Statistical Analysis Plan

Sponsor Name:	Auris Medical Inc.
Protocol Number and Title:	AM-111-CL-15-01 Efficacy and Safety of AM-111 as Acute Sudden Sensorineural Hearing Loss Treatment (ASSENT)
Protocol Version and Date:	Version 3.0 and 24 May 2017
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Author(s):	[redacted]
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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
Alb	Albumin
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
cFUV	Conditional Follow-Up Visit
Ca	Calcium
Cl	Chloride
CRE	Creatinine
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
dB	Decibel
D-JNKI-1	D-stereoisomer of c-Jun N-terminal Kinase Inhibitor
FUV	Follow-up Visit
γ-GTP	Gamma-Glutamyl Transpeptidase
HBV	Hepatitis B Virus
Hct	Hematocrit
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HHIA	Hearing Handicap Inventory for Adults
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

Abbreviation	Description
IRB	Institutional Review Board
ISSNHL	Idiopathic Sudden Sensorineural Hearing Loss
K	Potassium
kHz	Kilohertz
LDH	Lactate Dehydrogenase
Na	Sodium
P	Phosphorus
PGIC	Patient Global Impression of Change
Plt	Platelet
PTA	Pure Tone Average
Q25	25%-Quantile
Q75	75%-Quantile
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subject Contact
SD	Standard Deviation
T-bil	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TAQ	Tinnitus Annoyance Question
TLQ	Tinnitus Loudness Question
TP	Total Protein
TV	Treatment Visit
UA	Uric Acid
VNG	Videonystagmography
WHO	World Health Organization
WBC	White Blood Cell
WRS	Word Recognition Score

Abbreviation	Description
$WRS_{(60\ dB)}$	Word Recognition Score at 60 dB
$WRS_{(80\ dB)}$	Word Recognition Score at 80 dB

2 PURPOSE

This Statistical Analysis Plan (SAP) is created based on Protocol Number AM-111-CL-15-01 Version 3.0, 24 May 2017. The purpose of this SAP is to outline the planned analyses [redacted] to support the completion of the Clinical Study Report (CSR). This SAP describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Any important or clinically significant post-hoc analysis results will be fully documented in the CSR.

2.1 RESPONSIBILITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control (QC) of all tables, figures, and listings related to all efficacy endpoints as well as all safety endpoints.

2.2 TIMINGS OF ANALYSES

The primary analysis of safety and efficacy is planned after all enrolled subjects complete the final study visit or terminate early from the study. Only descriptive analyses will be conducted due to the early termination of the study

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of the trial is the confirmation of the efficacy of AM-111 in the recovery of severe to profound idiopathic sudden sensorineural hearing loss (ISSNHL).

3.2 SECONDARY OBJECTIVES

The secondary objectives of the trial are:

- Evaluation of the dose-response relationship for AM-111 in the recovery of ISSNHL;
- Assessment of the efficacy of AM-111 in the recovery of speech discrimination (word recognition in quiet);
- Assessment of the efficacy of AM-111 in achieving complete remission of ISSNHL-related tinnitus;
- Assessment of safety and local tolerance of AM-111.

[redacted]

4 BRIEF DESCRIPTION

This Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center trial will study the efficacy and safety of AM-111 in the treatment of subjects suffering from ISSNHL.

A total of approximately 300 subjects aged ≥ 18 years and experienced unilateral ISSNHL with mean hearing loss of 60 decibel (dB) or greater at the 3 most affected contiguous test frequencies with onset within 72 hours prior to study treatment were supposed to be randomized at approximately 80 sites located in the U.S., Canada and South Korea. However, the study enrolled only 56 patients at early termination. The trial consists of one Treatment Visit (TV) and a 13-week follow-up period with follow-up visits (FUV) at D3, D7, D28 and D91, one conditional follow-up visit (cFUV) at D14 and one subject contact at D56.

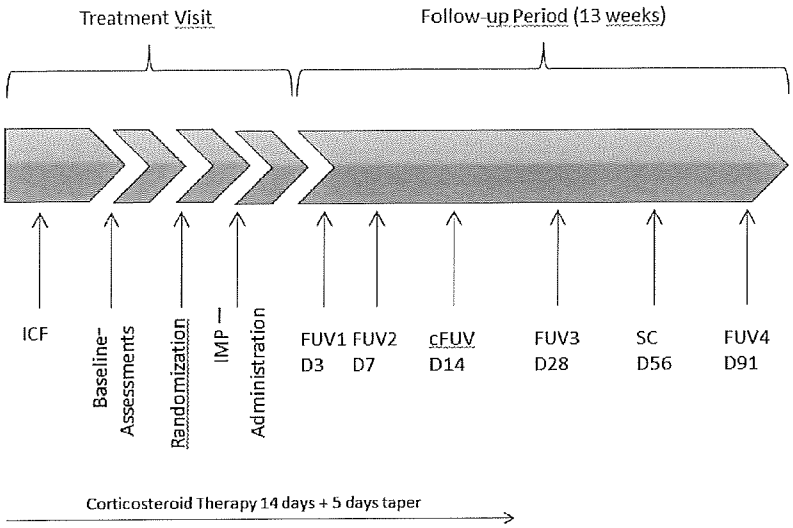
The primary efficacy endpoint is the absolute improvement of pure tone average (PTA) in dB from baseline to FUV4 based on the average of the three most affected contiguous audiometric test frequencies that were determined at baseline. The main secondary efficacy endpoint is the absolute improvement in $WRS_{(80dB)}$ from baseline to FUV4. Absolute improvement in PTA from baseline to FUV1, FUV2 and FUV3; Absolute improvement in $WRS_{(80\ dB)}$ from baseline to follow-up visits FUV1, FUV2 and FUV3; and Frequency of complete tinnitus remission in subjects with ISSNHL-related tinnitus at baseline, determined at FUV4 are the secondary efficacy endpoints. [redacted]

The primary safety endpoint is the occurrence of clinically relevant hearing deterioration (defined as increase in air conduction hearing threshold ≥ 10 dB at the average of any two contiguous test frequencies) from baseline to FUV3 in the treated ear. It is repeated with bone conduction hearing thresholds. [redacted]

Subjects meeting all entry criteria will be randomized on D0 (Day 0) to receive the Investigational Medicinal Product (IMP) (AM-111 0.4 mg/mL, 0.8 mg/mL or placebo) at a 1:1:1 ratio. Subject recruitment was stopped on 28Nov2017 after enrolment of 56 subjects. [redacted] Trial participants will receive an intratympanic injection of the IMP (AM-111 or placebo) into the affected ear at TV (D0).

The duration of subject participation is 91 days (TV, FUV1 to FUV4). Figure 1 gives the Trial flow chart and the Table 1 shows the schedule of visits and assessments.

Figure 1 Trial flow chart



D=Day; TV=Treatment Visit; FUV=Follow-Up Visit; cFUV=conditional Follow-Up Visit; SC=Subject Contact.

