CLINICAL STUDY PROTOCOL

A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Presence of SENS-401 in the Perilymph after 7 days of repeated oral administration in Adult Participants Scheduled for Cochlear Implantation

Protocol Number:	**SENS-401-203**
Investigational Product:	**SENS-401 ((R)-azesetron besylate) as oral tablet**
IND Number:	**Not applicable**
EudraCT Number:	**2021-006615-28**
Sponsor:	**Sensorion Australia Pty Ltd** **Suite 2003, 109 Pitt Street** **Sydney, NSW 2000** **Australia** [redacted]
Sponsor Signatory:	[redacted] **Chief Medical Officer** [redacted]
CRO:	[redacted]
Medical Monitor:	[redacted] **Sensorion Australia Pty Ltd** [redacted]
Date and Version:	**Version 3.0, 08 February 2023**

Confidentiality Statement

History of the protocol version

Version	Date	Reasons
2.0	25 April 2022	-
3.0	08 February 2023	• **No upper limit of age for participants** • **Screening period is 42 days maximum instead of 28 days maximum** • **Subjects can be randomised up to 8 to 14 days prior to the cochlear implant surgery**

1 PROTOCOL SUMMARY

1.1 PROTOCOL SYNOPSIS

Protocol Title	A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Presence of SENS-401 in the Perilymph after 7 days of repeated oral administration in Adult Participants Scheduled for Cochlear Implantation
IND Number	Not applicable
EudraCT Number	2021-006615-28
Protocol Number	SENS-401-203
Sponsor	Sensorion Australia Pty Ltd
Phase of Development	Phase IIa
Number of Study Sites	Up to 5 study sites in Australia and France
Investigational Medicinal Product and dose	Oral SENS-401 supplied as 14.5 mg (10 mg free base) *(R)*-azasetron besylate tablets: 3 tablets of 14.5 mg SENS-401 twice daily (morning and evening), oral route
Comparator	No treatment
Treatment Groups	Arm A: Participants scheduled for cochlear implantation and randomized to be treated with oral 43.5 mg SENS-401 twice daily (b.i.d.) for 49 days (7 days prior to cochlear implant surgery, and 42 days from day of surgery inclusive). Arm B: Participants scheduled for cochlear implants and randomized to not be treated with SENS-401.
Participant Population	Adults aged from 18 years and older with preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80dB or better (i.e., ≤80 dB) at 500Hz, who meet the locally approved indication for, and have already consented to receiving, cochlear implant Cochlear™ Nucleus® C1622 prior to study entry.
Duration of Study	Participants will be on study for a maximum of 168 days: • up to 42 days for the screening period; • up to 56 days for the treatment period;

	• up to 70 days for the follow-up period.
Objectives	*Primary*: To detect the presence of SENS-401 in the perilymph of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401. *Secondary*: • To measure the SENS-401 concentrations in the perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401. • To compare the SENS-401 concentrations in perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401. • To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery at the Day 49 visit and at EOS/ET. • To assess the safety and tolerability of SENS-401 for the whole duration of the study. *Exploratory*: • To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery; here performed on a subset of participants with no electrophysiological evidence of basilar membrane fixation as described in Section 6.4.2. • To collect and store a biobank of plasma and serum to be able if necessary and possible to explore the correlation between biomarkers already pre-identified (e.g., prestin) or that will be identified in the future with clinical features of interest.
Endpoints	*Primary:* • Percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification on day of cochlear implant surgery after seven days of SENS-401. *Secondary*: Pharmacokinetics:

	• SENS-401 perilymph concentration on day of cochlear implant surgery after seven days of SENS-401. • SENS-401 plasma concentration on day of cochlear implant surgery after seven days of SENS-401. Efficacy: • Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS/ET. • Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS/ET. Safety: • Incidence of treatment emergent AEs and SAEs in each participant until the end of their study participation. • *Exploratory*: In a subset of participants assessed by a neurophysiologist to have no electrophysiological evidence of basilar membrane fixation: - Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA). - Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA). • Serum/plasma concentrations of selected biomarkers at baseline (i.e., Day 1, and pre-dose for Arm A), at the Day 49 visit, and at EOS/ET.
Study Description	The study is a Phase IIa, open-label, randomized and controlled study investigating repeated twice-daily administration of oral SENS-401 in adult participants with preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (i.e., ≤80 dB) at 500 Hz), who meet the locally approved indication for, and have already consented to receiving, cochlear implant Cochlear™ Nucleus® C1622. After written informed consent is obtained and screening procedures completed, 27 eligible

