descriptive statistics will include counts and proportions for categorical data, and the number of patients with available measurements ('n'), arithmetic/geometric mean, standard deviation, median, quartiles, and range for continuous data. Graphical data displays may also be used to summarize the data. For exploratory purposes, hearing measurement variables, especially high frequency PTA (12-16 kHz), will be additionally analyzed using statistical methods for the comparison between treatments. For continuous patient data observation a centralized monitoring will be conducted without any break-of-blind. The final statistical analysis will be done following the last visit of the last patient. The detailed methodology for summary and statistical analysis of each parameter will be documented in a Statistical Analysis Plan (SAP) that will be finalized prior to database lock and unblinding. This document may further specify and modify the plans and instructions outlined in the protocol. However, any major modification of endpoint definitions and/or analyses will be reflected in a protocol amendment.

CRO and Statistics: acromion GmbH, Europaallee 27-29; 50226 Frechen / Germany

Status: Final Protocol V4.0 from February 2024

Schedule of Trial Procedures

Trial Course (Chemotherapy and Transtympanic Injection of IMP/Placebo)				FU-Period	
INVESTIGATIONS/TESTS/ MEASUREMENTS/ ASSESSMENTS	**V1 (Day 1) g)**	**V2 (Day 22) g)**	**V3 (Day 43) g)**	**V4 (Day 64)**	**V5 h) i)**
	Start of Cycle 1 (Baseline)	**Start of Cycle 2**	**Start of Cycle 3**	**End of Cycle 3**	**End of Trial (EOT)**
Trial Days or Interval a)	**Days 1 to 21**	**Days 22 to 42**	**Days 43 to 63**	**Day 64**	**Day 150**
Informed Consent/Enrolment*)	X				
Demographics/Medical History b)	X				
In- and Exclusion Criteria	X				
Physical Examination	X			X	X
Microscopic Otoscopy	X	X	X	X	X
PTA (Air and Bone Conduction)	X	X	X	X	X
Tympanometry/Stapedius Reflex	X	X	X	X	X
OLSA Tests in quiet and noise	X	X	X	X	X
Freiburger Tests: SRT and SPL	X	X	X	X	X
Otoacoustic Emissions (DPOAE)	X	X	X	X	X
Nystagmus Test	X	X	X	X	X
Dizziness Handicap Inventory	X	X	X	X	X
Tinnitus Level and Intensity	X	X	X	X	X
H.-Brackmann & Stennert Index	X	X	X	X	X
Vital Signs and ECGs	X	X	X	X	X
Laboratory Tests c)	X	X	X	X	X
Transtympanic Injection d)	X	X	X		
Chemotherapy (cis-Pt-Regimen e))	X	X	X		
Concomitant Therapy (Update)		X	X	X	X h)
Adverse Event Recording f)	X	X	X	X	X

*): according to randomization list

a): a visit window of ±2 days for V2 (Day 22), V3 (Day 43), and V4 (Day 64) is defined to consider the patients' availability (eg, weekends, holidays, illnesses, etc.). For V5 (Follow-up Period) ±7 days are allowed.

b): including age, body height/weight, ethnic origin, ORL-history, previous/concomitant diseases and therapies

c): current laboratory results available per visit from oncology can be used and are not needed to be repeated

d): must be performed within maximum 48 hours prior to the start of each of the first three chemotherapeutic cycles in both ears according to randomization schedule by using the assigned patient/random numbers

e): a 3-week chemotherapeutic cycle can consist of Bleomycin 30 U/week, Etoposide 100 mg/m^2/day over 5 days, and Cisplatin 20 mg/m^2/day over 5 days or other clinically adequate combinations with 20mg/m^2/day cis-Pt and will be started always after the transtympanic injections

f): including injection-site reactions/local reactions in both ears

g): measures and assessments of V1/V2/V3 must be done always prior to the respective transtympanic injections (can be conducted at the same day as the injections but also during one or two days before)

h): more than the 3 planned chemotherapeutic cycles are possible during the trial period until V5 (then no preceding transtympanic injections for the additional cycles) and will be documented under concomitant therapy at V5

i): EOT=End of Trial Visit; in patients with premature trial withdrawal an update and completion of the investigations and assessments from the EOT (V5) should be conducted as complete as possible