Table 1: Schedule of visits and assessments

Study visit assessment	TV (D0)	FUV1 (D3±1)	FUV2 (D7±2)	cFUV[1] (D14±3)	FUV3 (D28±5)	SC (D56±7)	FUV4[2] (D91±7)
Informed consent	•						
Inclusion and exclusion criteria	•						
Demography/baseline characteristic	•						
Medical history (incl. hearing loss onset)	•						
Prior and concomitant medication recording	•	•	•	•	•	•	•
Tinnitus evaluation (history, characteristics)	•	•[3]	•[3]		•[3]		•[3]
Physical examination	•						
Vital signs (blood pressure, temperature, pulse)	•	•	•		•		•
Laboratory test (hematology, biochemistry)	•	•					
Laboratory test (virology)	•						
Urine pregnancy test, *if applicable*	•						•
HHIA questionnaire					•		•
$PGIC_{hearing\ loss}$ Scale			•		•		•

Tinnitus presence or absence and numerical rating scales ($TLQ_{Loudest}$, TAQ_{Worst})			Subject diary				
Otoscopy/microscopy	●	●	●	●	●		●
Tympanometry	●		●[4]	●[4]	●		●
Pure tone audiometry (air and bone conducted)	●[5,6]	●	●		●		●
Speech audiometry (WRS at 80 dB in quiet)	●[5,6]	●	●		●		●
Speech audiometry (WRS at 60 dB in quiet)	●[5,6]						●
Spontaneous nystagmus (Frenzel goggles or VNG)	●[5]	●	●		●		●
Balance test (Romberg's test)	●[5]	●	●		●		●
Suicidality questionnaire (C-SSRS)	●		●		●		●
Final eligibility check prior to randomization	●						
Randomization	●						
IMP intratympanic injection	●						
Background therapy (corticosteroid)[7]	●						
Dispense background therapy documentation card[7]	●						
Check completion of background therapy documentation card[7]		●	●	●	●		
Adverse event reporting	●	●	●	●	●	●	●

[1] Only to be performed if eardrum is not closed at FUV2 at D7.

[2] Or premature end of trial visit in case the subject terminates the trial prematurely.

[3] Only to be performed if tinnitus is present.

[4] Only to be performed if eardrum is fully closed.

[5] Assessment to be repeated, at the earliest, 24 hours from onset if subject presenting within the first 24 hours from ISSNHL onset. If eligibility is confirmed, this second assessment serves as baseline measure.

[6] If WRS ($WRS_{(80dB)}$ and $WRS_{(60\ dB)}$) and PTA assessments were done within 2 hours prior to subject inclusion (signing the informed consent form (ICF)) and within 5 hours prior to IMP administration, these assessments will be used as baseline values and therefore do not need to be repeated.

[7] Only to be done if subject receives background therapy. The background therapy documentation card is to be collected at FUV3.

4.1 SUBJECT SELECTION

This trial will include adult subjects (18 years or older on the day of screening) who suffer from ISSNHL with onset in the past 72 hours.

Once informed consent for this trial is obtained, screening procedures will be performed to assess if the subject meets the inclusion/exclusion criteria as listed below.

4.1.1 Inclusion Criteria

A subject will be eligible for inclusion in this trial if all of the following criteria apply:

1. Unilateral ISSNHL with onset within 72 hours prior to study treatment;
2. Mean hearing threshold of equal to or worse than (≥) 60 dB averaged across those 3 contiguous air conduction audiometric pure tone frequencies that show the highest mean hearing loss compared with the unaffected contralateral ear or, in case of history of asymmetric hearing, corresponding values from a pre-existing audiogram for the affected ear not older than 2 years prior to the ISSNHL incident (defined as "pure tone average", PTA)*;
3. Mean hearing loss of equal to or worse than (≥) 40 dB averaged across the air conduction thresholds at the pure tone average frequencies compared with the unaffected contralateral ear or, in case of history of asymmetric hearing, corresponding values from a pre-existing audiogram for the affected ear not older than two years prior to the ISSNHL incident*;
4. Age ≥ 18 years on the day of screening;
5. Negative urine pregnancy test for women of childbearing potential. Women are not considered to be of childbearing potential if they meet one of the following criteria:
   a. They have had a hysterectomy or tubal ligation at least one cycle prior to signing the Informed Consent Form (ICF) or
   b. They are post-menopausal, with at least one year since their last menstrual period.
6. Willing and able to attend the trial visits;
7. Able to read and understand trial documents and follow Investigator and trial personnel instructions during visits, including audiology measurements;
8. Willing and able to use adequate hearing protection and to refrain from engaging in activities or work involving loud noise exposure where sufficient hearing protection is not possible or ensured for the duration of their participation in this study;
9. Willing and able to protect the ear canal and middle ear from water exposure for as long as the tympanic membrane is not fully closed;
10. Signed Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approved ICF.

* In subjects assessed within the first 24 hours from ISSNHL onset inclusion criteria 2 and 3 have to be confirmed by a second measure that is conducted, at the earliest, 24 hours after the onset of ISSNHL. This confirmatory assessment will serve as baseline value.

4.1.2 Exclusion Criteria

A subject will not be eligible for inclusion in this trial if any of the following criteria apply:

1. Bilateral ISSNHL;
2. Acute hearing loss from noise trauma, barotrauma or head trauma;

3. Air-bone gap higher than 20 dB at the average of 3 contiguous frequencies below 4 kHz, when the air-bone gap is measurable;
4. History of autoimmune hearing loss, radiation-induced hearing loss, endolymphatic hydrops or Menière's disease in either ear;
5. History of chronic inflammatory or suppurative ear disease or cholesteatoma in the affected ear;
6. Current evidence or history of acoustic neuroma or other retrocochlear damage in the affected ear;
7. History of otosclerosis in the affected ear;
8. Suspected perilymph fistula or membrane rupture in the affected ear;
9. Congenital hearing loss;
10. History of ISSNHL in the past 2 years;
11. Otitis media or otitis externa that is ongoing or ended within 7 days prior to study treatment;
12. Radiation therapy in the head and neck area within the past 5 years;
13. Abnormality of the tympanic membrane in the affected ear that would preclude intratympanic administration;
14. Any pre-treatment or ongoing treatment for ISSNHL-related hearing loss or tinnitus (except for oral corticosteroid background therapy that was started within 36 hours prior to randomization);
15. Any other planned pharmacological or non-pharmacological treatment for hearing loss or tinnitus for the duration of the trial;
16. Any therapy known as ototoxic (e.g. aminoglycosides [systemic or ototopical with middle ear exposure], cisplatin, loop diuretics, quinine etc.) in the 3 months prior to treatment visit;
17. History within the past 2 years or presence of drug abuse or alcoholism;
18. Subjects with diagnosed anxiety disorders, psychosis, depression, schizophrenia, attempted suicide or other significant psychiatric conditions that can impact their ability to cooperate and comply with the study protocol;
19. Subjects who have answered "yes" to Suicidal Ideation question 4 or 5 of the Colombia-Suicide Severity Rating Scale (C-SSRS) in Appendix 1;
20. Any clinically relevant autoimmune, respiratory, cardiovascular, neurological disorder (except vertigo or tinnitus) or other abnormality that in the opinion of the Investigator may pose a safety risk to a subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation;
21. Known Human Immunodeficiency Virus (HIV), hepatitis B or hepatitis C, or symptomatic herpes zoster infection;

22. Women who are breast-feeding, pregnant or who are planning to become pregnant during the study;
23. Women of childbearing potential who are unwilling or unable to use an effective method of avoiding pregnancy from screening until the end of the study (FUV4). Effective methods of avoiding pregnancy are contraceptive methods with a Pearl index of less than 1 when used consistently and correctly (including implantable, injectable, oral and transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap, or a sterile sexual partner, or being abstinent);
24. Concurrent participation in another clinical study or participation in another clinical study within 30 days prior to randomization (TV).