	participants will be randomized on Day 1 to either Arm A or Arm B in ratio 2:1 (18 participants in Arm A and 9 participants in Arm B). Arm A participants will commence dosing with twice-daily oral 43.5 mg SENS-401 for 7 to 13 days prior to their cochlear implant surgery scheduled from Day 8 to Day 14. Dosing will continue on the day of surgery. Arm B participants will not receive any treatment other than their scheduled cochlear implant surgery. All participants will undergo audiometric testing at screening and Day 1 (baseline). From Day 1, Arm A participants will record each administration of SENS-401 into a study diary. Blood and perilymph samples for determining SENS-401 concentration will be collected from Arm A participants only on the day of cochlear implant surgery (blood sampling before the morning dose of SENS-401 and perilymph sampling during the course of the surgery). Electrocochleography will be performed for all participants (Arm A and Arm B) during cochlear implant surgery. All participants (Arm A and Arm B) will attend the Day 49 visit, when efficacy and safety assessments will be performed. Arm A participants will continue to take SENS-401 until this visit. All participants (Arm A and Arm B) will then return to the study site for the EOS on Day 105 for final safety and efficacy assessments. Blood samples for exploratory biomarker research will also be collected from all participants (Arm A and Arm B) on Day 1, Day 49 visit, and EOS. All the subjects receiving SENS-401 will have before EOS at least 4 weeks of follow-up after their last dose of SENS-401.
Sample Size	27 randomized participants. The sample size of this study is based on empirical considerations for the pharmacokinetic evaluation (primary objective of this study). For PK and safety: Although the sample size is not calculated based on statistical hypotheses, eighteen participants are generally considered sufficient to characterize the PK of a small molecule. In addition, the systemic PK profile of two dose levels of SENS-401 was previously evaluated in a Phase I healthy volunteer study and further documented in a phase 2a study (SENS-401-201). The main purpose here of the PK sampling is to determine if SENS-401 can be detected in the perilymph and to compare the levels of SENS-401 in two different body compartments.

