Auris Medical
Cochlear therapies

Protocol Version Final 3.0
dated 24 May 2017

Investigational product:	AM-111 gel for injection
Indication:	Treatment of idiopathic sudden sensorineural hearing loss
Clinical phase:	Phase III
Study code:	**AM-111-CL-15-01**
Study title:	Efficacy and Safety of AM-111 as **A**cute **S**udden **Sen**sorineural Hearing Loss **T**reatment (**ASSENT**)
IND:	122780
EudraCT:	2016-005166-58
Sponsor:	Auris Medical Inc. 500 North Michigan Avenue Suite 600 Chicago, IL 60611
EU Legal Representative	Auris Medical Ltd. The Black Church, St. Mary's Place Dublin 7, Ireland

Good Clinical Practice (GCP) Compliance
The trial will be performed in compliance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) Guidelines, the US Code of Federal Regulations 21 CFR 50, 54, 56, 312 and 314, and in accordance with the Declaration of Helsinki.

Signature Page

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Reviewed and approved by:

Sponsor

Corporate Confidential Information

Signature page for the Investigator

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This Clinical Trial will be conducted in accordance with the trial protocol, the International Conference on Harmonisation (ICH) harmonized tripartite guideline on Good Clinical Practices (GCP) (ICH E6), as well as Food and Drug Administration (FDA) regulations for investigational new drugs outlined in 21 CFR, Section 312, 50 and 56, and the ethical principles outlined in the Declaration of Helsinki dated 1989 (US sites), respectively in its most current version.

As an Investigator for the trial, I have read this protocol and agree to follow this protocol in accordance with all the above-mentioned regulations.

Date: _____

Signature: _____

Name: _____
Printed or typed

Site name _____
and address: _____
_____
_____
_____

Address list of involved organizations

Sponsor

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Legal Representative in the European Union

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Dublin 7, Ireland
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Emergency Medical Contact (24/7)

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Clinical Sites

Approximately 80 sites located in the U.S., Canada, South Korea, Belgium, Czech Republic, France, Poland, Republic of Serbia and possibly other countries will participate in this trial. A list of principal investigators and their affiliations is kept in the Trial Master File (TMF).

Contract Research Organization

[redacted]

Biostatistics

[redacted]

Medical Monitors

[redacted]

[redacted]

[redacted]

[redacted]

SAE Reporting Line

[redacted]

Central Clinical Laboratory

[redacted]

[redacted]

[redacted]

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List of abbreviations

AAT ..... Acute Acoustic Trauma
AE ..... Adverse Event
Alb ..... Albumin
ALT ..... Alanine Aminotransferase
ALP ..... Alkaline Phosphatase
ANCOVA ..... Analysis of Covariance
ASNHL ..... Acute Sensorineural Hearing Loss
AST ..... Aspartate Aminotransferase
BUN ..... Blood Urea Nitrogen
°C ..... Degree Celsius
cFUV ..... Conditional Follow-Up Visit
Ca ..... Calcium
cGMP ..... Current Good Manufacturing Practices
Cl ..... Chloride
CONSORT ..... Consolidated Standards of Reporting Trials
CP ..... Conditional Power
CRA ..... Clinical Research Associate
CRE ..... Creatinine
CRF ..... Case Report Form
CRO ..... Contract Research Organization
CSF ..... Cerebrospinal Fluid
C-SSRS ..... Columbia-Suicide Severity Rating Scale
D ..... Day
daPa ..... Deca Pascal
dB ..... Decibel
D-JNKI-1 ..... D-stereoisomer of c-Jun N-terminal Kinase Inhibitor
eCRF ..... Electronic Case Report Form
EDC ..... Electronic Data Capture
ENT ..... Ear Nose Throat
FUV ..... Follow-up Visit
γ-GTP ..... Gamma-Glutamyl Transpeptidase
GCP ..... Good Clinical Practice
GMP ..... Good Manufacturing Practice
HBV ..... Hepatitis B Virus
Hct ..... Hematocrit
HCV ..... Hepatitis C Virus
Hgb ..... Hemoglobin
HHIA ..... Hearing Handicap Inventory for Adults
HIV ..... Human Immunodeficiency Virus
IB ..... Investigator's Brochure
ICH ..... International Conference on Harmonisation
ICF ..... Informed Consent Form
IDMC ..... Independent Data Monitoring Committee
IEC ..... Independent Ethics Committee
IMP ..... Investigational Medicinal Product
IRB ..... Institutional Review Board
ISF ..... Investigator Site File
ISO ..... International Organisation for Standardisation
ISSNHL ..... Idiopathic Sudden Sensorineural Hearing Loss
ITT ..... Intention to Treat
i.v. ..... Intravenous
IWRS ..... Interactive Web Response System
JNK ..... c-Jun N-terminal Kinase

K ..... Potassium
kHz ..... Kilohertz
LDH ..... Lactate Dehydrogenase
LOCF ..... Last Observation Carried Forward
LS ..... Least Square
µg ..... Microgram
Na ..... Sodium
NOAEL ..... No Observed Adverse Event Level
P ..... Phosphorus
PGIC ..... Patient Global Impression of Change
Plt ..... Platelet
PP ..... Per Protocol
PTA ..... Pure Tone Average
Q25 ..... 25%-Quantile
Q75 ..... 75%-Quantile
QC ..... Quality Control
q.s. ..... quantum satis
RBC ..... Red Blood Cell
RSI ..... Reference Safety Information
RWM ..... Round Window Membrane
SAE ..... Serious Adverse Event
SAP ..... Statistical Analysis Plan
SAR ..... Serious Adverse Reaction
SC ..... Subject Contact
SD ..... Standard Deviation
SOP ..... Standard Operating Procedure
SPL ..... Sound Pressure Level
SUSAR ..... Suspected Unexpected Serious Adverse Reaction
T-bil ..... Total bilirubin
TEAE ..... Treatment Emergent Adverse Event
TAQ ..... Tinnitus Annoyance Question
TLQ ..... Tinnitus Loudness Question
TMF ..... Trial Master File
TP ..... Total Protein
TV ..... Treatment Visit
UA ..... Uric Acid
USA / US ..... United States of America
VNG ..... Videonystagmography
WHO ..... World Health Organization
WBC ..... White Blood Cell
WMA ..... World Medical Association
WRS ..... Word Recognition Score
$WRS_{(60\ dB)}$ ..... Word Recognition Score at 60 dB SPL
$WRS_{(80\ dB)}$ ..... Word Recognition Score at 80 dB SPL

1 Protocol Summary

Study title	Efficacy and Safety of AM-111 as **A**cute Sudden **Sen**sorineural Hearing Loss **T**reatment (**ASSENT**)
Study code	AM-111-CL-15-01
IND	122780
EudraCT	2016-005166-58
Sponsor	Auris Medical Inc.
Investigational Medicinal Product	AM-111 gel for injection
Study phase	Phase III
Indication	Treatment of idiopathic sudden sensorineural hearing loss
Introduction and rationale	The investigational medicinal product (IMP) is AM-111 gel for injection. The active ingredient of AM-111 is D-JNKI-1, a synthetic cell-penetrating peptide, consisting of 31 dextrorotatory amino acids. The peptide acts as a c-Jun N-Terminal Kinase (JNK) ligand that selectively blocks phosphorylation of the transcription factor c-Jun as well as other nuclear substrates by competitive inhibition, thereby attenuating or blocking apoptosis or inflammatory responses. To date, no pharmaceutical treatment for acute sensorineural hearing loss (ASNHL) with clear evidence-based efficacy is available or has been approved by the FDA. Commonly, corticosteroids are administered orally as an initial therapy over 10 to 14 days; alternatively they are administered intratympanically every 3 to 7 days for a total of 3-4 doses (Stachler *et al.*, 2012) as initial or salvage therapy. The current clinical practice guideline of the American Academy of Otolaryngology – Head and Neck Surgery Foundation for sudden hearing loss acknowledges the lack of unequivocal evidence for efficacy, but provides for corticosteroids as a treatment option (Stachler *et al.*, 2012). Non-clinical studies with D-JNKI-1 have shown that inhibition of the JNK signaling pathway is successful in protecting cochlear hair cells and spiral ganglion neurons and thus preserving auditory function. A therapeutic exploratory Phase II clinical trial demonstrated that a single dose of AM-111 is safe and effective in the treatment of severe to profound hearing loss within 48 hours from ASNHL onset. Subjects with severe to profound hearing loss from acute acoustic trauma or idiopathic sudden sensorineural hearing loss (ISSNHL) treated with AM-111 0.4 mg/mL showed a statistically significantly better improvement in pure tone hearing thresholds as well as in speech discrimination, assessed by word recognition, than subjects in the placebo group. The superior improvement, which was also clinically relevant, was observed as early as 3 days after treatment, and persisted to D7, D30 and as trend to D90. The present Phase III trial is being conducted to confirm the efficacy and safety of AM-111 in patients suffering from ISSNHL. A detailed description of the chemistry, pharmacology, and safety of AM-111 is provided in the Investigator's Brochure.

Objectives	**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. **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 the safety and local tolerance of AM-111. [redacted].
Subject population	• Subjects suffering from unilateral ISSNHL within 72 hours from onset. • A sufficient number of subjects will be enrolled in order to randomize approximately 300 subjects to either a single dose of AM-111 0.4 mg/mL (100 subjects), AM-111 0.8 mg/mL (100 subjects) or placebo (100 subjects).
Inclusion and exclusion criteria	**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 2 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. **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 greater than 20 dB at the average of 3 contiguous test 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 C-SSRS; 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 HIV, hepatitis B or hepatitis C infection, 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).
Investigational plan	This is a Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center, efficacy and safety trial of AM-111 in the treatment of subjects suffering from ISSNHL. Subjects meeting all entry criteria will be randomized in a 1:1:1 ratio. [redacted] The study consists of one treatment visit (TV) and a 13-week follow-up period with follow-up visits (FUVs) at D3, D7, D28 and D91, one conditional FUV (cFUV) at D14 and one subject contact at D56. Study participants will receive, after topical anesthesia of the tympanic membrane, the IMP (AM-111 0.4 mg/mL or 0.8 mg/mL or placebo) administered into the affected ear at TV (D0). Following the administration, subjects will rest in a supine or reclined position for 30 minutes. Study participants will receive a course of oral corticosteroids as background therapy for 14 days followed by 5-day taper unless medically contraindicated or declined by the subject. See Table 1: Schedule of visits and assessments.
Clinical sites	Approximately 80 sites
Visit schedule and duration of treatment	Treatment Visit (TV) D0 Follow-up Visit 1 (FUV1) D3±1 Follow-up Visit 2 (FUV2) D7±2

	Conditional Follow-up Visit (cFUV) D14±3 Follow-up Visit 3 (FUV3) D28±5 Subject Contact (SC) D56±7 Follow-up Visit 4 (FUV4) D91±7
Study procedures	**Efficacy assessments** • Pure tone audiometry (air and bone conduction); • Speech audiometry (WRS) at 80 dB and 60 dB Sound Pressure Level (SPL); • Tinnitus evaluation (presence/absence, patient-rated loudness and annoyance); • Hearing Handicap Inventory for Adults score (HHIA); • Patient global impression of change (PGIC) of hearing loss severity. **Safety assessments** • Vital Signs; • Otoscopy/microscopy; • Tympanometry; • Pure tone audiometry; • Spontaneous nystagmus (Frenzel goggles or videonystagmography); • Balance test (Romberg's test); • Hematology (hemoglobin, hematocrit, red blood cell, white blood cell, platelet and white blood cell differential); • Blood biochemistry: (sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, total protein and albumin); • Urine pregnancy test (if applicable); • Adverse Events (AEs); • Concomitant medications; • Columbia-Suicide Severity Rating Scale (C-SSRS).
Test product and dose	AM-111 0.4 mg/mL, [redacted] AM-111 0.8 mg/mL, [redacted]
Reference therapy and dose	Placebo (matching the AM-111 gel), [redacted]
Mode of administration	Intratympanic injection.
Non-investigational product (background treatment)	Oral corticosteroid course for 14 days followed by a 5-day taper; either • Prednisone or prednisolone 1 mg/kg/day, at a maximum 60 mg/day (taper 50 mg, 40 mg, 30 mg, 20 mg, and to 10 mg), or • Methylprednisolone 0.8 mg/kg/day, at a maximum 48 mg/day (taper 40 mg, 32 mg, 24 mg, 16 mg, and to 8 mg). The dose is to be taken undivided in the morning and can be started within 36 hours prior to randomization. The background corticosteroid treatment may be omitted in case of medical contraindication of oral corticosteroids or if declined by the subject.

Study endpoints	**Efficacy endpoints** *Primary efficacy endpoint* Absolute improvement in PTA from baseline to FUV4. *Main secondary efficacy endpoint* • Absolute improvement in $WRS_{(80dB)}$ from baseline to FUV4 *Other secondary efficacy endpoints* • Absolute improvement in PTA from baseline to FUV1, FUV2 and FUV3; • Absolute improvement in $WRS_{(80dB)}$ from baseline to follow-up visits FUV1, FUV2 and FUV3; • Frequency of complete tinnitus remission at FUV4 in subjects with ISSNHL-related tinnitus at baseline. [redacted] **Safety endpoints** *Primary safety endpoint* 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. *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 Ad-

	verse Events (SAEs), assessed for causal relationship with respect to: o The IMP, and /or o The intratympanic IMP administration procedure. [redacted]
Statistical methods	**Analysis Sets** The Efficacy Analysis Set includes all randomized subjects who were treated with either AM-111 or placebo, 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. The Per Protocol (PP) analysis set includes all subjects from the Efficacy Analysis Set without major protocol deviations which would interfere with the analysis of the primary endpoint or main secondary endpoint. Subjects are analyzed according to the treatment received. The Safety Analysis Set includes all subjects who were treated with either AM-111 or placebo. Subjects are analyzed according to the treatment received. **Statistical methods** 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), [redacted]

	[redacted] **Sample Size Calculation** The sample size calculation is based on the primary endpoint. [redacted] **Interim Analysis** After 50% of the subjects have reached FUV4, an independent statistician will perform an interim analysis to check the assumptions made for sample size calculation and increase the sample size if necessary. No stopping for efficacy or futility is planned.
Trial timelines	Planned start date (first subject enrolled): Q2 2016 Planned completion date (last subject last visit): Q2 2018

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.

2 Introduction

2.1 Background

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) is one of the most frequently occurring types of acute sensorineural hearing loss (ASNHL). ISSNHL is a "suddenly occurring, usually unilateral sensorineural hearing loss of varying severity up to complete deafness without any apparent reason" (AWMF, 2014).