[redacted]

4.3 TREATMENT ASSIGNMENT & BLINDING

The IMP will be provided as [redacted]. Subjects will receive one single dose [redacted] of IMP into the affected ear intratympanically at TV. Subjects will receive either AM-111 (0.4 and 0.8 mg/mL, respectively) or placebo. [redacted] AM-111 0.4 mg/mL [redacted] D-stereoisomer of c-Jun N-terminal Kinase Inhibitor (D-JNKI-1) and [redacted] of AM-111 0.8 mg/mL [redacted].

The background therapy consists of an oral corticosteroid course with prednisolone or methylprednisolone which is self-administered by eligible and consenting subjects for 14 days followed by a 5-day taper, starting on TV (or at the earliest within 36 hours prior to randomization).

The Investigators as well as the subjects will be blinded regarding the dose of IMP administered during the trial. This applies also to trial personnel at the Sponsor and the Contract Research Organization (CRO), except for designated unblinded staff at the CRO. In particular, the gel formulation will be of the same appearance for AM-111 0.4 mg/mL, AM-111 0.8 mg/mL and placebo and will reveal no differences during or following injection, neither to the Investigator, nor to the subject. None of the Investigators will be aware of the randomization schedule.

The interim analysis will be performed by an independent statistician. The Sponsor and any persons who are involved in the ongoing conduct and management of the trial shall not see or have access to any group or individual patient unblinded data viewed by the independent statistician, for the duration of the trial. Due to early termination, an interim analysis is not done.

4.4 ADMINISTRATION OF STUDY MEDICATION

Trial subjects will receive an intratympanic administration of the IMP (AM-111 0.4 mg/mL, AM-111 0.8 mg/mL or placebo) as assigned by [redacted] the IMP is gently injected into the middle ear. The timing of the IMP administration is to be documented in the source documents and on the case report form (CRF).

Subjects will also receive a course of oral corticosteroids for 14 days followed by a 5-day taper unless medically contraindicated or declined by the subject. This corticosteroid therapy is not mandatory. The intake of the corticosteroid therapy has to be recorded by the subject on a background therapy documentation card.

5 ENDPOINTS

5.1 EFFICACY ENDPOINTS

5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute improvement of PTA in dB from baseline to FUV4 based on the average of the three most affected contiguous audiometric test frequencies. Improvement is defined as the baseline PTA value minus FUV4 value (positive numbers indicating improvement). If for any post-baseline assessment, a measurement of one of the three PTA frequencies is missing, the average of the available 2 most affected frequencies is still considered valid.

5.1.2 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated in this study:

5.1.2.1 Main Secondary Efficacy Endpoint

• Absolute improvement in WRS $_{(80dB)}$ from baseline to FUV4. An improvement in WRS of at least 15 percentage points is considered clinically relevant.

5.1.2.2 Other Secondary Efficacy Endpoints

- Absolute improvement in PTA from baseline to FUV1, FUV2 and FUV3;
- Absolute improvement in WRS $_{(80\ dB)}$ from baseline to follow-up visits FUV1, FUV2 and FUV3; and
- Frequency of complete tinnitus remission in subjects with ISSNHL-related tinnitus at baseline, determined at FUV4.

[redacted]

[redacted]

5.2 SAFETY ENDPOINTS

5.2.1 Primary Safety Endpoints

Occurrence of clinically relevant hearing deterioration (defined as increase in air conduction hearing threshold ≥ 10 dB at the average of any two contiguous test frequencies) from baseline to FUV3 in the treated ear. The analysis will also be conducted with bone conduction hearing threshold values.

5.2.2 Secondary Safety Endpoints

- Occurrence of clinically relevant hearing deterioration in the treated ear (air conduction) from baseline to all FUVs (other than FUV3);
- Difference in occurrence of clinically relevant hearing deterioration from baseline to all FUVs between treated and untreated contralateral ear;
- Occurrence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), assessed for causal relationship with respect to:
    - Investigational Medicinal Product (IMP);
    - The intratympanic IMP administration procedure.

[redacted]

6 ANALYSIS SETS

A listing will present each randomized subject with flags denoting the analysis sets to which each belongs. A comment in the listing will describe why each subject is excluded from any of the analysis sets described below.

6.1 RANDOMIZED SET

The Randomized Set will include all subjects randomized. Unless specified otherwise, this set will be used for subject listings and for summaries of subject disposition.

6.2 EFFICACY ANALYSIS SET

This analysis set is based on the Intention to Treat (ITT) principle and includes all randomized subjects who:

- were treated with either AM-111 or placebo and
- have a valid PTA measure at baseline and
- have a valid post-treatment PTA-measure (FUV1 or later).

Subjects are analyzed according to the randomized treatment.

An Independent Data Monitoring Committee will decide whether a PTA measure is considered valid or not. As the study is prematurely terminated, it has been decided to reduce the review and focus on the data that are most likely to be relevant for further analysis. An independent expert will review audiograms (TV, FUV3 and FUV4) of subjects with baseline PTA measure of ≥ 90 dB and decide whether the PTA measure is valid or not.

A PTA measure is considered valid if a review by an IDMC member or an independent expert confirms the pure tone hearing thresholds were determined in accordance with the protocol and are of sufficient quality to calculate a mean hearing threshold and a mean hearing loss, notably:

- the unaffected ear was masked if the difference between the air conduction threshold in the affected ear and the bone conduction threshold in the unaffected ear was > 50 dB for determining air conduction thresholds;
- the unaffected ear was masked if the difference between the bone conduction threshold in the affected ear and the bone conduction threshold in the unaffected ear was > 10 dB for determining bone conduction thresholds; and
- the hearing thresholds have been recorded properly in the audiogram and the application of masking was documented.

6.3 PER PROTOCOL ANALYSIS SET

This analysis set includes all subjects from the Efficacy Analysis Set without major protocol deviations which would interfere with the analysis of the primary efficacy endpoint or main secondary efficacy endpoint. Protocol deviation definitions are described in detail in the Statistical Analysis Plan (See Section 6.5) which also lists possible reasons for exclusion of subjects from analysis populations in case of major violations. However, the impact of specific deviations (e.g. from a pre-specified time-window) may additionally be discussed during the Blind Data Review Meeting. Major violations may include, but are not limited to:

- Violation of major entry criteria for study participation;
- Intake of forbidden concomitant medication.

Subjects are analyzed according to the treatment received.

6.4 SAFETY ANALYSIS SET

This analysis set includes all subjects who were treated with either AM-111 or placebo. Subjects are analyzed according to the treatment received.

6.5 PROTOCOL DEVIATIONS

Protocol deviations will be documented during the study period as one of the following categories:

Inclusion Criteria, Exclusion Criteria, Randomization Error, ICF, Other GCP breaches, SAE not reported, Visit out of window, Missed Study Visit, Safety Procedure not per protocol, Efficacy Procedure not per protocol, Other Procedure not per protocol, Prohibited Medication, Background therapy deviation, IMP handling, and Others.

A listing including information captured on the CRF and determined in the Blind Data Review Meeting will be generated with the date the deviation occurs, the deviation term (description), the category, and the reason of the deviation.

7 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1 GENERAL METHODS

The data analyses will be conducted using [redacted].