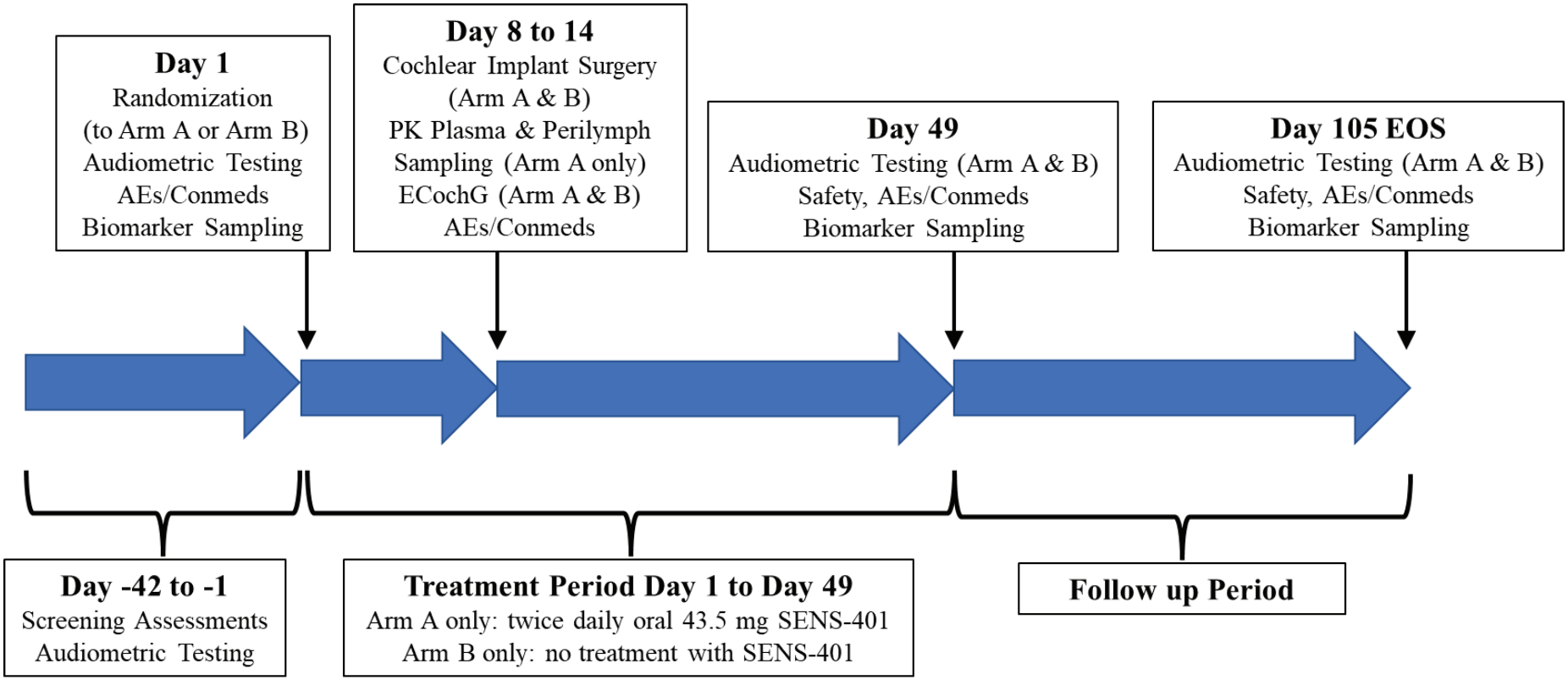
	For efficacy: 27 participants are expected to provide enough data to evaluate a trend of efficacy. A sufficient number of participants will be screened in order to randomize 27 participants.
Inclusion Criteria	Potential participants must fulfil all of the following inclusion criteria to be eligible for the study: 1. Adults aged from 18 years and older. 2. Meets the locally approved indication for cochlear implantation with the Cochlear™ Nucleus® C1622 and has preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (i.e., ≤80 dB) at 500 Hz. The individual must have freely consented to the cochlear implant surgery before being offered to participate in the SENS-401-203 study. 3. Signed and dated written informed consent. 4. Females who have or may have male sexual partners must meet one of the following criteria at Screening: • Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause), surgically sterile, or abstinent; or • A woman of childbearing potential (WOCBP) (any female who has experienced menarche and who is not permanently sterile or postmenopausal) practicing a method of highly effective birth control that is listed in Appendix 11.1 and is willing to continue to use highly effective contraception (as per Appendix 11.1) for the duration of study participation and for at least 30 days after the final dose of study drug. All WOCBP must have a negative serum pregnancy test at screening before the first dose of study drug is taken. Participants randomized to Arm B on Day 1 will not be required to further adhere to the contraception requirements of the study. *Note: No contraception measures are needed for male participants, including those with pregnant or non-pregnant WOCBP partner.* 5. Vaccinated against coronavirus disease 2019 (COVID-19) per local vaccination schema requirement or previously contracted the disease and recovered within the last six months.

Exclusion Criteria	Individuals will be excluded from the study if any of the following criteria apply: 1. Moderate to severe renal impairment defined by a creatinine clearance ≤ 60 ml/min (calculated with the Cockcroft-Gault formula for individuals <65 years old and with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or the Modification of Diet in Renal Disease Study (MDRD) equation for individuals ≥65 years old). 2. Any condition that, in the opinion of the Investigator, may compromise the safety or compliance of the participant or would preclude the participant from successful completion of the study. 3. Unable or unwilling to comply with the protocol requirements. 4. Any therapy known as ototoxic (e.g. aminoglycosides, cisplatin, quinine etc.) at the current time or in the past 6 months prior to study inclusion. Loop diuretics at normal therapeutic doses are permitted. 5. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction. 6. Pregnant or breast-feeding. 7. Treatment with any investigational agent within 4 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer). 8. Either a history of significant arrhythmia, or a history of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, long QT Syndrome, hypokalemia) . 9. Radiological evidence of bony obliteration of the round window membrane on pre-operative high-resolution CT imaging of the temporal bone. 10. Loss of cochlear fluid signals on pre-operative MRI imaging, suggestive of fibrosis or ossification of the cochlea. 11. Any probihited concomitant therapy listed in the §5.8.1 Other prohibited concomitant therapies.
Statistical Analysis	*Pharmacokinetic (PK) Analysis:* The number and percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification on day of cochlear implant will be summarised. Paired tests will be performed for