ISSNHL may be accompanied by other symptoms of cochlear dysfunction such as tinnitus, or of vestibular dysfunction such as vertigo (Cvorovic *et al.*, 2008) and frequently prompts an urgent medical visit (Stachler *et al.*, 2012). Different theories about the etiology of ISSNHL exist (e.g. infection, vascular impairment, autoimmune disease, membrane rupture), but in most cases it remains unknown.

The natural course of ISSNHL is characterized by frequent partial or complete recovery of hearing loss in the days and weeks following the incident. While spontaneous recovery rates varying between 35 and 68% have been reported in the literature for ISSNHL, these numbers are not considered reliable due to methodological shortcomings, especially a lack of an appropriate control population (Labus *et al.*, 2010). If it persists, permanent or chronic hearing loss results, which may have serious impact on professional and personal lives. Severe to profound hearing loss has been shown to result in high societal costs mostly due to reduced work productivity (Kochkin, 2005; Mohr *et al.*, 2000). Individuals with unilateral deafness experience major challenges when communicating in situations with background noise, in poor acoustic surroundings, and experience feelings of exclusion and reduced well-being (Wie *et al.*, 2010).

Despite extensive research into the pathophysiology of ASNHL and considerable clinical interest, there still exists no therapy that has shown unequivocal evidence of efficacy in the treatment of ISSNHL. The most commonly used therapeutics for the treatment of ISSNHL are steroids to reduce inflammation and swelling, and treatments which seek to improve the blood circulation and oxygenation of the inner ear such as vasodilators, plasma expanders, or hyperbaric oxygen. However, Cochrane reviews and other meta-analyses found no evidence of therapeutic benefit for currently employed treatments such as steroids, rheologics or hyperbaric oxygen (Agarwal & Pothier, 2009; Awad *et al.*, 2012; Bennett *et al.*, 2012; Conlin & Parnes, 2007a, 2007b; Wei *et al.*, 2013). The molecular mechanisms underlying corticosteroid treatment are still not well characterized (Meltser & Canlon, 2011). Nevertheless, considering the devastating effect of SSNHL and the profound impact on quality of life, the clinical guidelines of the American Academy of Otolaryngology-Head and Neck Surgery 2012 conclude that even a small possibility of hearing improvement makes this a reasonable treatment to offer to patients, and therefore propose initial corticosteroids as a treatment option: "Clinicians may offer corticosteroids as initial therapy to patients with ISSNHL" (Stachler *et al.*, 2012).

As there is no treatment option with clear evidence of benefit, a treatment for ISSNHL that protects sensorineural structures and thus prevents permanent sensorineural hearing loss is a clear unmet medical need.

2.2 Name and description of the Investigational Medicinal Product

The investigational product is AM-111. Its active pharmaceutical ingredient is the D-stereoisomer of c-Jun N-terminal Kinase Inhibitor 1 (D-JNKI-1), a synthetic cell-penetrating peptide consisting of 31 D-amino acids. The peptide is a c-Jun N-terminal kinase (JNK) ligand that selectively blocks the JNK MAPK cascade by a competitive mechanism within the cell, thereby preventing apoptosis of sensorineural structures in the cochlea. In addition, the peptide inhibits activation of genes which encode inflammatory molecules. Thanks to its active transporter sequence, D-JNKI-1 has the capability to effectively cross biological membranes and transfect cells and their nuclei – it crosses the round window membrane (RWM) quickly, diffuses rapidly inside the cochlea up to the apex and transfects hair cells, supporting cells and other tissues. In addition, due to its dextrorotatory structure the compound has a prolonged pharmacological activity, allowing for an extended therapeutic benefit with one single administration.

2.3 Summary of findings

2.3.1 Summary of efficacy data

Non-clinical studies with D-JNKI-1 demonstrate that the investigational medicinal product (IMP) is effective in treating ASNHL provoked by various cochlear stress incidents. Locally applied D-JNKI-1 crosses the round window membrane rapidly, and within hours it has been taken up by virtually all cochlear structures, including hair cells, spiral ganglion neurons, supporting cells and spiral ligament. D-JNKI-1 has been shown to protect from permanent hearing loss in case of overexposure to noise, cochlear electrode insertion trauma, cochlear ischemia, bacterial otitis media, labyrinthitis or aminoglycoside ototoxicity (Barkdull *et al.*, 2007; Eshraghi *et al.*, 2013; Eshraghi *et al.*, 2006c; Grindal *et al.*, 2010; Omotehara *et al.*, 2011; Wang *et al.*, 2007; Wang *et al.*, 2003). D-JNKI-1 can rescue hair cells and therefore hearing function when the treatment is administered 3 days prior to acoustic trauma or within several hours after the insult. The otoprotective effect is dose-dependent and reaches a maximum at 0.2 to 0.4 mg/mL in the guinea pig when administered within several hours from an acute acoustic trauma (AAT).

Local administration to the inner ear allows using much lower doses than with systemic administration. This reduces systemic exposure and limits the potential for adverse events. In tissues, D-JNKI-1 is scavenged into macrophages and macrophage-type cells. The stability of the D-JNKI-1 peptide can primarily be attributed to its D-amino acid configuration.

Single dose toxicity studies with topical administration to the inner ear of guinea pigs and rabbits confirmed the favorable safety profile of D-JNKI-1. Histopathological examinations revealed no significant loss of hair cells up to 11.4 mg/mL in guinea pigs and up to 6 mg/mL in rabbits. Overall, local tolerance of D-JNKI-1 in the middle ear was shown to be very good. Occurrence of hair cell loss at 12 or 36 mg/mL suggests a proapoptotic effect of D-JNKI-1 at high concentrations. The 'no observed adverse event level' (NOAEL) was determined at 6 mg/mL in rabbits and 11.4 mg/mL in guinea pigs, corresponding to an absolute dose of 1.2 mg and 1.1 mg, respectively. Based on the planned concentrations for human use of 0.4 mg/mL and 0.8 mg/mL this corresponds to a safety factor of 114 x to 125 x and 57 x to 63 x, respectively.

AM-111 is administered to subjects in [redacted]. Following this well established minimally-invasive procedure, subjects will rest in a supine or reclined position for 30 minutes with their treated ear facing upwards to allow for diffusion across the RWM into the cochlea, the target site of action. A gel formulation was chosen to facilitate the contact with the RWM and to retain AM-111 in the middle ear, thereby avoiding loss via the Eustachian tube that might be caused due to swallowing, sneezing, or brusque head movements.

The first clinical trial (AM-111-AAT-PI) with AM-111 gel for injection was conducted in January 2006 as a randomized, double-blind, parallel dose trial in two centers in Germany with 11 subject suffering from AAT as a consequence of exposure to New Year's firecrackers (Suckfuell *et al.*, 2007). This first clinical trial showed that AM-111 at 0.4 and 2.0 mg/mL was well tolerated, and that the drug product was safe. It further provided some first indications of efficacy.

A second clinical trial (AM-111-CL-08-01) in subjects suffering from acute hearing loss following AAT or ISSNHL was completed in 2012 (Suckfuell *et al.*, 2014). This double-blind, randomized, placebo-controlled and multicenter trial evaluated the efficacy, safety and local tolerance of AM-111 0.4 mg/mL and 2.0 mg/mL. In total, 210 subjects presenting within 48 hours following AAT or idiopathic sudden sensorineural hearing loss were included and treated with a single intratympanic administration of AM-111 or placebo.

The trial failed to demonstrate a statistically significant treatment benefit for the entire trial population as mild to moderate ASNHL cases showed unexpectedly strong spontaneous recovery. For severe to profound ASNHL subjects (PTA $\geq$ 60 dB) treated with AM-111 0.4 mg/mL post-hoc analysis revealed a statistically significant, clinically relevant and persistent improvement in hearing and speech discrimination and a higher frequency of complete remission of ASNHL-related tinnitus compared to placebo. Comparison of AM-111 0.4 mg/mL versus placebo in this population showed that PTA improvement at Day 7 was 12.1 dB higher (p=0.017), relative PTA improvement 19.5 percentage points

better (p=0.021); the frequency of complete recovery was 17.7 percentage points higher in the logistic regression (p=0.044). The word recognition score also showed statistically significantly better improvement: at Day 7, 21.5 and 18.3 percentage points at 60 and 80 dB (p=0.023 and 0.019, respectively). The high dose group overall showed improvement against both the low dose and the placebo group, without reaching statistical significance. The study medication as well as the intratympanic administration procedure was well tolerated.

[redacted]

2.3.2 Summary of accumulated adverse event data

A total of 221 subjects were included in the two clinical trials conducted with AM-111 (AM-111-AAT-PI, AM-111-CL-08-01). Seventy-five subjects received a single dose [redacted] AM-111 at a concentration of 0.4 mg/mL (low dose), 74 subjects received AM-111 at the concentration of 2.0 mg/mL (high dose) and 72 subjects were randomized to receive the matching placebo.

In subjects who received any dose of AM-111, 57 patients reported at least 1 adverse event, of which 18 reported treatment-related AEs. Only four treatment-related adverse event terms were reported in more than 1 patient, and these were tinnitus (7 patients, 4.7%), hearing impaired (6 patients, 4.0%), ear pain (3 patients, 2.0%), and incision site complications (2 patients, 1.3%). Ear discomfort, vertigo, autophony, otitis externa, otitis media, nausea and otoacoustic emission test abnormal were each reported by 1 patient. One serious adverse event (SAE) of deafness neurosensory was considered related to study drug. No fatal or life-threatening AE was reported.

The majority of AEs were local, mild or moderate in severity and concerned hearing and tinnitus. Detailed analysis of hearing deterioration at Days 3 and 7 pointed most often to the ongoing underlying pathology as cause; three cases were related to the myringotomy, and one case to middle ear infection (fully resolved). The majority of tinnitus-related AEs was observed only after Day 7 and thus considered unrelated. The number of subjects with procedure-related AEs (ear discomfort or pain, incision site complications, middle ear infection) was < 5%. By Day 7, the tympanic membrane was closed again in all patients except 7 (mild, fully resolved subsequently). Vital signs essentially remained stable throughout the observation period, and the incidence of spontaneous nystagmus decreased in all treatment groups. Further details of the adverse event profile are provided in the Investigator Brochure of AM-111.

In summary, the trials confirmed the safety and local tolerance of a single dose intratympanic administration of AM-111 in subjects suffering from ASNHL. The drug product was well tolerated in the middle ear, did not negatively impact the auditory or vestibular function, and there were no systemic adverse events. The frequency of expected transient procedure related effects such as transient caloric vertigo, middle ear inflammation, ear pain or injection site pain, altered hearing or tinnitus, was low.

2.4 Trial rationale

Clinical experience with AM-111 shows that a single dose of intratympanic AM-111 at a concentration of up to 2.0 mg/mL is well tolerated, and that the drug product is safe. Trial outcomes showed rapid and clinically relevant improvement in various measures of hearing function, speech discrimination and also in ASNHL-related tinnitus.

The present trial aims to demonstrate and confirm that a single dose of AM-111 0.4 mg/mL will provide a therapeutic benefit through a significant improvement in hearing following an incident of severe to profound ISSNHL. An improvement in hearing threshold of ≥10 dB is considered as clinically relevant. Improvement in hearing recovery shall be supported by improvement in word recognition in quiet as well as in the rate of complete tinnitus remission. The trial shall further evaluate potential incremental treatment benefits from the use of a higher concentration, 0.8 mg/mL, and the safety and local tolerance of AM-111.

2.5 Potential benefits and risks

2.5.1 Potential benefits

If left untreated, severe to profound ISSNHL may have chronically debilitating consequences in the form of irreversible, chronic sensorineural hearing loss and seriously impact professional and personal lives, e.g. through:

- irritability, negativism and anger;
- fatigue, tension, stress and depression;
- avoidance or withdrawal from social situations;
- social rejection and loneliness;
- reduced alertness and increased risk to personal safety (loss of monitoring of environmental warning sounds);
- impaired memory and ability to learn new tasks;
- reduced job performance and earning power;
- diminished psychological and overall health.

To date, no satisfactory pharmacological treatment for ISSNHL exists with clear treatment benefits proven in prospective randomized clinical studies (Suckfuell et al., 2014). Nevertheless, the trial takes into account current clinical practice and the relevant treatment guideline by allowing for oral corticosteroids as a background therapy. Corticosteroids are offered to all study participants, unless medically contraindicated or declined by trial subjects.

When participating in this clinical trial with AM-111, subjects suffering from ISSNHL may have the opportunity to effectively and quickly recover their hearing loss beyond spontaneous recovery and reduce its impact on their well-being and quality of life. Accumulating clinical experience suggests that treatment with AM-111 allows for a more rapid and sustained recovery of hearing and speech discrimination and improves chances for complete remission of ISSNHL-related tinnitus. Through the treatment, the subject's risk of a perpetuation of the disorder and chronic suffering may be reduced or completely eliminated.

Even when receiving placebo, subjects will be treated with oral corticosteroids in line with the current treatment guideline and further benefit from participating in this trial by receiving extensive medical care throughout the trial and by learning more about their ISSNHL, which may help to reduce tension and stress related to the condition.

2.5.2 Potential risks and risk mitigation strategy

The potential risks to subjects participating in this trial include:

Risks related to the administration procedure

The IMP is applied by an intratympanic administration into the middle ear from where the drug substance diffuses across the RWM into the inner ear. A small incision in the tympanic membrane is performed (myringotomy), through which the IMP is applied, or the needle penetrates the eardrum directly (tympanopunction). Myringotomy and tympanopuncture are minor procedures that are frequently performed in otolaryngology in adults and children.

A healthy tympanic membrane closes quite rapidly following myringotomy and even more so after tympanopunction – in the majority of cases full closure occurs after 2-5 days. In the two preceding clinical trials with AM-111, a total of 221 subjects received intratympanic injections. In the Phase II clinical trial AM-111-CL-08-01 only 3% of tympanic membranes were not fully closed by the Day 7 visit. In 6 out of these 7 cases, the tympanic membrane was closed by the Day 30 visit; in one case, closing took place between the Day 30 and Day 90 visits.

When the tympanic membrane is not fully closed, the subject is advised to avoid exposing the treated ear to water for risk of middle ear infections or temporary hearing deterioration. Such potential complications could be treated with anti-infective or anti-inflammatory agents. In trial AM-111-CL-08-01, one case of middle ear infection occurred, which was of transient nature.

Sometimes a small blood crust from wound healing will remain on the tympanic membrane following intratympanic administration. It will either fall off spontaneously after some time or may be removed by the Investigator. In the AM-111-CL-08-01 trial, a blood crust from wound healing was observed on the eardrum in only 2 cases at Day 3. This was an expected event, and was neither severe nor serious.