Unless otherwise specified, all continuous efficacy and safety data will be summarized descriptively by treatment group and time point including changes from baseline (n, arithmetic mean, standard deviation, minimum, 25%-quantiles (Q25), median, 75%-quantiles (Q75) and maximum). [redacted] The stratification of initial PTA frequency range will be conducted on the 3 contiguous air conduction audiometric pure tone frequencies at TV. The 0.25 - 1kHz, 0.5 - 2 kHz and 1 - 3 kHz will be defined as ≤ 2 kHz. The 2 - 4 kHz, 3 - 6 kHz, and 4 - 8 kHz will be defined as > 2 kHz.

Categorical variables will be summarized with frequencies and percentages by treatment group and time point. [redacted]

For categorical variables, the number and percentage of subjects in each category will be summarized. Percentages will be displayed to one decimal place, except 100%, which will not show any decimals. Counts of zero will not have percentage displayed in order to draw attention to non-zero counts. Ratios will be displayed to 2 decimal places.

Unless otherwise specified, all efficacy and safety data summarized will include scheduled visits.

All data collected on CRFs and clinical database will be presented in by-subject listings for randomized set unless specified otherwise

7.2 KEY DEFINITIONS

Baseline:

Baseline is defined as pre-intratympanic administration assessment or baseline is the last non-missing assessment value before the first dose of study IMP. This definition will be used for all baseline and change from baseline analyses, unless specified otherwise.

Pure tone audiograms measured in subjects presenting within the first 24 hours from ISSNHL onset have to be confirmed by a second measure that is conducted, at the earliest, 24 hours after the onset of ISSNHL. This new confirmatory assessment will serve as baseline value.

Speech audiometry, spontaneous nystagmus and balance test will be assessed, at the earliest, 24 hours after ISSNHL onset, and this measurement will serve as baseline value.

First Dose Date:

For subjects randomized to AM-111, the first dose date will be defined as the date of TV Day 0.

Study Day:

Study day is defined as the number of days from the date of first dose to the event/visit date. It is calculated as follows: Study Day = Event or Visit Date - First Dose Date.

Hence, the date of first dose is referred to as Day 0. The previous day is Day -1.

7.3 MISSING DATA

Complete missing or partial date will be presented in the listings as reported on CRFs. Missing or incomplete onset dates for adverse events and concomitant medications will be imputed as needed in order to determine treatment emergence or determine the prior and concomitant medications. The partial start date will be imputed as the first day of that month or year. The partial stop date will be imputed as the last day of that month or year.

Except the date imputation specified above, no missing data imputation will be applied to the descriptive analysis of efficacy and safety analysis of this study.

7.4 VISIT WINDOWS

In general, all efficacy and safety data will be summarized by scheduled visits based on the scheduled events indicated in Table 1. The visits indicated on the eCRF (i.e., eCRF visit) will be used as the analysis visits for the efficacy and safety analysis.

The presence or absence of tinnitus and numerical rating scales for subjective tinnitus loudness "at its loudest" ($TLQ_{Loudest}$) and subjective tinnitus annoyance "at its worst" (TAQ_{Worst}) is collected at all visits from TV until FUV4. The data of tinnitus collected at all visits will be summarized by the scheduled visits.

In addition, a subject diary will be used for the subjects to self-record weekly the presence or absence of tinnitus and numerical rating scales. The data of tinnitus from the subject diary will be listed. Missing data are not imputed.

7.5 POOLING OF CENTERS

No pooling of centers will be done.

7.6 SUBGROUPS

No subgroups summary analysis will be done.

8 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

8.1 SUBJECT DISPOSITION AND WITHDRAWALS

The number of subjects screened, number and percentage of subjects who failed screening and reasons for screen failures (Withdrawal of consent, Not meeting eligibility criteria, Decision of investigator, and other) will be tabulated. A listing will also be provided for screen failures with the reason for screen failure.

[redacted]

The number and percentage of subjects in the different analysis sets is also summarized. The listing will be presented for the same together with the reasons for exclusion of subjects from the analysis sets.

Subject disposition will be summarized for all randomized subjects. Subjects who completed the study and discontinued early from the study will be summarized together with the primary reasons (Adverse Events, Death, Withdrawal of Consent, Protocol violation, Lost to follow-up, Investigator does not consider trial participation to be in the subject's best interest, and other) for discontinuation from the study. All percentages will be based on the number of randomized subjects within the treatment group. The same summary table will be presented by initial strata as well as country. Details on end of study/early withdrawals will be provided in a separate by-subject listing.

8.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All subjects' demographic data and baseline characteristics will be summarized and listed for all subjects in Randomized Set. Summary statistics (n, arithmetic mean, standard deviation, minimum, Q25, median, Q75 and maximum) will be provided for quantitative data (age, baseline weight, height). For qualitative data (gender, ethnicity, race, etc.) frequency tables will be provided. Age will be determined at the time of informed consent. The same summary table will be broken down by the strata as well.

8.2.1 History of Current Hearing Loss and Baseline Hearing Characteristics

History of current hearing loss will be recorded at the TV prior to randomization. The frequencies of the affected ear (left, right, both) as well as the mean, median and range of baseline time from ISSNHL onset (in hours), baseline PTA of the affected ear (in dB), and baseline hearing loss will be tabulated by treatment group. The same summary statistics will be provided by the strata and for the initial hearing loss severity and initial PTA frequency range subgroups.

8.2.2 Baseline Tinnitus Characteristics

The presence or absence of tinnitus (Appendix 2) will be tabulated at the baseline. If tinnitus is present, tinnitus history (onset, tinnitus inducing event, laterality) and tinnitus characteristics (persistence, pitch, sound) will be summarized and listed at the baseline.

For determining TLQ and TAQ at baseline, patients will be asked to fill the 'Tinnitus numerical rating scales Questionnaire (Appendix 3). The tinnitus loudness and annoyance by treatment group will be summarized and listed.

8.2.3 Baseline Word Recognition Score (WRS)

Frequencies for the baseline word recognition score ($WRS_{(80\ dB)}$) of the affected ear ($\leq$ 30% and > 30%) as well as the summary statistics for WRS at 60 dB and 80 dB will be tabulated by treatment groups.

8.2.4 Baseline Pregnancy Test Results

Frequencies will be tabulated and listed for the baseline pregnancy test results (positive or negative) by treatment groups.

8.3 MEDICAL HISTORY

Any medical condition already present at the baseline medical assessment will be documented as medical history. The patient's medical history, including a detailed otolaryngological history, will be taken at the TV and documented in the subject's record. Medical history that is clinically relevant will be recorded in the CRF.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized and all percentages will be based on the number of subjects in the safety analysis set. If a subject had a medical history term more than once, the subject will be counted only once under any given SOC or PT.

A medical history listing will be provided for all randomized subjects.

8.4 PRIOR MEDICATION AND CONCOMITANT MEDIACTION

Prior medication means all medications taken by a subject before the first dose of IMP administered. Concomitant medication refers to all medication taken by the subject during the trial (encompassing TV until end of follow-up).

Prior and concomitant medication will be classified according to World Health Organization (WHO)-Drug Dictionary prior to providing tabulated overviews. Concomitant medications will be summarized by treatment and presented by WHO Drug

Dictionary Anatomic-Therapeutic-Chemical Code (ATC) level 4 and preferred term in decreasing order in the overall column.

The local anesthetic selected and used by the Investigator in preparation of the intratympanic administration procedure for application of the IMP will not be recorded as concomitant medication, but will be recorded separately with the IMP administration in the CRF.