	comparison of drug concentration between perilymph and plasma. *Efficacy Analysis*: All efficacy data will be tabulated by treatment group and overall. The primary efficacy analysis will be performed using the Full Analysis Set (FAS). ANCOVA: analysis of covariance model will be used to assess changes in the values from baseline at Day 49 visit and at EOS/ET. *Safety Analysis:* All safety data will be presented in tables and listings. Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with AEs and the number of AEs will be presented in tables by system organ class (SOC) and preferred term (PT), as well as by relationship to the study drug and by severity grade. At the same time, each participant will be counted only once within system organ class and preferred term with relationship to the study drug and the highest severity grade. Serious AEs (SAEs) will be additionally presented in separate tables. <u>Laboratory data</u> Statistical characteristics of laboratory test findings will be presented in tables. All laboratory data will also be presented in listings. Vital signs, physical examination, body measurements and 12-Lead ECG will be listed for all participants and (except for physical examination) descriptively summarised per treatment group and overall. *Exploratory analysis:* Participants who have impairment of the basilar membrane as detected by the ECochG latency shift and/or mid peak amplitude will be listed, grouped by arm. The number and percentage of participants with impairment of the basilar membrane will be summarised by arm. ANCOVA analysis and descriptive statistics to assess changes in hearing threshold from baseline, at Day 49 visit and at EOS/ET, will be repeated excluding participants with impairment of the basilar membrane.

	Biomarker exploratory analyses (if performed) will be described in the statistical analysis plan (SAP) finalized before database lock.

1.2 SCHEMA



ABBREVIATIONS: AE = adverse event; conmeds = concomitant medications; ECochG = electrocochleography; EOS = end of study visit; PK = pharmacokinetic
NOTE: Early termination visit (ET) procedures as per EOS

1.3 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Study Period	**Screening**	**Treatment Period[a]**					**Follow-up Period**
				Implant[b]			**EOS/ET[c]**
Study day		**Day 1[a]**		**Day 8[b]**		**Day 49[c]**	**Day 105**
Visit window	**D-42 to D-1**			**Day 8 to 14**		**± 7 days**	**± 21 days**
Visit number[d]	**1**	**2**	**Pre-implant Outpatient**	**3**	**Post-implant Outpatient**	**4**	**5**
Informed Consent[e]	X						
Demographics, medical history, prior medicine/treatment	X						
Height (cm), weight (kg)	X						
Physical examination[f]	X					X	X
12-lead resting ECG[g]	X					X	X
Vital signs (SBP, DBP, HR, RR, Temp)[h]	X					X	X
Clinical Laboratory testing (haematology, chemistry)[i]	X					X	X
Pregnancy test for WOCBP[j]	X					X	X
Concomitant medication/treatments[k]	X	Xk		X		X	X
Inclusion and exclusion criteria[l]	X	X					
Testing for COVID-19[m]		X					
Biomarker blood sampling[n]		Xn				X	X
Randomization, dispensing of SENS-401 & diary[o]		X					
SENS-401 43.5 mg twice daily[a] (Arm A)		X	X	X	X	X	

Study Period	Screening	Treatment Period[a]					Follow-up Period
				Implant[b]			EOS/ET[c]
Study day		Day 1[a]		Day 8[b]		Day 49[c]	Day 105
Visit window	D-42 to D-1			Day 8 to 14		± 7 days	± 21 days
Visit number[d]	1	2	Pre-implant Outpatient	3	Post-implant Outpatient	4	5
Check study diary and perform drug reconciliation[p]				X		X	
SENS-401 plasma collection[q] (Arm A)				X			
SENS-401 perilymph collection[r] (Arm A)				X			
Hearing Test – PTA (0.125 to 4 kHz)[s]	X	Xs				X	X
Otoscopic Examination[s]	X	Xs				X	X
Immitance Audiometry[s]	X	Xs				X	X
Cochlear Implant Surgery[t]				X			
Electrocochleography[u]				X			
AEs/ SAEs[v]		Xv	X	X	X	X	X

ABBREVIATIONS: AE = adverse event; b.i.d. = twice daily; COVID-19 = coronavirus 2019; D = study day; DBP = diastolic blood pressure; ECG = electrocardiogram; EOS = end of study visit; ET = early termination visit; HR = heart rate; PTA = pure tone audiometry; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; Temp = temperature (ºCelcius); WOCBP = woman of child-bearing potential.