Temporary oral dysesthesia may occur if the injection needle inadvertently touches the chorda tympani (nervus facialis, 7th cranial nerve). This risk is minimized by performing the intratympanic administration in the posterior-inferior quadrant of the tympanic membrane. To date, no cases of oral dysesthesia have been observed in clinical trials with AM-111.

As with any surgical intervention or injection, the myringotomy or tympanopunction or the intratympanic administration may cause momentary localized discomfort or pain. Correct application of a local anesthetic and observance of the induction time before proceeding with the incision and injection, as recommended by this protocol, greatly mitigates the risk of experiencing such AEs. In the AM-111-CL-08-01 trial, four cases of ear pain and 3 cases of ear discomfort were reported.

The inner ear is temperature sensitive. If the IMP's temperature is not close to body temperature, some subjects may experience caloric vertigo upon administration. It is therefore recommended to warm the IMP before application (e.g. by hand-warming). In trial AM-111-CL-08-01, one subject in each treatment group experienced spontaneous nystagmus in the first 3 days after treatment. All three cases were transient.

Intratympanic administration is a safe procedure when performed by an experienced otolaryngologist. Adverse events related to this procedure are of transient nature.

Risks related to the IMP

Intratympanic administration of AM-111 gel allows for a very site specific administration at low concentration and with minimal systemic exposure. The cochlea represents a small, well-defined pharmacokinetic compartment from which there is only limited further distribution. As shown in animal pharmacokinetic studies (guinea pig), D-JNKI-1 following local administration onto the RWM was well distributed in the cochlea. In plasma, small traces (10 ng/mL) could be detected after 2 hours, but not thereafter. No traces could be detected in the cerebrospinal fluid (CSF) or in brain tissue.

[redacted]

Further, D-JNKI-1 (XG-102) was shown to be safe and well tolerated in a total of three studies conducted by Xigen with systemic or sub-conjunctival administration. Single dose intravenous (i.v.) XG-102 was well tolerated in 24 healthy volunteers when tested at up to 80 µg/kg body weight and in 10 stabilized stroke patients when tested up to 0.01 mg/kg. In the first of the two i.v. studies maximal plasma concentration was reached within one hour (C_{max} 362 ng/mL). $T_{1/2}$ is relatively short and ranged from 0.36 up to 1.02 hours, depending on the injected dose. In patients suffering from post-surgical uveitis, single dose sub-conjunctival administration of XG-102 was well tolerated when tested up to 0.1 mg/mL.

In the two clinical trials conducted with AM-111 to date, there were no apparent differences in frequency, intensity or relationship of local AEs between treatment groups. AEs were of transient nature, and there were no indications of dose-limiting adverse reactions of the IMP. While previous trial protocols did not differentiate between drug-emergent and procedure-emergent AEs, treatment-related local AEs can be presumed to be procedure-related in their entirety since no difference was observed between treatment groups. This is further supported by the observation that most of the local AEs occurred during or around the time of IMP administration.

Local events (mostly ear and labyrinth disorders) were transient and accounted for approximately 60% of reported treatment emergent adverse events (TEAEs), most frequently "hearing impaired" and "tinnitus". The frequency of occurrence of clinically relevant hearing deterioration (defined as ≥15 dB averaged at 2 contiguous frequencies in the previous studies) overall was low (1-7% for all trial visits), and there was no statistically significant difference between treatment groups. In all treatment groups,

few subjects experienced a worsening of their tinnitus and even fewer the onset of new tinnitus in the treated ear in the first 7 days following the treatment (< 6%). These cases were likely related to the procedure or the underlying pathology and most were resolved by Day 30.

Accumulated clinical data do not show any effect of D-JNKI-1 on the vestibular function, as measured by the occurrence of spontaneous nystagmus.

Risks related to the background therapy (corticosteroids)

The risk of suppression of the hypothalamic-pituitary axis with a short course of corticosteroid treatment as proposed in this study is minimal. Nevertheless, corticosteroids should not be administered to patients with

- Hypersensitivity to any ingredients in the formulation;
- Systemic infections unless specific anti-infective therapy is employed;
- Ocular herpes simplex due to the possibility of perforation;
- Medical conditions which can be affected by corticosteroids, such as insulin-dependent or uncontrolled diabetes mellitus, tuberculosis, peptic ulcer, etc.

For details, including adverse reactions, interaction with other medicinal products and other forms of interactions as well as conditions where caution is necessary, refer to the summary of product characteristics of the relevant corticosteroid used. This study provides the option for patients not to take the background steroids if they are not suitable for steroid therapy or if they refuse the therapy for any reason.

Risks related to the audiology assessment

The audiological methods applied in this trial are non-invasive and have been widely used for decades in audiology and otolaryngology. These methods do not pose any known risks to subjects.

Risks of drawing blood

The risks of drawing blood include temporary discomfort from the needle stick, bruising, bleeding, and rarely, infection.

Other risks

There may be other additional AEs than those listed above or other risks that are not yet known. No suicide, suicidal ideation or behavior have been reported in studies with AM-111 however, suicidality has to be assessed for all study participants as a requirement by the US FDA. Therefore, in this trial, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be applied.

2.5.3 Conclusions

Accumulated clinical data show that AM-111 is well tolerated in the middle ear, and the treatment does not negatively impact the auditory or vestibular function. Systemic exposure is minimal, and no systemic adverse reactions have been observed. The procedure of intratympanic administration is well established and safe; its known side effects are transient and of mild to moderate severity. Careful execution of the procedure by an experienced otolaryngologist in accordance with this trial protocol will mitigate the risk of their occurrence.

The AM-111-CL-08-01 trial established proof of concept for the efficacy of AM-111 in the treatment of acute sensorineural hearing loss. By participating in the present trial subjects have the opportunity to benefit from an innovative treatment in addition to the current standard of care. Treatment with AM-111 may allow for a more rapid and sustained recovery of hearing and speech discrimination and improve chances for complete tinnitus remission in ISSNHL compared with both placebo and spontaneous recovery. Through the treatment, the subject's risk of a perpetuation of the disorder and chronic suffering may be reduced or completely eliminated.

As for all subjects, subjects randomized to the placebo group will receive background therapy, unless the use is contraindicated or the patient refuses corticosteroids. Subjects may also benefit from participating in this trial by receiving additional medical care throughout the trial and by learning more about their ISSNHL, which may help to reduce tension and stress related to the condition.

In the Sponsor's view, the anticipated benefits clearly outweigh the potential harmful effects, and provide for a favorable benefit-risk ratio.

Any new findings that may raise safety concerns will be identified immediately and included in the ongoing benefit-risk evaluation of AM-111.

3 Trial 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.

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.

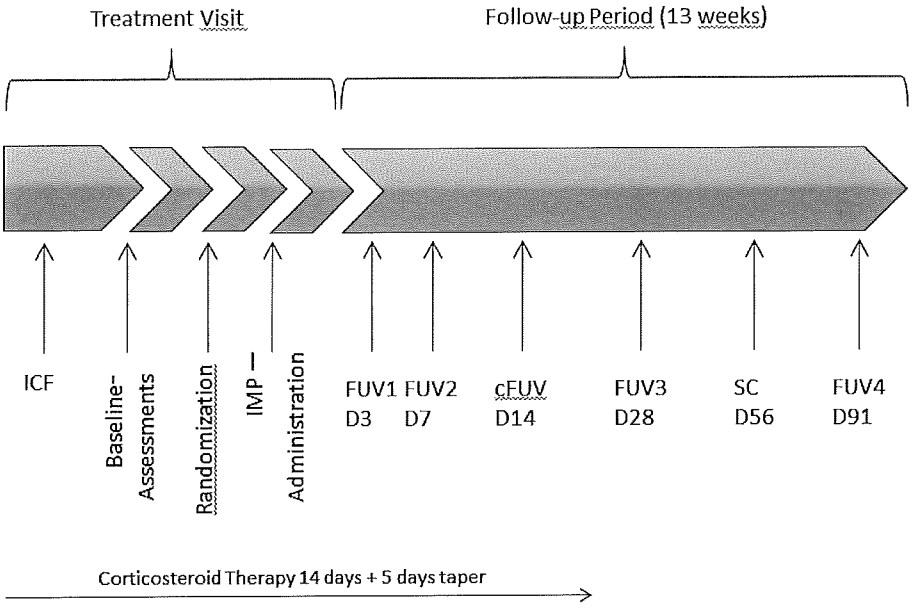
4 Trial design

4.1 Overall trial design and plan

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

A total of approximately 300 subjects will be randomized at approximately 80 sites. Investigative sites will be selected based on their experience with the indication and their access to the trial specific population, in addition to their ability to perform all trial related procedures in accordance with the protocol, International Conference on Harmonisation of Good Clinical Practice Guidelines (ICH GCP) and local regulations.

Figure 1 Trial flow chart



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

The trial consists of one treatment visit (TV) and a 13-week follow-up period with follow-up visits at D3, D7, D28 and D91, one conditional FUV at D14 and one subject contact at D56.

Subjects meeting all entry criteria will be randomized on D0 to receive the IMP (AM-111 0.4 mg/mL, 0.8 mg/mL or placebo) at a 1:1:1 ratio. Subject recruitment will be stopped once the overall target number of 300 subjects is reached.

[redacted]

Trial participants will receive, after topical anesthesia of the tympanic membrane, an intratympanic injection of the IMP (AM-111 or placebo) into the affected ear at TV (D0). Following the administration, subjects will rest in a supine or reclined position for 30 minutes with their treated ear facing upwards.

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.

See Table 1 (protocol summary) for the schedule of visits and assessments.

4.2 Discussion of trial design

In this trial subjects will receive AM-111 (0.4 mg/mL or 0.8 mg/mL) or placebo with a corticosteroid background therapy. The most commonly used therapeutics for ISSNHL subjects are steroids to reduce inflammation and swelling, and treatments aimed at improving the blood circulation and oxygenation of the inner ear such as vasodilators, plasma expanders, or hyperbaric oxygen. However, no evidence could be found that any of these treatments achieved a better result than spontaneous recovery, which can be substantial. Therefore, placebo was chosen as reference therapy.

In the AM-111-CL-08-01 trial the concentration of AM-111 0.4 mg/mL has shown a statistically significant, clinically relevant and persistent improvement in hearing and speech discrimination and a higher frequency of complete tinnitus remission compared with placebo. The 0.8 mg/mL concentration was additionally chosen for the present trial since AM-111 2.0 mg/mL showed less pronounced improvement in the previous trial, and non-clinical data have shown a bell-shaped dose-response relationship with maximum efficacy at 0.2 to 0.4 mg/mL. It appears possible that 0.4 mg/mL is on the ascending and 2.0 mg/mL on the descending slope of the clinical dose-response curve. Hence, an intermediate concentration will conceivably offer at least the same therapeutic effect as 0.4 or 2.0 mg/mL, if not better. The concentration of 0.8 mg/mL doubles the most effective concentration in the AM-111-CL-08-01 trial, which is in line with the ratio of 2:1 for the most effective concentrations observed in a non-clinical study.

Due to the lack of pharmacologic therapeutics or a standard of care with unequivocal efficacy in the treatment of ISSNHL, a placebo arm is included in the present trial to obtain scientifically sound and reliable data. This is deemed acceptable since the placebo administration poses a low risk on the subjects. Inclusion of a placebo arm is also essential to control for the substantial spontaneous recovery in the weeks following the ISSNHL incident. Oral prednisolone or prednisone is the standard of care for the treatment of ISSNHL in the U.S. and many other countries, although there is no clear evidence for their efficacy (Wei et al., 2013). It is provided as a background therapy in spite of the lack of clear evidence of efficacy as a treatment option in line with current treatment guidelines (Stachler et al., 2012) and as *de facto* standard of care. Because no treatment effect is anticipated from corticosteroids, subjects who refuse treatment with corticosteroids or for whom corticosteroids are contraindicated can also be enrolled into this trial.

In the present trial only ISSNHL patients will be included. In the preceding trial only a few of the enrolled patients had experienced AAT, which probably reflects both a lower incidence of AAT as compared to ISSNHL, and the fact that AAT incidents provoking a hearing loss of at least 30 dB at three contiguous test frequencies (one of the study's inclusion criteria) may not occur that often. This will be even more apparent for a hearing loss of at least 40 dB at three contiguous test frequencies, as required in the present trial. In order to avoid a potential source of variability and the inclusion of a highly restricted subgroup of patients, it was decided to exclude AAT cases from the present trial.

The enrolment window in the present trial is 72 hours from onset, which is 24 hours longer than in the AM-111-CL-08-01 trial. In that previous trial spontaneous recovery in the first 12 hours post ASNHL was very high. While its rate decreased substantially thereafter, hearing recovery in patients treated with AM-111 held steady, resulting in a widening of the therapeutic effect between 24 and 48 hours. Given the absence of a time-dependent decrease in therapeutic effect up to 48 hours and the expected continuation of pathologic inner ear processes, e.g. inflammatory responses, the extension of the enrolment window appears to be warranted.

As in the previous clinical trials with AM-111, single dose administration was selected. Due to its dextrorotatory structure AM-111 has a prolonged pharmacological activity in the cochlea.

4.3 Duration of the trial

The duration of subject participation is 91 days (TV, FUV1 to FUV4).

Expected trial start: Q2 2016 (first subject first visit).

Expected trial completion: Q2 2018 (last subject last visit).

5 Selection of subjects

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. A sufficient number of subjects will be enrolled to randomize approximately 300 subjects.

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.

5.1 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.

5.2 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 C-SSRS;
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 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).

5.3 Discontinuation of IMP treatment and subject withdrawal from the trial

5.3.1 Screening failures

Screening failures are subjects who have been enrolled in the trial (i.e. ICF signed), but discontinue the trial during TV before randomization for whatever reason (withdrawal of consent, not meeting eligibility criteria, by decision of Investigator, etc.). For screening failures, no further procedures should be performed.

5.3.2 Withdrawals

The Investigator should make all efforts to keep a subject in the trial.

Withdrawals are subjects who have been enrolled in the trial (i.e. ICF signed), but discontinue the trial after randomization. This may occur under the following circumstances:

1. The subject withdraws his/her informed consent to participate in the clinical trial. Subjects have the right to prematurely withdraw from the trial at any time and without any obligation to justify their decision;
2. The subject is lost to follow-up;
3. Subject's death;
4. The Investigator does not consider trial participation to be in the subject's best interest.

Any reasons for withdrawal after randomization must be documented carefully in the subject's medical records and in the case report form (CRF). If possible, the subject should attend a premature end of trial visit (see Section 7.4), which follows the course of assessments scheduled for FUV4.