8.4.1 Other Therapies

As background therapy, an oral corticosteroid course will be offered for 14 days followed by a 5-day taper.

The background corticosteroid treatment may be omitted in case of medical contraindication of oral corticosteroids or if declined by the subject. The other therapies will be listed by subject level.

The following treatments are not allowed during the course of the trial (from TV to FUV4):

- Any concomitant pharmacological or non-pharmacological treatment of ISSNHL-related hearing loss or tinnitus (other than the background therapy that may be started up to 24 hours prior to randomization);
- Any therapy known as potentially ototoxic (e.g. aminoglycosides [systemic or ototopical with middle ear exposure], cisplatin, loop diuretics, quinine etc.);
- Any other pharmacological or non-pharmacological treatment for hearing loss other than the IMP and background therapy unless that treatment was taken for another condition prior to the current ISSNHL incident and started at least 4 weeks prior to randomization; such treatment should be continued unchanged throughout the trial.

9 EFFICACY

All efficacy analyses will be conducted on the Efficacy Analysis Set.

All continuous efficacy data will be summarized descriptively by treatment group and time point including changes from baseline (n, arithmetic mean, standard deviation, minimum, Q25, median, Q75 and maximum). Categorical variables will be summarized with frequencies and percentages by treatment group and time point. [redacted].

9.1 PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is the absolute improvement of PTA in dB from baseline to FUV4 based on the average of the three most affected contiguous audiometric test frequencies. Improvement is defined as the baseline PTA value minus FUV4 value (positive numbers indicating improvement).The descriptive analysis of the primary efficacy endpoint will be performed using Efficacy Analysis Set and Per-protocol Analysis Set.

9.2 SECONDARY EFFICACY ENDPOINT(S) AND ANALYSES

9.2.1 The Main Secondary Efficacy Endpoint Analysis

The main secondary efficacy endpoint is

- Absolute improvement in $WRS_{(80\ dB)}$ from baseline to FUV4;

The descriptive analysis of the main secondary efficacy endpoint will be performed using Efficacy Analysis Set and Per-protocol Analysis Set.

9.2.2 The Other Secondary Efficacy Endpoints Analysis

All other secondary efficacy endpoints will be summarized in the Efficacy Analysis Set as described below.

- Absolute improvement in PTA from baseline to FUV1, FUV2 and FUV3;
- Absolute improvement in $WRS_{(80\ dB)}$ from baseline to follow-up visits FUV1, FUV2 and FUV3;

  The absolute improvements are continuous data which will be summarized descriptively.
- Frequency of complete tinnitus remission in subjects with ISSNHL-related tinnitus at baseline, determined at FUV4. Complete tinnitus remission is achieved when a

subject answers the question about tinnitus presence with "No". Frequency of complete tinnitus remission will be summarized categorically.

[redacted]

[redacted]

10 SAFETY

All safety analyses will be conducted on the Safety Analysis Set.

10.1 EVALUATION OF SAFETY ENDPOINTS

Primary, secondary and [redacted] safety endpoints will be analyzed as follows.

10.1.1 Primary Safety Analysis

The percentage of subjects with clinically relevant hearing deterioration (defined as increase in hearing threshold ≥ 10 dB at the average of any two contiguous test frequencies) in the treated ear from baseline to FUV3 will be determined per treatment group and overall for both air conduction or bone conduction results and summarized.

Hearing thresholds will be determined by pure tone audiometry in both ears at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz (air conduction), and at 0.5, 1, 2, 3, 4 kHz (bone conduction). The hearing threshold is defined as the lowest tone level at which the test subject hears the tone, and which is confirmed by a second measure.

Since the audiometry response is a continuous variable, summary statistics will be provided by treatment group at the baseline and FUV3 for the affected ear. The summaries will include actual values and change from baseline for air and bone conduction.

10.1.2 Secondary Safety Analysis

The following secondary safety analyses will be performed:

1. The percentage of subjects with clinically relevant hearing deterioration in the treated ear from baseline to FUV1, FUV2 and FUV4 will be summarized in the same way as the primary safety endpoint.

   A summary table of audiometric assessments for air and bone conduction will be presented with change from baseline to all FUVs. This will cover the primary and the main secondary safety endpoint analysis.

2. The difference in occurrence of clinically relevant hearing deterioration from baseline to all FUVs between treated and untreated contralateral ear will be summarized.
3. The incidence of post-treatment AEs and SAEs will be described overall and analyzed by relatedness to IMP and to intratympanic IMP administration procedure as shown in section 10.1.2.1.

4. The incidence of AEs will be summarized by system organ class, preferred term, severity and the relationship categories as outlined in section 10.1.2.1. Summaries will be presented by treatment group and overall.

10.1.2.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An event that emerges during treatment having been absent prior to treatment or worsening relative to the pre-treatment state is defined as treatment emergent adverse event (TEAE).

A SAE is defined as any untoward medical occurrence that

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that requires intervention to prevent one of the above

Exceptions are defined in the protocol.

An overall summary table of TEAEs will be provided with the following categories:

- Number and percentage of subjects with TEAEs
- Number and percentage of subjects with a treatment-related TEAE
- Number and percentage of subjects with an intratympanic IMP administration procedure -related TEAE
- Number and percentage of subjects with a TEAE resulting in study withdrawal
- Number and percentage of subjects with a Serious TEAE
- Number and percentage of subjects with a treatment-related serious TEAEs
- Number and percentage of subjects with an intratympanic IMP administration procedure-related serious TEAEs
- Number and percentage of subjects with a TEAE leading to death

The TEAEs will be summarized by SOC and PT by presenting the number and percentage of subjects with a TEAE in each corresponding category

The TEAE summary will be produced for the following categories:

- TEAEs by SOC and PT
- TEAEs by PT
- Serious TEAEs by SOC and PT
- TEAEs leading to study withdrawal by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- TEAEs by SOC, PT, and strongest relationship to study drug
- Treatment-related TEAEs by SOC and PT
- Administration procedure related TEAEs by SOC and PT
- Treatment-related serious TEAEs by SOC and PT
- Administration procedure related serious TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT

In the summary subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are counted only once. If a subject has the same TEAE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event will be presented and the highest drug relationship, reclassified into related and not related, will be presented on the respective tables. Missing severity is assumed to be severe, and missing relationships are assumed to have a definite relationship to the IMP or intratympanic IMP administration procedure. Percentages are based on the number of subjects in the safety population.

Listings will be provided for all AEs, AEs leading to discontinuation, and SAEs.

[redacted]

[redacted]

[redacted]

10.2 PHYSICAL EXAMINATION

At TV a general physical examination will be conducted by the Investigator or designee. This examination serves to detect obvious and severe abnormalities, which are to be documented on the respective CRF page. The physical examination should be performed prior to the final determination of the subject's eligibility. Body height and body weight will also be recorded. The results of physical examination along with body height & weight will be listed.

10.3 OTHER SAFETY

All other data, such as concomitant medication or findings from tympanometry, otoscopy, nystagmoscopy or Romberg's test will be presented in individual data listings. Concomitant medication will summarized as specified in the section 8.4.

10.3.1 Pregnancy Test

Women of childbearing potential will have a urine pregnancy test performed with a urine dipstick at the site prior to randomization. This test must be negative for the subject to be randomized and to receive IMP. The pregnancy test will be repeated at FUV4. The results of the pregnancy tests will be listed.