a. See Section 6.1.2. All participants must attend Day 1 visit ensuring that if randomized to Arm A, they will adhere to the fasting restrictions (see Section 5.1.1). Only participants randomized to Arm A will be treated with study drug (see footnote [o]). On the morning of Day 1, Arm A participants will be dispensed one kit (12 bottles of 30 tablets each) and will take the first dose under supervision at the study site as per Section 5.1.1. Study staff will explain dosing and storage instructions and importance of treatment compliance (at least 70% compliance in the 3 days prior to cochlear implant surgery and for the morning dose on day of surgery [i.e. no more than 2 missed doses], and at least 70% compliant overall for the dosing period prior to surgery [i.e. no more than 4 missed doses if surgery occurred at Day 8, 5 if at Day 9 or 10, and 6 if at Day 11],…). Treatment period: Commencing Day 1, 43.5 mg oral SENS-401 will be administered as described in Section 5.1.1 twice-daily from 7 to 13 days (see also footnote [b]), on the day of cochlear implant surgery (morning dose after blood collection for PK), and twice-daily until attending the Day 49 visit.

b. All participants will undergo cochlear implant surgery between Day 8 and 14 as indicated in footnote [t]. Participants must have consented to cochlear implant surgery prior to being approached for this study..

c. All participants will attend the study site for the Day 49 visit (Arm A participants will continue to take study drug until attending this visit) and for the EOS. Arm A participants will return all study drug containers (even if empty) and any unused study drug at the Day 49 visit. Both visits should ideally but not necessarily coincide with standard-of-care cochlear implant assessment visits. If a participant withdraws or is withdrawn from the study, they will be asked to attend an early termination (ET) visit with the same procedures as EOS, including audiometric testing and biomarker sampling if willing. Visit windows: Day 49 visit ± 7 days; EOS: Day 105 ± 21 days.

d. All participants will attend the study site for 5 visits as indicated and will be advised to contact the study site during outpatient periods if they have queries or concerns. Such contact will be documented. Unscheduled visits for study-related safety are at the discretion of the Investigator and will be documented in source document and in the eCRF.

e. Voluntary, signed, informed consent on forms approved by the Ethics Committee is required prior to the first screening assessment.

f. Physical examination will be conducted by the Investigator (physician) as per Section 7.1. Unscheduled symptom-directed physical examination during the study are at the discretion of the Investigator if required for safety.

g. Single 12-lead ECG will be performed after participant supine for at least 10 minutes (see Section 7.3). Unscheduled ECGs during the study are at the discretion of the Investigator if required for safety.

h. Vital signs will be measured after the participant is supine for at least 5 minutes (see Section 7.2.1). Unscheduled vital signs during the study are at the discretion of the Investigator if required for safety.

i. Fasting blood samples will be collected from all participants (Arm A and Arm B) for haematology and chemistry (see Section 7.4.1; fasted for at least 8 hours). Unscheduled samples collected for clinical laboratory testing during the study are at the discretion of the Investigator if required for safety.

j. Blood samples will be collected from all WOCBP for serum pregnancy testing (human chorionic gonadotropin [hCG]) at screening, and urine samples collected from Arm A WOCBP only for pregnancy testing (hCG) at the Day 49 visit and EOS/ET.

k. All concomitant medications and treatments will be documented and entered into the eCRF. **On Day 1**: to be checked before randomization with any concomitant medication/treatment required on Day 1 after randomization also recorded.

l. Eligibility for all participants must be confirmed prior to randomization and first dose on Day 1.

m. Participants will be tested for SARS-Cov-2 (COVID-19) on Day 1 prior to randomization as per Section 7.4.3. If positive, the participant will be deemed a screen failure and must not be randomized. Any other COVID-19 screening or testing will be as per Institutional and local regulatory guidelines and requirements.

n. Blood samples will be collected from all participants (Arm A and Arm B) for biomarker research as per Section 6.6. **On Day 1**: to be collected after randomization for both Arm A (**pre-first dose**) and Arm B participants.

o. In the morning of Day 1 after confirming eligibility, participants will be randomized pre-dose to either Arm A or Arm B. Arm A will be dispensed SENS-401 kit and study diary (see footnote [p]) on Day 1 and treated with SENS-401 as per footnote (a). Arm B (control group) will not be treated with SENS-401 at any time. The study is open-label and there is no placebo treatment.