A subject is considered lost to follow-up when the Investigator cannot reach the subject or, if contact details are available and permission has been obtained, the subject's relatives should be contacted by phone to obtain a reason for the subject not to attend a visit (e.g. an AE). If at least 6 phone calls or other contact efforts (e.g. e-mails, text messages) at different times of the day during a course of three weeks are not answered, a registered letter should be sent to the patient. All contact attempts should be documented in the patient's source documents. If the subject prefers to withdraw due to an AE, the Investigator should try to motivate the subject to continue until the event has stabilized with no further change expected, or the Investigator states the AE is not clinically significant and no further follow-up is required, but still encouraged. If the subject returns to the site at a later time point, the Sponsor should be informed to discuss further steps.

5.4 Termination of the trial

5.4.1 Regular termination of trial

The clinical trial will be considered complete once all randomized subjects have completed the study.

5.4.2 Premature trial termination

Subject enrolment and randomization will be stopped if, based on a review of safety and tolerability data by the Sponsor, further study treatments are deemed not acceptable.

The Sponsor reserves the right to discontinue the trial at any time and for any reason. In the event of emerging evidence from literature or other scientific sources demonstrating that the investigational drug may be ineffective or may affect the subjects' safety, the Sponsor will decide about trial termination.

In addition, the Sponsor reserves the right to discontinue a trial site in case of major protocol deviation or insufficient enrolment.

6 Trial procedures

6.1 Principal Investigator and trial team

The Principal Investigator may delegate trial specific tasks to other members of the trial team. The delegation must however be documented in writing prior to the involvement of the team member. The Principal Investigator is responsible for appropriate training of his/her team members on the trial specific requirements prior to their involvement in the trial in accordance with GCP and local regulations. The Sponsor and/or the Clinical Research Associate (CRA) may assist the Principal Investigator in staff training and may provide supporting training material. Training shall be documented adequately.

Any trial team member performing trial specific assessments and procedures must be qualified and licensed professionally where applicable and according to the local standard medical practice.

All procedures should first be documented in the source documents (e.g. subject's medical file) before being transcribed into the CRF.

6.2 Schedule of visits

A schedule of visits and trial assessments is provided in the Protocol Summary (Table 1) and in Section 7.

6.3 Informed Consent

The currently valid IRB/IEC approved version of the participant information sheet and informed consent form (ICF) will be used to inform the subject about the trial and to document the subject's agreement to participate in the trial. The Investigator, or designee, will obtain a written, dated, timed and signed ICF from each subject prior to performing any trial-specific procedure on the subject. The informed consent process will be documented in the source documents. The Investigator will retain the original copy of the signed ICF, and a copy will be provided to the subject.

The Investigator will ensure that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical trial.

Depending on local requirements, routine standard of care assessments prior to ICF signature might not need to be repeated to reduce the burden to the subject under the following circumstances:

- Assessment was done as standard of care regardless of potential study participation.
- Assessment was done on the day of study treatment.
- For pure tone and speech audiometry, assessments were done not more than 2 hours prior to ICF signature and within 5 hours to IMP administration (i.e. study treatment must be done within 5 hours from pure tone and speech audiometry).

Standard of care routine assessments are:

- Demography/baseline characteristics
- Medical history (incl. hearing loss onset)
- Prior and concomitant medication recording
- Tinnitus evaluation
- Vital signs
- Otoscopy/microscopy
- Tympanometry
- Spontaneous nystagmus
- Balance test
- Pure tone and speech audiometry.

NOTE: Section 13.4 of this protocol should be referred to as the subjects go through the informed consent process prior to their participation in the trial.

6.4 Allocation of subject number

After informed consent is obtained, the subject will be assigned a subject number which serves as unique subject identifier. Upon randomization an IMP kit number will be assigned to the subject.

6.5 Baseline Assessments

6.5.1 Inclusion and exclusion qualification

Each subject will be screened and must meet all inclusion criteria and none of the exclusion criteria to qualify for randomization. To verify eligibility, each subject will be asked the specific questions outlined in the inclusion/exclusion criteria by an authorized trial team member; the answers will be documented in each subject's source documents. Documentation of audiology reports, laboratory reports and other source documents are to be filed with the subject's records.

6.5.2 Demographics and baseline characteristics

Demographic and baseline characteristics including but not limited to age, gender, and race/ethnicity, will be recorded in the subject's source documents and entered into the CRF as per local requirements.

6.5.3 Medical history, prior and concomitant medication

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.

Any drug known as ototoxic taken up to 3 months before randomization (TV) should be recorded in the CRF. Any medication that is ongoing or was taken within 2 weeks prior to randomization should be recorded in the CRF. This includes prescription medicines as well as non-prescription medicines, herbal medicines and vitamins and mineral supplements.

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.

6.5.4 Hearing loss onset

The time of the subject's ISSNHL onset will be recorded at the TV prior to randomization, rounded to the nearest hour. For example if the hearing loss occurred at 6:29 am then 6 am will be recorded; in case of 6:30 or 6:45 am, 7 am will be assigned.

If no precise time is known, the following assumptions will be made:

- "Morning": between 6 am and noon; midpoint at 9 am
- "Afternoon": between noon and 6 pm; midpoint at 3 pm
- "Evening": between 6 pm and midnight; midpoint at 9 pm
- "Night": between midnight and 6 am; midpoint at 3 am

6.5.5 Tinnitus history and characteristics

At TV, the concept of tinnitus will first be explained by the Investigator to the subject with a description of the symptom, and the presence or absence of tinnitus will be assessed (see Appendix 1). If tinnitus is present, tinnitus history (onset, tinnitus inducing event, laterality) will be recorded at TV and tinnitus characteristics (persistence, pitch, sound) will be recorded at all visits (except cFUV).

6.5.6 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 (in particular to support the evaluation of exclusion criterion 20). Body height and body weight will also be recorded.

6.6 Safety Assessments

6.6.1 Vital signs

Sitting blood pressure will be taken with the same arm at each visit (except cFUV). The arm should be positioned at heart level using the same sphygmomanometer at each visit. The subject should be seated for approximately 5 minutes prior to measurement. Vital signs (blood pressure and pulse) and body temperature will be measured at each visit.

6.6.2 Blood testing

A blood sample will be drawn at TV and at FUV1 and shipped for evaluation to the central laboratory. A manual will be provided containing trial specific instructions for handling and shipping of the sample. The Investigator should review the central laboratory report for any out of range values and their clinical relevance promptly upon receipt, and confirm the review by signing and dating the report. Virology and HbA_{1c} will be assessed at TV only.

The following parameters will be tested:

Hematology

- Hemoglobin (Hgb),
- Hematocrit (Hct),
- Red blood cell (RBC),
- White blood cell (WBC),
- Platelets (Plt),
- WBC differential.

Biochemistry

- Sodium (Na),
- Potassium (K),
- Chloride (Cl),
- Glucose,
- Glycated hemoglobin (HbA_{1c})
- Blood urea nitrogen (BUN),
- Creatinine (CRE),
- Calcium (Ca),
- Phosphorus (P),
- Uric acid (UA),
- Alanine aminotransferase (ALT),
- Aspartate aminotransferase (AST),
- Gamma-glutamyl transpeptidase (γ-GTP),
- Lactate dehydrogenase (LDH),
- Alkaline phosphatase (ALP),
- Total bilirubin (T-bil),
- Total protein (TP),
- Albumin (Alb).

Virology:

- Human immunodeficiency virus (HIV),
- Hepatitis B (HBV),
- Hepatitis C (HCV),
- Herpes Zoster (Varicella).

Should the laboratory report be incomplete or non-analyzable, a retest should be done as soon as possible.

It is the responsibility of the Investigator to assess if an abnormality on the central laboratory report is to be considered as clinically significant or not. All laboratory values that, in the Investigator's opinion, show any clinically significant abnormality must be reported as an AE and will be subject to follow-up by the Investigator.

Refer to the corresponding manual for further details.

6.6.3 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.

6.6.4 Questionnaires and numerical rating scales

Questionnaires and numerical rating scales will be administered as outlined in Table 1. At all follow-up visits they must be completed at applicable visits prior to performing the audiology assessments. At Treatment Visit, the questionnaires may be completed after audiology assessment, but have to be completed in any case prior to IMP administration. Subjects should be seated in a quiet environment and have ample time for completion. A member of the study team will explain the purpose and use of the assessment, but subjects should complete the questionnaires on their own without being influenced or directed by the study team member. Subjects should however have the chance to ask questions and ask for assistance, should this be required. Responses from the previous visit will not be accessible for subjects or made available to them.

6.6.4.1 HHIA Questionnaire

The 25-item Hearing Handicap Inventory for Adults (HHIA; (Newman *et al.*, 1990)) focuses on the impact of the hearing loss on the subject's daily life and evaluates the change in condition severity after treatment initiation. It is self-administered at FUV3 and FUV4. Response categories for all 25 items are "yes", "no", or "sometimes". The questionnaire is shown in Appendix 3.

6.6.4.2 PGIC scale

The Patient Global Impression of Change (PGIC) scale for hearing loss severity evaluates the change in condition severity after treatment initiation and is administered at FUV2, FUV3 and FUV4. It is shown in Appendix 4.

6.6.4.3 Tinnitus numerical rating scales

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 self-administered at all visits from FUV1 until FUV4, for the $TLQ_{Loudest}$ and TAQ_{Worst} also at TV.

At TV, the presence or absence of tinnitus is assessed by the investigator, using the questionnaire in Appendix 1.

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. If a subject diary entry is missing within +/-4 days of a visit, it may be replaced by the visit based values. Subjects will not have access to their previous ratings. Complete remission of ISSNHL-related tinnitus will be given as soon as a subject rates both $TLQ_{Loudest}$ and TAQ_{Worst} as 0, and answers the question about tinnitus presence with "No". Refer to Appendices 1 and 2.

6.6.5 Otologic and audiologic assessments

A detailed description of the trial specific procedures for otologic and audiologic assessments will be provided to all trial sites.

6.6.5.1 Otoscopy or 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.

6.6.5.2 Tympanometry

Tympanometry will be performed to check for the presence of otitis media or Eustachian tube dysfunction. It will be performed at TV and, provided the tympanic membrane is closed, also at all follow-up visits starting at FUV2.

Tympanic peak pressure pass is between +25 daPa and -160 daPa. Maximum compliance pass is between 0.3 and 1.4 mL. For further details refer to the corresponding manual.

6.6.5.3 Pure tone audiometry

Air and bone conduction hearing thresholds will be tested at all visits (excluding cFUV).

All tests will be performed by certified audiologists or adequately trained site staff and conducted in a sound attenuated booth/room with doors closed, using standard earphones or earphone inserts.

Compliance with relevant standards will be verified and documented during source data verification. In order to assure overall quality and consistency, individual or all pure tone audiometry data may be reviewed by an independent expert designated by the Sponsor.

Timing of Baseline Assessment

Results of audiograms previously performed as part of routine clinical practice at the investigational site should not be older than 2 hours prior to signing the ICF, and 5 hours prior to the IMP administration (i.e. study treatment must be done within 5 hours from pure tone audiometry) to be considered valid for baseline, otherwise the measures have to be repeated. Pure tone audiograms performed for subjects presenting within the first 24 hours from ISSNHL onset have to be confirmed by a new assessment that is conducted at the earliest 24 hours after onset of ISSNHL. The high possibility of spontaneous remission early after ISSNHL onset may otherwise lead to the inclusion of patients who would recover on their own. The new confirmatory measure will serve as baseline value.

Assessment of Hearing Thresholds

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) in accordance with ISO standard 8253-1 and any other relevant standards.

For each frequency, hearing threshold is to be determined by (A) approaching the hearing threshold in 20 dB steps, followed by (B) fine tuning steps in 5 dB steps or smaller. Fine tuning determination occurs by detecting, at least twice, the level at which the subject no longer hears the tone and the level at which the subject starts to hear the tone. 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.

Determination of the three most affected contiguous frequencies

At baseline, the three most affected contiguous frequencies which are used for the calculation of Pure Tone Average (PTA) are defined relative to the reference values which is either the unaffected contralateral ear or, in case of asymmetric hearing, corresponding values from a pre-existing audiogram for the affected ear not older than 2 years.

For the evaluation of the eligibility of the subject, the three most affected contiguous air conduction audiometric pure tone frequencies are used. These represent the frequencies with the highest hearing loss (defined as difference to the reference values). The determination of the hearing loss is done as follows:

1. For each frequency the difference between the hearing threshold of the affected ear and the hearing threshold of the reference (i.e. unaffected contralateral ear or in case of asymmetric

hearing in medical history: pre-existing audiogram not older than 2 years) is calculated (subtract hearing threshold$_{affected}$ ear from the reference value (e.g. hearing threshold$_{unaffected\ ear}$).
2. The three contiguous frequencies with the highest absolute hearing loss (i.e. hearing loss difference) values are used to calculate the average hearing loss (inclusion criterion no. 3).
3. If the average hearing loss is the same across different sets of frequencies the set of lower contiguous frequencies is used.
4. The same frequencies are used to calculate the average hearing threshold to evaluate if inclusion criterion no. 2 is met.

Further details are provided in the corresponding manual.

The pure tone average frequencies are determined from the pure tone audiometry (air) at baseline and are fixed throughout the trial, to evaluate hearing 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.

6.6.5.4 Speech audiometry

The speech discrimination (Word Recognition Score in quiet) will be determined in both ears with country-/language-specific word lists at 60 and 80 dB sound pressure level (SPL). WRS at both stimulus levels ($WRS_{(60\ dB)}$ and $WRS_{(80\ dB)}$) will be determined, at the earliest, 24 hours after ISSNHL onset and this result will serve as baseline value.

When testing, at each stimulus level, 40 to 50 mono- or bisyllabic words from language-specific standard lists (e.g. CID-W22 for American English and Auditec Spanish BiSyllable Word Recognition test in U.S.) without background noise will be presented in random order from a recorded source. Full lists are to be used. After each word is presented to the subject, the subject will be asked to repeat it, and to guess it if he/she is not sure of the word. The testing will start with the unaffected ear. The WRS will be calculated (as the percentage of correct responses) for each ear.

Speech audiometry at 80 dB will be performed at all trial visits (excluding cFUV) for both ears. WRS at 60 dB will be performed at TV and FUV4 only. Results of previously performed speech audiometry tests performed at the investigational site should not be older than 2 hours prior signing the ICF and 5 hours prior to IMP administration (i.e. study treatment must be done within 5 hours from speech audiometry) to be considered valid for baseline, otherwise the measurements have to be repeated.