10.3.2 Otology and Audiology Assessments

10.3.2.1 Otoscopy and Microscopy

Otoscopy or microscopy will be performed to ensure that the ear canal of the affected ear is clear and to check for the presence of any relevant otologic disease or abnormality such as otitis media, myringitis, or tympanic membrane perforation. It will be performed with an otoscope or ear microscope and appropriately sized speculum

that best fits the ear canal. Otoscopy or microscopy will be performed at each visit. The results of assessment (normal or abnormal) and different type of abnormality will be summarized by treatment and visit.

10.3.2.2 Tympanometry

Tympanometry will be performed to check the presence of otitis media or Eustachian tube dysfunction. It will be performed at TV and all follow-up visits stating at FUV2 (provided tympanic membrane is closed). The results of assessment (normal or abnormal) will be summarized by treatment and visit.

10.3.2.3 Spontaneous Nystagmus

The number of spontaneous nystagmus beats is measured with Frenzel goggles. The assessment is performed in a darkened room and involves a thorough examination of the eye movements to check if the movements are conjugate. Spontaneous nystagmus beats will be recorded for 30 seconds and documented with the direction of beat. The exam will be performed at each visit (excluding cFUV). Observation of > 10 beats / 30 seconds is considered clinically relevant. The test may also be performed by videonystagmography (VNG). The number of spontaneous nystagmus beats in 30 seconds and results of examination (normal, clinically significant abnormal, and not clinically significant abnormal) will be summarized by treatment and visit.

10.3.2.4 Balance Test

Romberg's test (balance test) will be performed at each trial visit (excluding cFUV).

The essential features of the test are as follows:

1. The subject stands with feet together, eyes open and hands by the sides.
2. The subject closes the eyes while the Investigator, or designee, observes for a full minute.

During the test the Investigator, or designee, stands close by as a precaution in order to stop the subject from falling over and hurting himself or herself.

Romberg's test is positive if the patient sways or falls. The result (negative and positive) of the Romberg' will be summarized by treatment and visit.

10.4 EXTENT OF EXPOSURE

All subjects will receive their single dose IMP administered at the clinical site. Thus the extent of exposure will be one day for all subjects.

10.5 TREATMENT COMPLIANCE

The IMP is administered only once and at the site. Compliance with the background therapy regimen will be checked via the background therapy documentation card. It will be recorded by the Investigator or designee in the CRF and subject records. Background

therapy compliance card will be checked and verified at FUV1 and FUV2, and returned to site at FUV3. All used and/or unused packaging has to be returned by the subject to the site. Treatment compliance will be listed.

11 INTERIM ANALYSES

Due to the study being terminated early, the interim analysis is not performed.

12 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Due to the early termination of the study, only 56 subjects are enrolled. The following are changes from the protocol:

- Only partial and missing dates of adverse events and medications are imputed to determine treatment emergence or determine the prior and concomitant medications. All other Imputation of missing values specified in the Protocol section 11.2 is not performed.
- Due to the small sample size, only descriptive analysis is performed in efficacy and safety endpoints.
- Interim analysis will not be performed and conditional power will not be calculated.
- Additional enrollment of subjects based on the results of interim analysis is no longer applicable.
- Tinnitus complete remission is considered given when the subject answers the question about tinnitus presence with "No"; it is not required that in addition both the Tinnitus Loudness Question ($TLQ_{Loudest}$) and Tinnitus Annoyance Question (TAQ_{Worst}) are rated as zero.
- Addition of analysis of efficacy outcomes by severity subgroup (profound / ≥ 90 dB PTA, severe / < 90 dB PTA at baseline).

[redacted]

13 REFERENCE LIST

Efficacy and Safety of AM-111 as Acute Sudden Sensorineural Hearing Loss Treatment (ASSENT): Protocol Number AM-111-CL-15- 01 Version 2.0, 12 Feb 2016.

Bretz, F., Maurer, W., Brannath, W., et al. (2009). A graphical approach to sequentially rejective multiple test procedures. *Stat Med, 28*(4), 586-604.

Cui, L., Hung, H. M., & Wang, S. J. (1999). Modification of sample size in group sequential clinical trials. *Biometrics, 55*(3), 853-857.

Mehta, C. R., & Pocock, S. J. (2011). Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med, 30*(28), 3267-3284.

Newman, C. W., Weinstein, B. E., Jacobson, G. P., et al. (1990). The Hearing Handicap Inventory for Adults: psychometric adequacy and audiometric correlates. *Ear Hear, 11*(6), 430-433.

Nilsson, M.E. , Suryawanshi, S. , Gassmann-Mayer, C., et al. (2013). Columbia-Suicide Severity Rating Scale.

14 SPECIFICATIONS

All tables, listings, figures (TLFs), and statistical analyses will be generated using [redacted] Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. GENERAL CONSIDERATIONS

- [redacted]
- One output file can contain several outputs. / Each output will be stored in a separate file.
- Output files will be delivered in rtf format.
- Numbering of TLFs will follow International Conference on Harmonisation (ICH) E3 guidance.

14.2. TABLE, LISTING, AND FIGURE FORMAT

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:

  Auris Medical
  Protocol AM-111-CL-15-01

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.
- TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- Except TLF specific footnotes, all outputs should include the following at the bottom of each page:

  Program: [redacted] Table/Listing/Figure Generation: DDMMYYYY HH:MM

14.2.3. Display Titles

- Each TLF will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is used . A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Efficacy Analysis Set)

14.2.4. Column Headers

- Analysis set sizes will be presented for each treatment arm in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are left-justified; and
- numbers containing fractional portions are central aligned.

14.2.5.2. Table Conventions

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment arms in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean, Q25, median and Q75 for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Median	XXX.X
Std Dev	X.XX
Q1, Q3	XXX, XXX
Min, Max	XXX, XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). For values that round down to 0.0, it will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment arm who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the ATC level 2, ATC level 4 or SOC with the highest occurrence in the "Overall" column in decreasing order, assuming all terms are coded. Within the ATC level 2, ATC level 4, or SOC, medical history (by preferred term), drugs (by preferred term), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

[redacted]

[redacted]

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing.

15 QUALITY CONTROL

[redacted] developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] provide an overview of the development of such [redacted]

[redacted] describes the QC procedures that are performed [redacted]. Quality control is defined here as the operational techniques and activities undertaken to verify [redacted] produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16 PLANNED TABLES, FIGURES AND LISTINGS