6.6.6 Vestibular function

A detailed description of the trial specific procedures for assessment of vestibular function will be provided to all trial sites in the corresponding manual. Vestibular function will be assessed by means of Romberg's test and Frenzel goggles, at the earliest, 24 hours after ISSNHL onset and this result will serve as baseline value.

6.6.6.1 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).

6.6.6.2 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 of the test is to be recorded.

6.6.7 Suicidality

Suicidality (suicidal ideation and behavior) will be assessed by means of the C-SSRS by a study team member that has been trained and certified according to the requirements. A clinical training or medical degree is not required for the rater as the questionnaire is designed for suicide risk identification in a wide range of settings by lay persons who have completed the required training. The C-SSRS is shown in Appendix 5. The C-SSRS will be assessed at TV (Baseline version), FUV2, FUV3 and FUV4 (Since-Last-Visit version).

6.7 Randomization

Once all procedures at TV have been performed (i.e. all baseline and safety assessments as described in sections 6.5 and 6.6) and the subject has been confirmed to be eligible for the trial the Investigator, or designee, will randomize the subject using an Interactive Web Response System (IWRS).

Subjects will be randomized to receive either AM-111 (0.4 mg/mL or 0.8 mg/mL) or placebo in a 1:1:1 ratio. [redacted]

At the time of randomization, the IWRS will assign the subject a unique IMP kit number; details are described in the corresponding manual.

6.8 IMP administration

Trial subjects will have the tympanic membrane of the treatment ear topically anesthetized as per standard practice at the respective site and then receive an intratympanic administration of the IMP (AM-111 0.4 mg/mL, AM-111 0.8 mg/mL or placebo) as assigned by IWRS.

For the application procedure, trial subjects are to sit on a reclined ear nose throat (ENT) exam chair or lie supine on an examination couch. The head is placed in a position tilted approximately 45° towards the non-treated contralateral ear, so that the ear to be treated is pointing upwards. Following cleaning of the ear canal, a local anesthetic is applied topically onto the eardrum. The local anesthetic may be chosen by the Investigator as per local practice (e.g. lidocaine) and must be recorded in the source documents and on the CRF. The use of phenol is discouraged, as it may lead to slower healing of the tympanic membrane. Upon induction of anesthesia and prior to the administration of the IMP, any remaining anesthetic must be carefully and gently (avoiding loud noise) suctioned off from the ear canal.

For the intratympanic administration, the IMP is supplied in pre-filled syringes with a luer lock. At the Investigator's discretion either a spinal needle or a micro suction tube may be used; the choice of injection cannula must be recorded in the source documents and on the CRF. Prior to the administration, the drug must be warmed up gently to about body temperature (e.g. by hand-warming) to prevent caloric vertigo.

The administration is performed preferably in the posterior-inferior quadrant (left ear: about 3 o'clock, right ear about 9 o'clock), preferably close to the limbus. Alternatively, the administration may be performed in the anterior-inferior quadrant; the choice needs to be documented in the source documents and on the CRF. At the Investigator's discretion, the tympanic membrane may be punctured with the needle for injection (tympanopunction) or a small myringotomy may be performed first; in this case the needle will penetrate through the incision. If deemed necessary, at the Investigator's discretion, an outlet for displaced air may be created through a second tympanopunction or myringotomy superior to the first one. The choice of the approach is to be noted in the source documents and in the CRF.

[redacted] the IMP is gently injected into the middle ear. Following IMP administration, trial subjects remain in their position for 30 minutes to allow for diffusion of the active substance across the RWM. Subjects are asked to refrain from movements of the head, swallowing, yawning, sneezing or talking during the resting period, if possible. The timing of the IMP administration is to be documented in the source documents and on the CRF. The syringe is to be kept for drug accountability, as per country specific requirements documented in the operations manual.

For a more detailed description of the IMP administration procedure please refer to the instructions included in the Operations Manual.

6.9 Background therapy administration

As background therapy, an oral corticosteroid course will be offered for 14 days followed by a 5-day taper as follows (in line with clinical practice guidelines for sudden hearing loss (Stachler et al., 2012):

- Prednisone or Prednisolone at 1 mg/kg/day, at a maximum 60 mg/day (taper 50 mg, 40 mg, 30 mg, 20 mg, and to 10 mg), or
- Methylprednisolone at 0.8 mg/kg/day, at a maximum 48 mg/day (taper 40 mg, 32 mg, 24 mg, 16 mg, and to 8 mg).

The dose should be adjusted to the next available strength. It is to be taken undivided in the morning and can be started within 36 hours prior to randomization. If the course is started within 36 hours prior to randomization, the maximum dose will be given from Day -2 until Day 12. If the course is started on TV, the maximum dose will be given until Day 13.

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

Corticosteroids should not be administered to patients with the following conditions:

- Hypersensitivity to any ingredients in the formulation.
- Systemic infections unless specific anti-infective therapy is employed.
- Ocular herpes simplex due to the possibility of perforation.
- Medical conditions which can be affected by corticosteroids, such as insulin-dependent or un-controlled diabetes mellitus, tuberculosis, peptic ulcer, etc.

Treatment compliance is to be documented by the subject on a background therapy documentation card and will be verified by the Investigator. All used and/or unused packaging has to be returned by the subject to the site. Further details are provided in Section 8.45.

7 Trial visits and schedule of assessments

7.1 Baseline assessment, randomization and treatment

After having obtained informed consent from the subject, the baseline assessment begins at the treatment visit (TV) prior to randomization and IMP administration. It ends once all pre-randomization assessments have been completed. No trial specific procedure must be performed before the subject and the Investigator, or designee, have signed and dated the ICF. Signing the ICF defines the start of the trial. The time of signing the ICF and of the baseline assessments should be recorded in the source documents and on the CRF. Please refer to section 6.3 for details on timing of baseline assessments.

The required procedures may be done on different calendar days, however the day of randomization and treatment (IMP administration) is considered Day 0 (D0).

After ICF signature and prior to randomization, the following baseline assessments will be performed:

- Inclusion and exclusion criteria qualification (see 6.5.1.);
- Demography/baseline characteristics;
- Medical history;
- Hearing loss onset;
- Prior and concomitant medication;
- Tinnitus evaluation (history and characteristics);
- General physical examination, body weight, height;
- Vital signs (blood pressure, temperature, pulse);
- Tinnitus presence or absence and numerical rating scales;
- Otoscopy/microscopy;
- Tympanometry;
- Pure tone audiometry (air and bone conducted)*;
- Speech audiometry ($WRS_{(80\ dB)}$ and $WRS_{(60\ dB)}$)**;
- Spontaneous nystagmus (Frenzel goggles)**;
- Balance test (Romberg's test)**;
- Suicidality questionnaire (C-SSRS, Baseline version);
- Blood sampling for laboratory assessment (hematology, biochemistry, virology);
- Urine pregnancy test, if applicable;
- Adverse event reporting.

* 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.

Prior to randomization, results of all baseline assessments (except hematology, biochemistry and virology results, which will become available only later) will be reviewed. Subjects who do not meet all inclusion criteria and / or who meet one or more of the exclusion criteria are excluded at this point and will not be randomized (screening failures).

Eligible subjects are randomly allocated to either the active treatment (AM-111 0.4 or 0.8 mg/mL) or placebo.

After receiving the single dose of IMP, all subjects will be advised to avoid noisy situations until FUV4, and to protect the ear canal and middle ear of the treated ear from water exposure until the tympanic membrane is closed again.

For the background therapy the investigator prescribes or provides prednisone, prednisolone or methylprednisolone, and the background therapy documentation card documenting the compliance will be handed out to the subject.

7.2 Follow-Up Visits

Subjects enrolled and randomized will be asked to come back for FUV1 on D3 (± 1 day), FUV2 on D7 (± 2 days), FUV3 on D28 (± 5 days) and FUV4 on D91 (± 7 days) post-treatment. Unless otherwise specified, the following assessments will be performed at each Follow-up visit:

- Concomitant medications;
- Background Therapy Compliance Card (check and verify at FUV1 and FUV2, return to site at FUV3)
- Tinnitus characteristics;
- Vital signs (blood pressure, temperature, pulse);
- HHIA questionnaire (only at FUV3 and FUV4);
- PGIC (only at FUV2, FUV3 and FUV4);
- Tinnitus presence or absence and numerical rating scales;
- Otoscopy/microscopy;
- Tympanometry (only if the eardrum is fully closed);
- Pure tone audiometry (air and bone conducted);
- Speech audiometry ($WRS_{(80\ dB)}$ at each FUV, $WRS_{(60\ dB)}$ at FUV 4 only);
- Spontaneous nystagmus (Frenzel goggles);
- Balance test (Romberg's test);
- Suicidality (C-SSRS, Since-Last-Visit version);
- Laboratory test (hematology, biochemistry) (only at FUV1);
- Urine pregnancy test, if applicable (only at FUV4);
- Adverse event reporting.

Throughout the follow-up period, subjects will record weekly in a diary the presence or absence of tinnitus and their ratings of tinnitus loudness ($TLQ_{Loudest}$) and tinnitus annoyance (TAQ_{Worst}). Subjects should not have access to their previous ratings. Diary completion compliance should be monitored by the site throughout the trial and should be discussed with the subject (if applicable) at least at each study visit.

7.2.1 Conditional Follow-up Visit

In the event that the tympanic membrane of the treated ear is still open at FUV2 (as defined in Section 9.4.1.3), a conditional follow-up visit (cFUV) should be scheduled on D14 (± 3 days) in order to examine and document the healing process of the tympanic membrane. During this visit the ear canal and tympanic membrane will be examined by otoscopy/microscopy. If the tympanic membrane is closed at this visit, tympanometry will be performed. Additional measures may be conducted as deemed medically indicated by the Investigator. Findings will be recorded in the source documents and the CRF and an AE will be reported as specified in Section 9.4.1.

Additionally, other AEs and changes in concomitant medication will be recorded.

7.3 Subject contact

Subjects will be contacted via phone, text message or email by the Investigator or designee on D56 (±7 days) to collect information about any AEs and concomitant medication since FUV3. The subject contact and obtained information will be recorded in the subject's source documents and the CRF.

7.4 End of the trial (regular or premature)

If the subject completes all visits as per the protocol, then FUV4 is the regular end-of-the-trial visit.

In case the subject terminates the trial prematurely, for whatever reason, an unscheduled end-of-the-trial visit should be performed at the earliest convenience. This visit follows the same procedures as visit FUV4 (refer to Section 7.2). In case termination occurs before FUV1, blood samples for laboratory assessments as foreseen for FUV1 are to be taken.

8 Study medication and concomitant medication

8.1 Investigational Medicinal Product formulation and packaging

8.1.1 Drug substance

D-JNKI-1 is a stable, water soluble peptide containing 31 amino acids (a 19 amino acid effector domain, a 10 amino acid transporter domain and 2 proline spacers). All amino acids besides the achiral glycine are in D-form.

The chemical name for D-JNKI-1 is: H-D-Asp-D-Gln-D-Ser-D-Arg-D-Pro-D-Val-D-Gln-D-Pro-D-Phe-D-Leu-D-Asn-D-Leu-D-Thr-DThr-D-Pro-D-Arg-D-Lys-D-Pro-D-Arg-D-Pro-D-Pro-D-Arg-D-Arg-D-Arg-D-Gln-D-Arg-D-Arg-D-Lys-D-Lys-D-Arg-Gly-NH2 (IUPAC nomenclature).

8.1.2 Drug product

The IMP is manufactured under aseptic conditions in concentrations of 0.0 (placebo), 0.4 and 0.8 mg/mL D-JNKI-1. [redacted] provided in prefilled glass syringes filled [redacted] The placebo formulation is identical to AM-111 except for the active substance, which is lacking.

[redacted]

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

[redacted]

8.1.3 Manufacturer

The IMP is manufactured in accordance with current Good Manufacturing Practices (cGMP) by:

[redacted]

8.1.4 Labelling and packaging

The IMP is supplied to the trial sites in kits. Each kit contains 1 pre-filled syringe for the treatment of the subject's affected ear.

The IMP is labeled in appropriate local language according to Annex 13 GMP and country specific requirements, packaged, stored, released and distributed according to cGMP by:

[redacted]

Sample labels will be filed in the TMF.

A complete record of batch numbers and expiry dates of all IMP will be maintained in the TMF.

For all IMP, a system of kit numbering in accordance with the requirements of GMP will be used. This will ensure that for each subject, any dose of IMP can be identified and traced back to the original batch ware of the active ingredient.

Lists linking all numbering levels will be maintained by the provider in charge of IMP packaging. Before unblinding, these lists will not be accessible to any individual involved in trial operations.

8.2 Treatment

8.2.1 Dosage form

The IMP will be provided as a gel formulation in a pre-filled 1 mL glass syringe in [redacted]. It is supplied to the study sites in kits. Each kit contains 1 pre-filled syringe for the treatment of the subject's affected ear.

8.2.2 Route of administration

The IMP is administered intratympanically by the Investigator (see Section 6.8).

8.2.3 Dosing regimen

Subjects will receive one single dose [redacted] of IMP into the affected ear 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] of AM-111 0.8 mg/mL [redacted].

8.2.4 Background therapy

The background therapy (corticosteroid) 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 background therapy consists of an oral corticosteroid course with prednisolone or methylprednisolone as follows:

- Prednisone or prednisolone 1 mg/kg/day, at a maximum 60 mg/day (taper 50 mg, 40 mg, 30 mg, 20 mg, and to 10 mg), or
- Methylprednisolone 0.8 mg/kg/day, at a maximum 48 mg/day (taper 40 mg, 32 mg, 24 mg, 16 mg, and to 8 mg).

The dose is to be adapted to the next strength available and to be taken undivided in the morning and can be started within 36 hours prior to randomization. If the course is started within 36 hours prior to randomization, the maximum dose will be given from Day -2 until Day 12. If the course is started on TV, the maximum dose will be given until Day 13.

The background corticosteroid treatment may be omitted in case of medical contraindication of oral corticosteroids or if declined by the subject. The investigator will provide a background therapy documentation card for the subject to document the intake of the corticosteroid.

Procurement of the background therapy will be performed by the hospital / site directly.

8.3 Blinding

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 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.

For reasons and procedures concerning breaking the blind please refer to Section 9.5.

8.4 Storage and drug accountability

The Investigator or designee must confirm the receipt of the study medication (IMP) within the IWRS. The study medication must be stored in securely locked areas that are only accessible to authorized study team members until administered to the subjects.

All subjects will receive their single dose IMP administered at the clinical site. The Investigator or his/her designee must maintain an individual record for each subject. Each drug unit dispensed, received or returned must be recorded.

Study medication must not be used outside the frame of this protocol. The receipt, use, and any loss of study medication will be adequately recorded. An accountability form for all study medication supplies and their disposition subject by subject will be completed and collected by the Investigator or pharmacist and verified by the CRA.

Throughout the trial and at the end before trial site closure, all used IMP pre-filled syringes will be counted by the CRA. Details on return and destruction of IMP will be given in the Operations Manual.

The IMP kits containing the prefilled syringes are to be stored at 36-46°F (2 - 8°C).

8.5 Treatment compliance

The IMP is administered only once and at the site.

However, if the subject requests to refrain from treatment after randomization, but before the IMP administration, the Investigator or designee should encourage the subject to still complete all follow-up visits described in the protocol. Please refer to Section 5.3.

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.

8.6 Prior and concomitant medications

Prior medication means all medication taken before a subject is screened, while concomitant medication refers to all medication taken by the subject during the trial (encompassing TV until end of follow-up). Any medication known to be ototoxic taken up to 3 months before randomization (TV), any medication ongoing or initiated from within two weeks prior to TV and any medication taken during the trial up to FUV4 will be recorded in the source documents and on the CRF. This includes prescription-, non-prescription and herbal medicines as well as vitamins and mineral supplements. This documentation must include the name and dose of each medication, start and end date of use, frequency, route, and the reason for administration. Each concomitant medication entered in the CRF should correspond to either an entry in the subject's medical history, or an AE.

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 36 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.

Subjects will be instructed not to take any prescribed or over-the-counter medications without prior consultation with the Investigator or designee.

8.7 Further treatment after the end of the trial

After the end of the trial, the subjects may be treated according to local standard practice.

9 Adverse events

9.1 Definitions

9.1.1 Adverse Event

An Adverse Event (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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the IMP or intratympanic IMP administration procedure, or other trial procedure or other reasons not related to the trial.

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).

9.1.2 Serious Adverse Event

An 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

These characteristics / consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Exceptions(s):

1) The hospitalization or prolongation of hospitalization as a part of a routine procedure followed by the center (e.g. stent removal after surgery). The procedure must have been scheduled prior to the enrolment into the study.
2) The hospitalization for a survey visit, annual physicals, or social reasons.
3) Hospitalization qualifies for an SAE only for an inpatient treatment which includes an overnight stay.
4) A visit to the emergency room of a hospital without being admitted to inpatient stay regardless of the time of visit does not qualify for hospitalization.
5) Elective hospitalizations for pre-existing condition documented in the medical history that had not worsened (e.g. elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that had not worsened during the course of the trial).
6) Hospitalization for facilitating in-patient treatment of ISSNHL with other treatment options such as, for example, rheologic infusion therapy or hyperbaric oxygen, although these treatments are not permitted as per the protocol and will be documented as major protocol deviations.

9.1.3 Adverse Reaction

All noxious and unintended responses to the IMP related at any dose should be considered adverse reactions. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

9.2 Assessment of seriousness, causality, expectedness and severity

Seriousness: The judgment as to whether the event is serious or not is made by the Investigator. If the Medical Monitor or Sponsor is of the opinion that an AE should be rated as serious, the SAE form has to be completed by the site.

Causality **(causal relationship)**: An event can be either causally related or not causally related to the IMP, or causally related or not causally related to the intratympanic IMP administration procedure. The Investigator will assess the causal relationship of the AE with respect to:

- the IMP, and / or
- the intratympanic IMP administration procedure.

Related means that there are facts (evidence) or arguments that suggest a causal relationship. Investigators will assign causality at their respective sites during the trial. In case no causality is assigned by the Investigator, the Investigator is encouraged to express an opinion. The Medical Monitor of the trial will review all AE data for the assigned causality. If the Medical Monitor disagrees with the Investigator's causality assessment, the opinion of both the Investigator and the Medical Monitor will be provided.

Expectedness: The expectedness of an adverse reaction is determined by the Medical Monitor and is assessed in the light of the Reference Safety Information (RSI). The RSI is contained in the most current version of the IB. The term "expected", in pharmacovigilance, strictly refers to the event being mentioned or listed in the applicable RSI. It is not used to describe an event which might be anticipated from knowledge of the pharmacological properties of a substance. An event is also not to be described as "expected," merely because it was foreseeable due to the health status (e.g., age, medical history) of the trial subject.

Severity: The following three-point rating scale will be used by the Investigator to rate the maximum intensity of each AE:

- Mild: The subject is aware of signs or symptoms causing minimum discomfort but no disruption of usual daily activities consistent with what would be expected in an uneventful recovery period.
- Moderate: The event is sufficiently discomforting to the subject that it interferes with usual daily activities consistent with what would be expected in an uneventful recovery period (disturbing).
- Severe: Due to the event, the subject is unable to perform usual daily activities consistent with what would be expected in an uneventful recovery period (prevents).

9.3 Pregnancy exposure (exposure in utero)

Becoming aware of a pregnancy during the clinical trial does not necessarily lead to withdrawal of the subject. Pregnant subjects will be instructed to perform all follow-up visits. If a pregnancy is discovered while the subject is receiving background therapy, this therapy must be stopped immediately.

9.4 Reporting

9.4.1 Trial specific rules for reporting

All AEs, including SAEs and clinically relevant abnormalities in laboratory test variables, will be monitored and documented from the time point of ICF sign off during TV until FUV4 (see Section 9.1).

The Investigator should ask the trial subject in a non-leading manner about the state of his/her health in order to elicit information on AEs which may have occurred since the last visit. Any clinically significant observations made during the visit itself also constitute AEs. The Investigator should make an assessment for AEs at each visit and record the events in the source documentation and in the CRF on the "Adverse Events" pages. Follow up information must be entered as soon as available.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the CRF. However, if an observed or reported sign, symptom or clinically significant laboratory abnormality is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE in the source documents and on the CRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at the baseline medical assessment will be documented as medical history. If a medical condition or signs or symptoms present at baseline worsens (e.g. change in severity or seriousness) at any time during the trial, this should be reported as an AE.

SAEs will be followed until the event resolves or stabilizes or up to 2 months after FUV4. The Investigator is obliged to assist with the follow-up of SAEs. In case a SAE occurs after the subject has completed the trial and the Investigator considers this event related to the IMP or trial procedures, it should be reported immediately. The Investigator must contact the CRO Safety Manager to determine how the SAE should be documented and reported.

Any AE that is still ongoing after a subject's final visit will be recorded as ongoing in the CRF. However the Investigator will continue to follow up ongoing SAEs for the time frame described above and record information in the source documents and on the *Follow-Up SAE Form.*

For all AEs the Investigator is responsible for documenting the action taken and the outcome, as specified in the source documents and in the CRF.

The onset date of an SAE is the time as of which the event fulfils a criterion for seriousness, which will be captured on the SAE page in the CRF. For details on documenting worsening of hearing and worsening of tinnitus refer to Sections 9.4.1.1 and 9.4.1.2.

Adverse events which occur during the trial should be treated by established standards of care that will protect the life and health of the subject.

9.4.1.1 Worsening of hearing

A worsening of hearing in the treated ear is not to be recorded as AE. Any change of hearing thresholds and word recognition scores is subject of analysis under this protocol. The subject's subjective sensations will be captured by patient reported outcome measures (HHIA, PGIC).

9.4.1.2 Worsening of tinnitus

A worsening of tinnitus in the treated ear is not to be recorded as AE. Any change in tinnitus loudness or tinnitus annoyance is the subject of analysis under this protocol.

The occurrence of new tinnitus in the treated or untreated ear should be recorded as AE.

9.4.1.3 Tympanic membrane perforation

Observation of tympanic membrane perforation due to the intratympanic administration procedure is considered to be medically normal for up to 7 days following the procedure and is recorded in the source documents and on the CRF as a finding, and not as an AE.

The observation of a blood crust, swelling or redness on the tympanic membrane due to wound healing at the site of the intratympanic administration is also to be recorded in the source documents and on the CRF as a finding and not as an AE.

A tympanic membrane perforation persisting at FUV2 should be considered and recorded as an AE only if the perforation is judged by the Investigator to be involving > 5% of the surface area of the tympanic membrane as assessed by otoscopy / microscopy. If such a tympanic membrane perforation is present at FUV2, an additional follow-up visit has to be scheduled as described in Section 7.2.1.

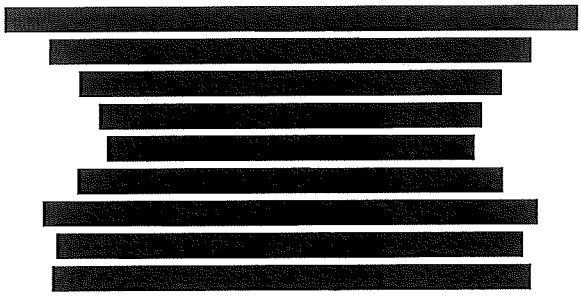
If the tympanic membrane perforation is still present and considered clinically significant at FUV3, the Investigator shall discuss the option of possible interventions to promote healing.

9.4.2 Reporting of SAE, pregnancy and pregnancy outcome by the Investigator

All SAEs, pregnancies, as well as pregnancy outcomes qualifying as serious must be reported to the CRO's Clinical Safety in an expedited manner, i.e. **within 24 hours** of awareness.

To report the SAE, the Investigator must complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, the CRO's Clinical Safety personnel will be notified electronically, will retrieve the information and will confirm receipt to the investigator by email. If the event meets seriousness criteria and it is not possible to access the eCRF, the Investigator must send an e-mail to the CRO's Clinical Safety or must send a fax of the completed paper SAE form within 24 hours of awareness.

Contact Information:



These events (regardless of the causality assessment) should be reported in writing (fax transmission, electronic form or via e-mail) or orally. Oral reports must be followed up with a written report as soon as possible and documented in source notes with date and time of communication. In all cases, the Investigator or designee must submit a completed Report Form within 24 hours after the study site became first aware of the event.

The minimum information to report is:

- Subject ID;
- Study code;
- IMP kit number;
- Date and time of administration of IMP;
- Date and time of start of SAE;
- Description of SAE (AE reported term);
- Severity of SAE;
- Assessment of causality relationship (will follow a yes/no category);
- Name, contact details of person reporting the event.

A CRO team member will then review all documentation together with the Medical Monitor and follow up with the investigative site to obtain all the additionally required information.

The Investigator must continue to follow the subject until the SAE resolves or stabilizes or up to 2 months after FUV4.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and must submit any supporting documentation (e.g., blinded subject discharge summary or autopsy reports) via email or fax to CRO's Clinical Safety. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

A pregnancy should be documented on a Pregnancy Report Form (paper) and sent by fax to the fax number above. The case must be reported within 24 hours of knowledge by the Investigator to the CRA and the CRO Safety Manager. The Investigator must follow up on pregnancies discovered after IMP administration until the end of pregnancy to document the outcome on the Pregnancy report form. The event fulfils the criterion for an SAE in case of a congenital anomaly (birth defect), fetus death or spontaneous abortion, or adverse reactions in the neonate that are classified as serious.

9.4.3 Reporting to the responsible IRB/IEC and Health Authorities/Regulatory Authorities

Expedited and periodic reporting required by the above mentioned functionaries and institutions will be fulfilled according to current local laws and regulations.

9.5 Unblinding

The treatment code must not be broken except in the event of medical emergencies, when the appropriate management of the subject necessitates knowledge of the treatment randomization. The Investigator is advised to discuss such cases with the Medical Monitor **prior** to unblinding the subject's treatment code.

Unblinding of a subject's treatment code may be performed by the Investigator or by the Medical Monitor within the IWRS. Refer to the corresponding manual.

Any case of unblinding must be documented by the Investigator in the subject's source documentation including the reason for unblinding.

All study subjects will have the telephone number of the Investigator and / or designee and instructions on how to contact the site during non-business hours.

10 Trial endpoints

Baseline data will be taken from baseline assessment during TV performed prior to randomization and subsequent treatment. The only exceptions are the questionnaires (HHIA and PGIC) that are assessed for the first time at FUV2 and FUV3, respectively, as they only evaluate the change in condition severity after treatment initiation.

10.1 Efficacy endpoints

10.1.1 Primary efficacy endpoint

The primary 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 three most affected contiguous frequencies which are used for the calculation of PTA are defined relative to the unaffected contralateral ear or, in case of asymmetric hearing, corresponding values from a pre-existing audiogram for the affected ear not older than 2 years. If the PTA is the same across different sets of frequencies the set of lower contiguous frequencies is considered as reference. The PTA frequencies are determined from the baseline assessment and are fixed throughout the trial to evaluate hearing 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.

An improvement in hearing threshold of at least 10 dB is considered clinically relevant.

10.1.2 Secondary efficacy endpoints

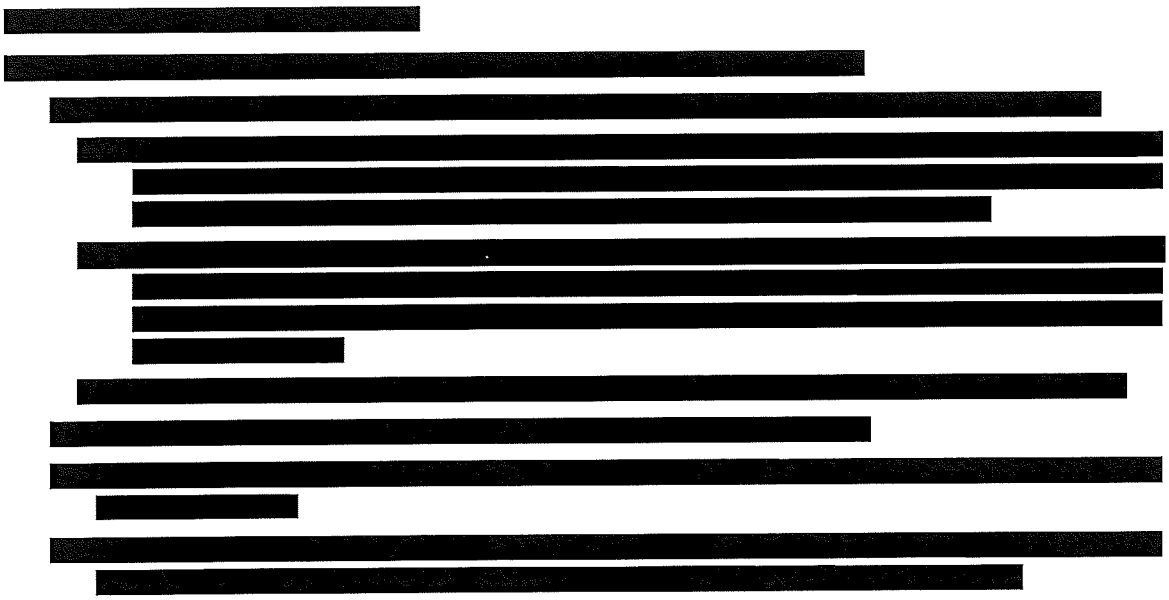
The following secondary efficacy endpoints will be evaluated in this study:

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.