Number	Title
Section 14.1.1	Subject Disposition
Table 14.1.1.1	Screen Failures: (All Subjects)
Table 14.1.1.2.1	Number of Subjects Randomized by Country, Site and Treatment Group: (Randomized Set)
Table 14.1.1.2.2	Number of Subjects Randomized by Initial Strata and Treatment Group: (Randomized Set)
Table 14.1.1.2.3	Number of Subjects by Severity of Hearing Loss, Initial Frequency Range, Background Therapy and Treatment Group: Randomized Set
Table 14.1.1.3.1	Subject Disposition: (Randomized Set)
Table 14.1.1.3.2	Subject Disposition by Initial Strata, Country, Severity of Hearing Loss, Initial Frequency Range, Background Therapy and Treatment Group: (Randomized Set)
Section 14.1.2	Protocol Deviations
Table 14.1.2	Protocol Deviations: (Randomized Set)
Section 14.1.3	Demographic and Baseline Characteristics
Section 14.1.3.1	Subject Demographic and Baseline Characteristics
Table 14.1.3.1.1	Demographics and Baseline Characteristics: (Randomized Set)
Table 14.1.3.1.2	Demographics and Baseline Characteristics by Initial Strata: (Randomized Set)
Table 14.1.3.1.3	Demographics and Baseline Characteristics by Country: (Randomized Set)
Section 14.1.3.2	Baseline Disease Characteristics
Table 14.1.3.2.1	Baseline Hearing Characteristics: (Randomized Set)
Table 14.1.3.2.2	Baseline Hearing Characteristics by Country: (Randomized Set)
Table 14.1.3.2.3	Baseline Hearing Characteristics by Hearing Loss Severity: (Randomized Set)
Table 14.1.3.2.4	Baseline Hearing Characteristics by Initial Strata: (Randomized Set)
Table 14.1.3.2.5	Baseline Hearing Characteristics by Initial Frequency Range: (Randomized Set)
Section 14.1.3.3	Medical History
Table 14.1.3.3.1	Medical History: (Safety Analysis Set)
Section 14.1.4	Medications
Table 14.1.4.1	Prior Medication: (Safety Analysis Set)
Table 14.1.4.2	Concomitant Medication: (Safety Analysis Set)
Section 14.1.5	Study Drug Exposure
Table 14.1.5	Study Drug Administration: (Safety Analysis Set)
Section 14.2	Efficacy Data Summary Tables
Section 14.2.1	Primary Efficacy Parameter
Table 14.2.1.1	Summary of Pure Tone Average (PTA) and Change from Baseline to Follow-up Visits: (Efficacy Analysis Set)

Number	Title
Table 14.2.1.2	Summary of Pure Tone Average (PTA) and Change from Baseline to Follow-up Visits: (Per-Protocol Analysis Set)
Section 14.2.2	Main Secondary Efficacy Parameter
Table 14.2.2.1	Summary of WRS(80 dB) and Change from Baseline to Follow-up Visits: (Efficacy Analysis Set)
Table 14.2.2.2	Summary of WRS(80 dB) and Change from Baseline to Follow-up Visits: (Per-Protocol Analysis Set)
Section 14.2.3	Other Secondary [redacted] Efficacy Parameter
Table 14.2.3.1	Summary of Complete Hearing Recovery Frequency from Baseline to FUV3 and FUV4: (Efficacy Analysis Set)
Table 14.2.3.2.1	Summary of Complete Tinnitus Remission Frequency by Visit: (Efficacy Analysis Set)
Table 14.2.3.2.2	Summary of Tinnitus Loudness and Tinnitus Annoyance and Change from Baseline by Visits: (Efficacy Analysis Set)
Table 14.2.3.3	Summary of $WRS_{(60\ dB)}$ and Change from Baseline to Follow-up Visit 4: (Efficacy Analysis Set)
Table 14.2.3.4	Summary of Hearing Handicap Inventory for Adults Scores by Visits: (Efficacy Analysis Set)
Table 14.2.3.5.1	Categorical Summary of Patient Global Impression of Change (PGIC) in Hearing Loss Severity by Visits: (Efficacy Analysis Set)
Table 14.2.3.5.2	Numeric Summary of Patient Global Impression of Change (PGIC) in Hearing Loss Severity by Visits: (Efficacy Analysis Set)
Table 14.2.3.6.1	Summary of No Improvement in PTA (< 15 dB) Frequency from Baseline to FUV3 and FUV4: (Efficacy Analysis Set);
Table 14.2.3.6.2	Summary of No Marked Improvement in PTA (< 30 dB) Frequency from Baseline to FUV3 and FUV4: (Efficacy Analysis Set).
Section 14.3	Safety Data Summary Tables
Section 14.3.1	Adverse Events
Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events (TEAE): (Safety Analysis Set)
Table 14.3.1.2	Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.3	Subjects with Treatment-Emergent Adverse Events by Preferred Term: (Safety Analysis Set)
Table 14.3.1.4	Subjects with Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.5	Subjects with Treatment-Emergent Adverse Events Resulting in Study Withdrawal by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.6	Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity: (Safety Analysis Set)
Table 14.3.1.7	Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Study Drug Relationship: (Safety Analysis Set)

Number	Title
Table 14.3.1.8	Subjects with Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.9	Subjects with Administration Procedure Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.10	Subjects with Treatment-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.11	Subjects with Administration Procedure Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: (Safety Analysis Set)
Table 14.3.1.12	Subject with Treatment-Emergent Adverse Events Leading to Death by SOC and PT: (Safety Analysis Set)
Section 14.3.2	Listings of Deaths, Other Serious and Significant Adverse Events
Table 14.3.2.1	On Study AEs Resulting in Deaths, Listing
Table 14.3.2.2	Serious Treatment-Emergent Adverse Events, Listing
Table 14.3.2.3	Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Drug, Listing
Section 14.3.4	Abnormal Laboratory Value (each patient)
Section 14.3.4.1	Clinical Laboratory Data
Section 14.3.4.1.1	Hematology Data
Table 14.3.4.1.1.1	Summary of Hematology Value and Change from Baseline: (Safety Analysis Set)
Table 14.3.4.1.1.2	Hematology Shift from Baseline: (Safety Analysis Set)
Section 14.3.4.1.2	Biochemistry Data
Table 14.3.4.1.2.1	Summary of Biochemistry Value and Change from Baseline: (Safety Analysis Set)
Table 14.3.4.1.2.2	Biochemistry Shift from Baseline: (Safety Analysis Set)
Section 14.3.4.1.3	Virology Data
Table 14.3.4.1.3	Summary of Virology Value: (Safety Analysis Set)
Section 14.3.4.2	Vital Signs
Table 14.3.4.2.1	Summary of Vital Signs and Change from Baseline: (Safety Analysis Set)
Section 14.3.4.3	Other Safety Summaries
Table 14.3.4.3.1	Summary of Pure Tone Audiometry in Air Conduction and Change from Baseline in All Frequencies: (Safety Analysis Set)
Table 14.3.4.3.2	Summary of Hearing Deterioration by Air Conduction: (Safety Analysis Set)
Table 14.3.4.3.3	Summary of Pure Tone Audiometry in Bone Conduction and Change from Baseline in All Frequencies: (Safety Analysis Set)
Table 14.3.4.3.4	Summary of Hearing Deterioration by Bone Conduction: (Safety Analysis Set)