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. Complete tinnitus remission is achieved when a subject rates both $TLQ_{Loudest}$ and TAQ_{Worst} as zero, and answers the question about tinnitus presence with "No".



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10.2 Safety endpoints

10.2.1 Primary safety endpoint

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.

10.2.2 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:
  - The IMP;
  - The intratympanic IMP administration procedure.

[redacted]

11 Statistical methods and data analysis

A statistical analysis plan (SAP) will detail the statistical evaluation. This plan is finalized prior to unblinding. In particular, changes of planned analyses outlined in the trial protocol will be documented in the SAP. Deviations from the approved SAP will be documented in the clinical trial report.

11.1 Sets analyzed

11.1.1 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 (IDMC) will decide whether a PTA measure is considered valid or not. A PTA measure is considered valid if a review by the IDMC member 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.

11.1.2 Per Protocol (PP) 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 endpoint or main secondary efficacy endpoint. Protocol deviation definitions are described in detail in the Statistical Analysis Plan 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.

11.1.3 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.

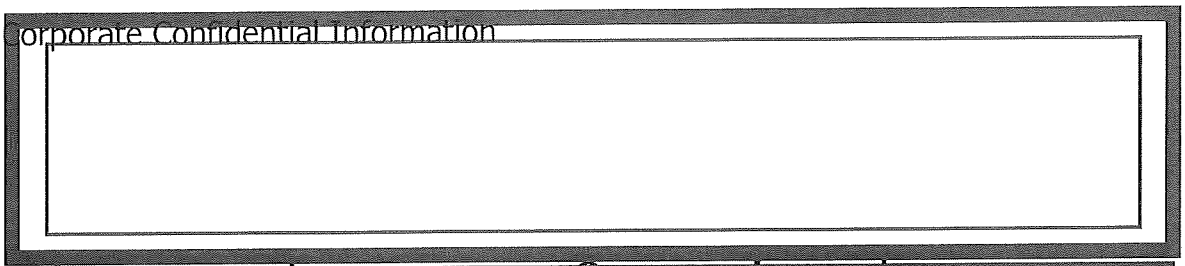
11.2 Imputation of missing values

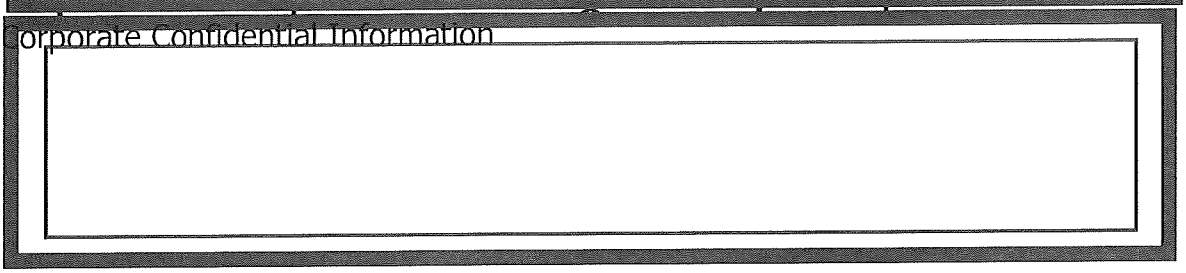
Statistical analysis is based on available data. With the exception of the rules outlined below, no missing values will be replaced.

[redacted]

[redacted]

[redacted]





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11.4 Evaluation of baseline data

The participant flow in the trial is summarized according to CONSORT 2010 guideline (Moher *et al.*, 2010). The number of subjects randomized is also summarized by country. The number of subjects in the different analysis sets is summarized together with the reasons for exclusion of subjects from the analysis set.

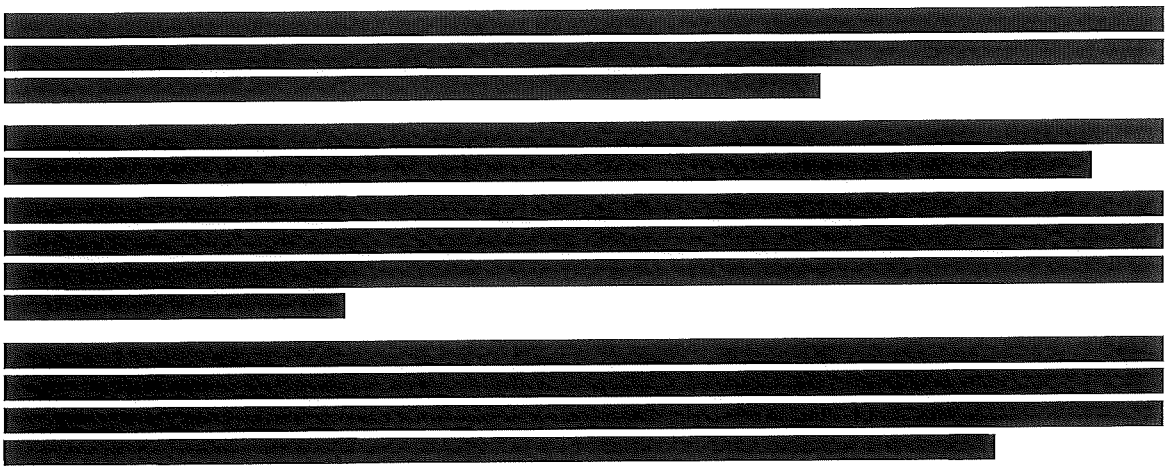
All subjects' demographic data and baseline characteristics will be listed and tabulated. Summary statistics (n, arithmetic mean, standard deviation, minimum, Q25, median, Q75 and maximum) will be provided for quantitative data. For qualitative data frequency tables will be provided.

11.5 Evaluation of efficacy endpoints

11.5.1 General statistical methods

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), and will be further broken down by initial $WRS_{(80\ dB)}$ ($\leq 30\%$ and $> 30\%$) and country.

Continuous endpoints will generally be analyzed using a repeated measurement mixed analysis of covariance model (ANCOVA) for the change from baseline in the respective endpoint. Such a model can be fitted by using PROC MIXED in SAS. The ANCOVA models will be stratified by initial $WRS_{(80\ dB)}$ of the affected ear ($\leq 30\%$ and $> 30\%$) and include the baseline value of the respective endpoint and initial PTA frequency range (≤ 2 kHz and > 2 kHz) as covariates, treatment group, visit, and treatment-by-visit interaction as fixed effects as well as subject as random effect. For all WRS endpoints, the initial $WRS_{(80\ dB)}$ range will not be included as a covariate in the model, as this is already accounted for by inclusion of $WRS_{(80\ dB)}$ ($\leq 30\%$ and $> 30\%$) as a stratum. Point estimates (least square [LS] means) at each visit will be calculated for each treatment difference "AM-111 0.4 mg/mL minus placebo" and "AM-111 0.8 mg/mL minus placebo" with two-sided 95% and 96 or 99% confidence



11.5.2 Primary and main secondary efficacy endpoints

The primary analysis uses a mixed ANCOVA model for repeated measurements on the Efficacy Analysis Set.

Superiority of an active dose compared to placebo is claimed if

- the p-value of the comparison between active dose and placebo is below the required threshold and
- the point estimate of the change from baseline shows higher improvement in active dose compared to placebo.

To account for the use of two doses of AM-111 and the need to assess both the primary and the main secondary endpoints per dose group, a multiplicity adjustment based on a combination of hierarchical testing and weighted Bonferroni-Holm procedure is used. For details refer to Section 11.3.

Sensitivity analyses with imputed missing values using the random imputation method (refer to Section 11.2) will be performed by applying an ANCOVA model with fixed effects for the baseline PTA value as covariate, treatment group and initial $WRS_{(80\ dB)}$ of the affected ear ($\leq$ 30% and > 30%) as a stratification factor on the absolute improvement of PTA or $WRS_{(80\ dB)}$ from baseline to FUV4.

Furthermore, a sensitivity analysis of the primary and main secondary endpoints is conducted by means of the PP, if applicable.

For the main secondary endpoint another sensitivity analysis over all subjects with an initial $WRS_{(80\ dB)}$ of $\leq$ 80% will be performed.

The complete list of analyses and methods will be described in the SAP.

11.5.3 Other secondary efficacy endpoints

The analyses of other secondary endpoints will be based on the Efficacy Analysis Set.

Continuous secondary endpoints, i.e. absolute improvement in PTA from baseline to FUV1, FUV2 and FUV3 as well as absolute improvement in $WRS_{(80\ dB)}$ from baseline to follow-up visits FUV1, FUV2 and FUV3 will be analyzed analogously to the primary endpoint. As sensitivity analyses, ANCOVA models with fixed effects for the baseline PTA value as covariate, treatment group and initial PTA frequency range ($\leq$ 2 kHz and > 2 kHz) as a stratification factor will be separately applied on the absolute improvements of PTA from baseline to FUV1, FUV2, and FUV3. Furthermore, for the absolute improvement in PTA from baseline to FUV3, sensitivity analyses with replacement of missing values by random imputation (refer to Section 11.2) will be performed. For the analysis of $WRS_{(80\ dB)}$, language of the word list will be used as an additional covariate.

The binary secondary endpoint Frequency of complete tinnitus remission at FUV4 in subjects with ISSNHL-related tinnitus at baseline will be evaluated using a logistic regression including treatment group and initial PTA frequency range ($\leq$ 2 kHz and > 2 kHz) as covariates; initial $WRS_{(80dB)}$ ($\leq$ 30% and > 30%) will be included as a stratification factor.. Treatment effect is expressed as an odds ratio.

[redacted]

11.6 Evaluation of safety endpoints

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

11.6.1 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. Between-group incidences will be compared with Fisher's exact test.

11.6.2 Secondary safety analyses

The following secondary safety analyses will be performed:

- The percentage of subjects with clinically relevant hearing deterioration in the treated ear from baseline to FUV1, FUV2 and FUV4 will be analyzed in the same way as the primary endpoint.
- The difference in occurrence of clinically relevant hearing deterioration from baseline to all FUVs between treated and untreated contralateral ear will be compared with McNemar's test.
- The incidence of post-treatment AEs and SAEs will be described overall and analyzed by relatedness to IMP and to intratympanic IMP administration procedure.
- The incidence of AEs will be summarized by system organ class, preferred term, severity and the relationship categories as outlined in Section 10.2.2. Summaries will be presented by treatment group and overall.
- Summaries for middle ear tolerance at the FUVs as well as between trial visits will also be presented with the absence or presence of AEs.

[redacted]

and visit including changes from TV to all FUVs. Shift tables will be provided by treatment group showing the number of subjects that have shifted from normal to abnormal from TV to all FUVs.

For vital signs, summary statistics will be provided by treatment group and visit including changes from baseline to each FUV.

For the C-SSRS, the following outcomes as defined in the official scoring guide (Nilsson *et al.*, 2013) will be determined: Suicidal behavior (yes / no), suicidal ideation (yes / no), suicidality (yes / no), suicidal ideation rating (0 – 5), suicidal ideation intensity (0 – 25). The suicidal ideation intensity will be analyzed descriptively by summary statistics, including changes from baseline. All other outcomes will be analyzed by absolute and relative frequencies, including shift tables.

11.7 Other data

All other data, such as concomitant medication or findings from tympanometry, otoscopy, nystagmoscopy or Romberg's test, will be presented in individual data listings and by appropriate descriptive statistics.

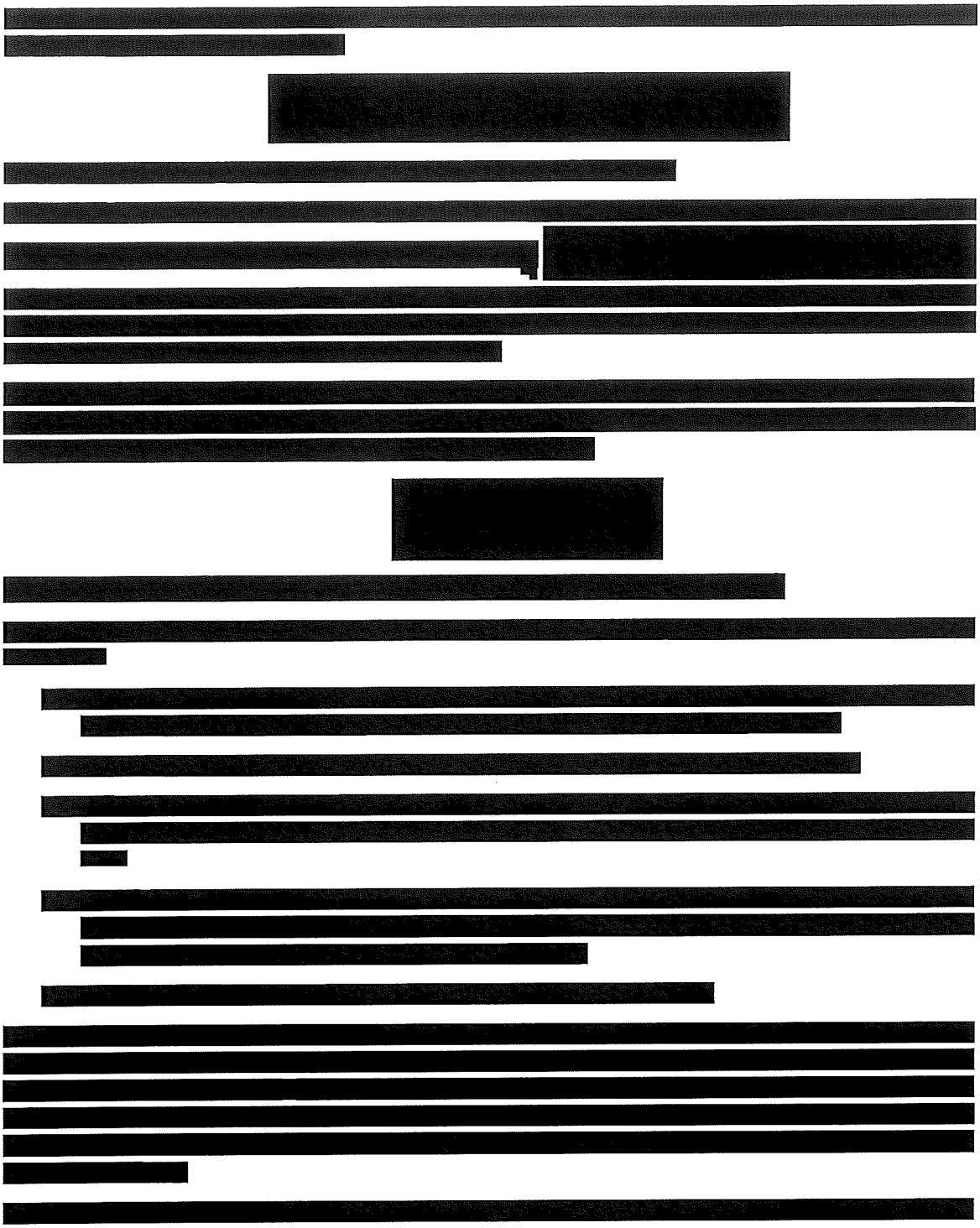
Concomitant medication will be classified according to World Health Organization (WHO)-Drug Dictionary prior to providing tabulated overviews.

11.8 Determination of sample size

The sample size calculation is based on the primary endpoint. [redacted]

11.9 Interim and main analysis

After 50% of the subjects have reached FUV4, an unblinded interim analysis will be performed to check the assumptions made for sample size calculation and increase the sample size if necessary. No early stopping for futility or efficacy is planned. This interim analysis will be conducted by an independent statistician, blind to the Sponsor. [redacted]



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Corporate Confidential Information

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12 Quality control and quality assurance

The accuracy, consistency, completeness and reliability of the trial data produced under this protocol will be assured through the quality control (QC) and quality assurance activities performed in accordance with the Standard Operating Procedures (SOPs) of the Sponsor or of the Sponsor representative (CRO).

The trial will be monitored according to the ICH-GCP Guidelines (E6 Section 5).

This trial will be monitored by CRAs from the Sponsor's designated representative. On-site visits will be made prior to the initiation of the trial center and at appropriate times during the period of the trial. Communication will also include telephone conversations and correspondence.

In accordance with GCP guidelines, the CRA must have direct access to the Investigator's source documentation in order to check:

- consistency of the data recorded in the CRFs;
- protection of safety and rights of subjects;
- trial conduct according to the currently approved protocol version and all applicable requirements.

The purpose of source data verification is to verify, to the extent possible, that the information in the CRF reflects the data recorded in the subject's medical records and data recorded by the subjects on their diaries. Source document verification will be performed with due regard for subject confidentiality. Source document verification will be undertaken on an ongoing basis as part of the monitoring visits.

The Investigator agrees by written consent to this protocol to fully co-operate with compliance checks by allowing direct access to all documentation by authorized individuals.

Any of the trial sites may be subject to an audit by an auditor appointed by the Sponsor or to an inspection by a regulatory agency or IEC/IRB. If such an audit/inspection occurs, the Investigator agrees to allow the auditor/inspector direct access to all relevant source documents and to allocate his/her time and relevant staff time to discuss the findings. The Investigator shall inform the Sponsor immediately of any upcoming audit or inspection.

13 Ethics

13.1 Ethical conduct of the trial

This clinical trial will be conducted in compliance with this protocol and in accordance with the ethical principles stated in the Declaration of Helsinki 1989 version (US sites), and in its most current version (Non-US sites), as provided in Appendix 6.

The trial will be conducted in accordance with all applicable laws and regulations of the country where the trial is conducted, and in compliance with Good Clinical Practice guidelines.

13.2 Data protection

The written Informed Consent will explain that trial data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative will be identified by subject number and trial code. Subject identity will be kept confidential at all times of the trial, by removing all identifiers from the subject samples and clinical documentation for this trial, as well as any report or publication.

The written Informed Consent will also explain that for data verification purposes the Sponsor, authorized representatives of the Sponsor, regulatory authorities (e.g. FDA or other national authorities), and IEC/IRBs may require direct access to parts of the hospital or clinic records relevant to the trial that include the subject's medical history.

The Informed Consent Form will be accompanied by or include a separate document incorporating HIPAA-compliant wording (U.S.) respectively applicable data protection regulations (Non-U.S.) by which the subjects authorize the use and disclosure of their Protected Health Information.

13.3 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

Prior to trial initiation, this Protocol, the proposed Informed Consent Form (ICF) as well as other documents required by current regulations will be submitted to an IEC/IRB.

A signed and dated statement that this Protocol and the ICF have been approved by the IEC/IRB must be filed. In accordance with GCP and applicable regulatory requirements, the trial will not start at a site before receiving the respective IEC/IRB's approval. A copy of the written approval of the IEC/IRB must be available before dispensing any IMP to trial subjects.

The IEC/IRB must be informed by the CRO of all subsequent protocol amendments, serious adverse reactions (SARs), and suspected unexpected serious adverse reactions (SUSARs), occurring during the trial that are likely to affect the safety of the subjects or the conduct of the trial. Information on pregnancies occurring during the clinical trial and pregnancy outcomes qualifying as serious are also to be provided to the IEC/IRB.

As required by local law, Protocol amendments referring to logistical or administrative changes (non-substantial) may be implemented with notification of the IEC/IRB and regulatory authority only.

The constitution of the IEC/IRB must meet the requirements of the participating countries and ICH-GCP.

A list of the IEC/IRB members with names and qualifications plus a statement that it is organized according to GCP and the applicable laws must be provided to the Investigator for filing in the Investigator Site File (ISF) and to the CRO for filing in the TMF as applicable per local law.

13.4 Informed Consent

An appropriate ICF will be created and reviewed and approved by an IEC/IRB to ensure that potential research subjects are fully informed about the nature and objectives of the clinical trial, the potential risks and benefits of trial participation, and their rights as research subjects. Prior to the first trial specific assessment (i.e. before starting baseline assessments other than routine assessments), all subjects will be fully informed verbally and in writing about the nature and aim of the trial. Subject information and the ICF must be in a language fully comprehensible to the prospective subject. The Investigator or

designee will ensure that the subject can read and understand the ICF or if the subject is unable to read, he/she is informed of the investigational nature of this trial and has given written informed consent in accordance with institutional, local, and national guidelines. Subjects will also be reminded that their participation is voluntary and that they are allowed to ask for withdrawal at any time without affecting their relationship with the Investigator or access to any future treatment. Subjects will be given ample time to review the ICF and will be given the chance to discuss any question related to the trial with the Investigator or designee. The subject will then sign and date the IEC/IRB approved consent form indicating that he/she has given his/her consent to participate in the trial.

The completion of the informed consent process will be documented by obtaining the subject's as well as the Investigator's (or designee's) handwritten signature, date and time on the ICF. The Investigator must document the informed consent process in the subject's source documents. Each subject's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities, the Sponsor and/or the CRO.

In the event of substantial changes to the clinical trial or to the risk-to-benefit ratio of trial participation, the Investigator will obtain the signed informed consent of subjects for continued participation in the clinical trial using only an IRB/IEC approved amendment to the ICF.

14 Data handling and record keeping

14.1 Confidentiality of data

All local legal requirements regarding protection of personal data must be adhered to.

The anonymity of trial subjects will be maintained. Throughout documentation and evaluation, the subjects will be identified on CRFs and other documents only by their year of birth and a subject number. Documents which identify the subject (e.g. the signed ICF) must be maintained in confidence by the Investigator. The subjects will be informed that all trial data will be stored on paper and by electronic means and will be handled in the strictest confidence.

Any results and documents derived from the trial will also be regarded as confidential. The Principal Investigators and all members of their research teams will not be allowed to disclose such information, except for authorized representatives of appropriate regulatory authorities, without prior written approval from the Sponsor.

14.2 Case report forms and source documents

For each subject, the Investigator or designee must enter all the requested data and findings as they occur during the study as source data into the source documents. The first documentation of an assessment result is considered the source data entered into the original source document.

The Investigator must keep the source documents in good order and up to date so that they always reflect the latest observations on the subjects enrolled in the study. From the source documents, the data will be entered into an electronic CRF (eCRF) in a timely manner. No data will be entered directly into the eCRF.

In order to assure highest quality standards, the Sponsor will assure 100% verification of CRF entries against source documents. The Investigator will therefore ensure that CRAs are entitled to compare CRF entries with source documents and to inform the Investigator about errors and omissions. Source documents for this study include all documents or (electronic) systems where study related data about study subjects are entered and stored. Source records include, but are not limited to, subject's medical records (electronic and or paper), referral and discharge letters, audiologist reports, other specialists' reports, nurses reports, laboratory reports, subject questionnaires and diaries, IMP dispensing logs, etc.

Corresponding information in the CRFs must be comprehensible and reproducible from the subject's records.

For further information please refer to the CRF completion guidelines.

14.3 Independent Data Monitoring Committee

An IDMC will perform an ongoing review of the audiograms for quality assurance. The IDMC will decide whether a PTA measure is considered valid or not. This will impact the assignment of the subjects to an analysis group as per section 11.1 of the ASSENT Protocol.

14.4 Background therapy documentation card

The background therapy documentation card in local language is intended for the daily documentation of the intake of oral corticosteroids in subjects receiving the background therapy.

The reserve therapy documentation card is dispensed at TV and will be used to document the complete course of corticosteroids. In case the subject received corticosteroids within 36 hours prior to randomization, it will be noted on the card. The card will be inspected at all follow-up visits until collected by the Investigator or designee on FUV3. Data entered by subjects on the reserve therapy documentation card will be entered in the CRF by the Investigator or designee. The completed card will be part of the source data.

14.5 Data handling

The database will be designed based on the final protocol, the System/Core Configuration, eCRF Specifications and Consistency Check Specifications.

Data management will be performed with the chosen Electronic Data Capture (EDC) platform Medidata RAVE.

Data will be entered directly from source notes at the site into the eCRF and will be verified by CRAs to ensure data integrity. Each data point is time stamped and stored within the clinical database. Only authorized site staff will be able to perform the single data entry within the system.

Some data discrepancies generated as a result of the data entry process will be automatically flagged as entry is being completed. In addition, Data Management will also review the entries for data consistency and accuracy via manual and ad-hoc checks.

The Investigator must electronically sign each subject's eCRF after completion of data entry, signifying that the data entered in the eCRF is complete and accurate. The eCRFs for all subjects who received IMP will be provided to the Sponsor after study completion.

14.6 Record maintenance and retention

The Investigator will maintain an ISF, which must be kept up-to-date on an ongoing basis. The ISF must contain all essential documents as outlined in the ICH Guideline for GCP E6.

The Investigator shall arrange for the retention of the subject identification codes, subject files and other source data until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, or the period required by local regulation, following the longest requirement. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained, and can be destroyed.

Subject files and other source data should be retained in accordance with applicable legislation and for the maximum period of time permitted by the hospital, institution or private practice.

After completion of the trial, all documents and data relating to the trial will be kept in an orderly manner by the Investigator in a secure trial file. This file will be available for inspection by the Sponsor or its representatives. After completing the trial, the Investigator will receive copies of the eCRF. Essential documents must be retained for at least 15 years after completion of the trial. The Investigator will appoint individuals responsible for the storage of essential documents and access to the documents will be restricted to those people. Any alterations to essential documents must be traceable.

No trial documents will be destroyed without prior written agreement between the Investigator and Sponsor. Should the Investigator wish to assign the trial records to another party, or move them to another location, the Sponsor must be notified in writing.

15 Financing and insurance

The Sponsor will pay for costs of treatments specifically related to the trial that would not ordinarily be incurred under the applicable standard of care. A separate financial agreement will be made (as appropriate) with the Investigator and/or institutions.

In case of any damage or injury occurring to a subject in association with the IMP or participation in the trial the Sponsor has taken out a subject insurance policy as required by applicable local law with insurance companies. A copy of the respective Insurance Agreement is filed in the ISF and the subject can request a copy of the terms and conditions.

Each Investigator (including any sub-Investigator) who is directly involved in the treatment or evaluation of subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant information regarding the financial disclosure will be filed in the TMF and the ISF.

16 Publication policy

The Investigator participates in this trial as part of a multicenter trial. The Sponsor recognizes the necessity for the Investigator to publish important scientific results from the trial. After a multicenter publication or twelve (12) months after completion of the trial, whichever occurs first, the Investigator may publish the results of his/her own data from the trial. The Investigator agrees to submit to the Sponsor an advance copy of any intended communication (e.g. abstract, poster, or article) at least sixty (60) days prior to the submission of such proposed publication or presentation to a journal, editor, or other third party. The Sponsor shall have sixty (60) days, after receipt of said copies, to object to such proposed presentation or proposed publication because there is patentable subject matter or proprietary information of the Sponsor that needs protection. In the event that the Sponsor makes such objection, the Investigator shall refrain from making such publication or presentation for a maximum of six months from date of receipt of such objection in order for the Sponsor to file patent application(s) with the European Patent Office and/or foreign patent office(s) directed to the patentable subject matter contained in the proposed publication or presentation.

Since the present trial involves multiple Investigators and sites, Investigators and their Institutions will publish or publicly present their results only together with the other sites (multicenter publication) unless specific written permission is obtained in advance from Sponsor to publish separate results.

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Appendices

Appendix 1: Tinnitus Presence or Absence

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

Subject instruction at baseline (to be read by the investigator to the patient):

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.

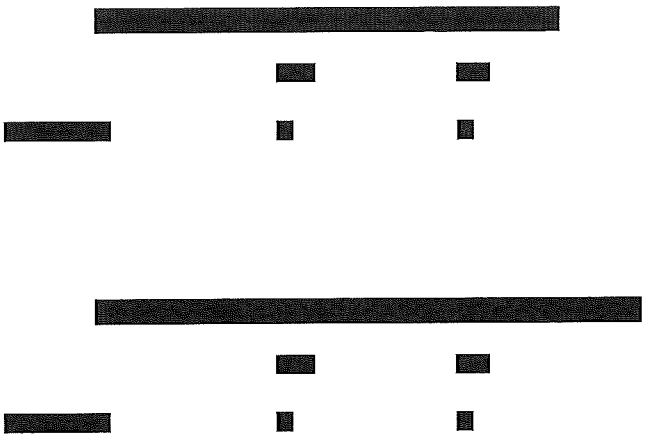
[redacted]

The Investigator will further investigate whether the tinnitus is related to the ISSNHL incident or a pre-existing condition.

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 2: Tinnitus numerical rating scales

Company Confidential Information

Appendix 3: 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

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Appendix 4: Patient Global Impression of Change

Company Confidential Information

Appendix 5: 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 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). 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 6: Declaration of Helsinki

Version 1989 (US sites)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.

Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The Investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Version 2013 (Non-US Sites)

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances

the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.