Number	Title
Listing 16.2.1.1	Subject Disposition: (All Subjects)
Listing 16.2.1.2	Eligibility: (All Subjects)
Listing 16.2.2	Protocol Deviations: (Randomized Set)
Listing 16.2.3	Subjects Excluded from Analysis Sets: (Randomized Set)
Listing 16.2.4.1.1	Demographics and Baseline Characteristics: (Randomized Set)
Listing 16.2.4.1.2	Baseline Hearing Characteristics: (Randomized Set)
Listing 16.2.4.2	Medical History: (Randomized Set)
Listing 16.2.4.3	History of Current Hearing Loss: (Randomized Set)
Listing 16.2.4.4	Pregnancy Test: (Randomized Set)
Listing 16.2.5.1	Prior and Concomitant Medication: (Randomized Set)
Listing 16.2.5.2	Study Drug Administration: (Randomized Set)
Listing 16.2.5.3	Background Corticosteroid Therapy: (Randomized Set)
Listing 16.2.6.1	Tinnitus History and Characteristics: (Randomized Set)
Listing 16.2.6.2	Tinnitus Description and Characteristics by Visit : (Randomized Set)
Listing 16.2.6.3	Tinnitus Presence or Absence, and Numerical Rating Scales by Visit: (Randomized Set)
Listing 16.2.6.4	Weekly Tinnitus Presence or Absence and Numerical Rating Scales by Diary: (Randomized Set)
Listing 16.2.6.5	Patient Global Impression of Change (PGIC) : (Randomized Set)
Listing 16.2.6.6	Pure Tone Audiometry (Air): (Randomized Set)
Listing 16.2.6.7	Improvement in Pure Tone Audiometry (Randomized Set)
Listing 16.2.6.8	Pure Tone Audiometry (Bone): (Randomized Set)
Listing 16.2.6.9	Speech Audiometry (WRS at 80 dB in quiet): (Randomized Set)
Listing 16.2.6.10	Speech Audiometry (WRS at 60 dB in quiet): (Randomized Set)
Listing 16.2.6.11	HHIA Questionnaire: (Randomized Set)
Listing 16.2.7.1	Treatment Emergent Adverse Events: (Randomized Set)
Listing 16.2.8.1.1	Laboratory Parameters: Hematology: (Randomized Set)
Listing 16.2.8.1.2	Laboratory Parameters: Biochemistry: (Randomized Set)
Listing 16.2.8.1.3	Laboratory Parameters: Virology: (Randomized Set)
Listing 16.2.8.1.4	Laboratory Parameters: HbA1c: (Randomized Set)
Listing 16.2.8.2.1	Vital Signs: (Randomized Set)
Listing 16.2.8.2.2	Spontaneous Nystagmus: (Randomized Set)
Listing 16.2.8.2.3	Physical Exam Results: (Randomized Set)
Listing 16.2.8.2.4	Otoscopic Examination: (Randomized Set)
Listing 16.2.8.2.5	Tympanometry: (Randomized Set)
Listing 16.2.8.2.6	Columbia-Suicide Severity Rating Scale (C-SSRS) - At Treatment Visit: (Randomized Set)
Listing 16.2.8.2.7	Columbia-Suicide Severity Rating Scale (C-SSRS) - Since Last Visit: (Randomized Set)
Listing 16.2.8.2.8	Balance Test: (Randomized Set)
Listing 16.2.8.2.9	Day 56 Follow-Up: (Randomized Set)

17 APPENDICES

APPENDIX 1: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

At Treatment visit (TV) prior IMP administration:

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on on living with the pain or how you were feeling) (0) Does not apply	____
SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime

Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐ Total # of preparatory acts _____

Suicide: Suicidal behavior was present during the assessment period?			Yes ☐ No ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Since Last Visit version (FUV2, FUV3 and FUV4)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____
SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit

Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐ Total # of preparatory acts _____
Suicide: Death by suicide occurred since last assessment.	Yes ☐ No ☐
	Most Lethal Attempt Date:

Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 2: TINNITUS PRESENCE OR ABSENCE

TV (D0): Baseline assessment regarding the presence or absence of tinnitus

Subject instruction at baseline:

If someone hears sound or noise in one or both ear(s) or in the head which no one else can hear, then this is called tinnitus. If you are affected, you may hear a sound such as ringing, humming, hissing, buzzing, roaring or other sounds. You may hear the sounds all of the time or some of the time. The sound may appear to be louder or softer to you during the day or from day to day, that is the tinnitus loudness may vary, or the loudness is always more or less the same. Tinnitus does not have to be annoying, and it frequently disappears sometime after experiencing acute hearing loss. However, tinnitus may be very annoying to some people - especially if it persists, or at some particular times, for example when trying to relax or fall asleep.

D3 - D91: Tinnitus presence or absence

For follow-up assessments, questions "Are you experiencing tinnitus right now" and "Have you experienced tinnitus in the past week" will be answered by subjects at trial visits and on a weekly basis in a diary.

As explained to you by the Investigator, tinnitus is a sound or noise that you can hear in one or both ear(s) or in the head which no one else can hear. If you are affected, you may hear a sound such as ringing, humming, hissing, buzzing, roaring or other sounds. You may hear the sounds all of the time or some of the time. The sound may appear to be louder or softer to you during the day or from day to day, that is, the tinnitus loudness may vary, or the loudness is always more or less the same. Tinnitus does not have to be annoying, and it frequently disappears sometime after experiencing acute hearing loss. However, tinnitus may be very annoying to some people - especially if it persists, or at some particular times, for example when trying to relax or fall asleep.

APPENDIX 3: [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [redacted]
[redacted] [redacted]
[redacted] [redacted]s

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] [redacted]
[redacted] [redacted]

APPENDIX 4: HHIA QUESTIONNAIRE

The following questionnaire has 25 questions. The purpose of this questionnaire is to identify the problems your hearing loss may be causing you. You must choose only one answer for each question. Some questions are similar, but in reality they have subtle differences which enable a better assessment of the answers. There is no right or wrong answer. Circle No, Sometimes or Yes for each question; you should check the one you find most adequate to your case or situation. Do not skip a question if you avoid a situation because of a hearing problem.

Nr	Question	No	Some-times	Yes
1	Does a hearing problem cause you to use the phone less often than you would like?	O	O	O
2	Does a hearing problem cause you to feel embarrassed when meeting new people?	O	O	O
3	Does a hearing problem cause you to avoid groups of people?	O	O	O
4	Does a hearing problem make you irritable?	O	O	O
5	Does a hearing problem cause you to feel frustrated when talking to members of your family?	O	O	O
6	Does a hearing problem cause you difficulty when attending a party?	O	O	O
7	Does a hearing problem cause you difficulty hearing/understanding co-workers, clients, or customers?	O	O	O
8	Do you feel handicapped by a hearing problem?	O	O	O
9	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours?	O	O	O
10	Does a hearing problem cause you to feel frustrated when talking to co-workers, clients, or customers?	O	O	O
11	Does a hearing problem cause you difficulty in the movies or theatre?	O	O	O
12	Does a hearing problem cause you to be nervous?	O	O	O
13	Does a hearing problem cause you to visit friends, relatives, or neighbours less often than you would like?	O	O	O
14	Does a hearing problem cause you to have arguments with family members?	O	O	O
15	Does a hearing problem cause you difficulty when listening to TV or radio?	O	O	O
16	Does a hearing problem cause you to go shopping less often than you would like?	O	O	O
17	Does any problem or difficulty with your hearing upset you at all?	O	O	O
18	Does a hearing problem cause you to want to be by yourself?	O	O	O
19	Does a hearing problem cause you to talk to family members less often than you would like?	O	O	O
20	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?	O	O	O
21	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?	O	O	O
22	Does a hearing problem cause you to feel depressed?	O	O	O
23	Does a hearing problem cause you to listen to TV or radio less often than you would like?	O	O	O
24	Does a hearing problem cause you to feel uncomfortable when talking to friends?	O	O	O
25	Does a hearing problem cause you to feel left out when you are with a group of people?	O	O	O

Newman, C. W., Weinstein, B. E., Jacobson, G. P., & Hug, G. A. (1990). The Hearing Handicap Inventory for Adults: Psychometric adequacy and audiometric correlates. Ear & Hearing, 11, 430–433

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