p. Study staff will give Arm A participants a paper study diary on Day 1 and will explain how to record times and dates of study drug administration including number of tablets taken (daily first and last meal times will also be recorded). Participants will be reminded to bring the study diary and unused study drug with all empty or full bottles to subsequent site visits, at which study staff will review the study diary for treatment compliance and perform drug reconciliation. Study staff will transcribe drug administration details from the study diary into the eCRF. The study diary and study drug will be returned to the participant on Day 8 and reminded to return both (including empty bottles) at the visit on Day 49. The diary will be considered source document and study staff will retain the diary at the Day 49 visit.

q. One blood sample will be taken from Arm A participants only prior to the morning dose on the day of cochlear implant surgery to determine SENS-401 plasma concentration. See Section 6.2.1. Blood samples are not required from Arm B participants on Day 8.

r. During the cochlear implant surgery, one (1) perilymph sample of at least 1 µL will be collected from Arm A participants only to determine SENS-401 concentration as per Section 6.2.2. Perilymph samples are not required from Arm B participants.

s. See Section 6.3 for audiometric testing and Section 6.4.1 for otoscopic examination. At Screening, on Day 1, on Day 49, and EOS/ET, audiometric assessments will be conducted for all participants (Arm A and Arm B). **On Day 1**: to be conducted after randomization for both Arm A participants (**pre-first dose**) and Arm B participants. **On Day 49 and EOS/ET:** to be conducted with the Cochlear™ Nucleus® C1622 turned off.

t. Cochlear implant surgery will be performed as standard of care using model Cochlear™ Nucleus® C1622. See Section 6.5.

u. Electrocochleography will be performed during cochlear implant surgery for all participants (Arm A and Arm B) as per Section 6.4.2.

v. Adverse events will be recorded throughout the study from the time of informed consent for all participants (Arm A and Arm B). See Section 7.5. **On Day 1**: to be checked before randomization and any AEs experienced on Day 1 post-randomization also recorded.

TABLE OF CONTENTS

List of Tables in Text

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABR	Auditory brain stem responses
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance model
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical therapeutic class
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to time 24 hours
b.i.d.	Twice daily
CI	Confidence interval
CIO	Cisplatin-induced otoxicity
CKD-EPI	Chronic Kidney Disease Epidemiolog Collaboration equation for calculating creatinine clearance
CL/F	Apparent total clearance from plasma after oral administration
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
COVID-19	Corona virus disease 2019
CRO	Clinical research organisation`
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DPOAE	Distortion product otoacoustic emissions
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ECochG	Electrocochleography
EOS	End of study visit
ET	Early termination visit
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice

HDPE	High density polyethylene
hERG	Human ether-a-go-go gene
HR	Heart rate
HREC	Human Research Ethics Committee
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
INR	International normalized ratio
Investigator	Principal Investigator or designated co- or sub-Investigator
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
MDRD	Modification of Diet in Renal Disease Study equation for calculating creatinine clearance
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NOAEL	No observed adverse event level
PD	Pharmacodynamic
PICF	Participant informed consent form
PK	Pharmacokinetics
PN	Preferred name
PT	Preferred term
PTA	Pure tone audiometry
PTT	Pure tone threshold
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOA	Schedule of Assessments
SOC	System organ class
SSNHL	Sudden sensorineural hearing loss
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
$T_{1/2}$	Terminal half-life
Tmax	Time to maximum observed plasma concentration

WOCBP	Woman of child-bearing potential

PROTOCOL APPROVAL/ SIGNATURES

I approve the following protocol entitled "A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Presence of SENS-401 in the Perilymph after 7 days of repeated oral administration in Adult Participants Scheduled for Cochlear Implantation", Version 3.0 dated 08 February 2023.

SPONSOR SIGNATURE

Signature:	[redacted]
Name:	
Role:	
Date:	

PRINCIPAL INVESTIGATOR SIGNATURE

A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Presence of SENS-401 in the Perilymph after 7 days of repeated oral administration in Adult Participants Scheduled for Cochlear Implantation

Version: 3.0

Issue Date: 08 February 2023

Principal Investigator Agreement

I have read the above-mentioned protocol and am aware of my responsibilities as Principal Investigator for this study. As such, I agree to:

- Personally supervise the conduct of this trial;
- Conduct the trial in accordance with International Conference on Harmonization (ICH) E6 Good Clinical Practice: Consolidated Guidance (GCP), applicable regulatory requirements, and the protocol;
- Comply with the procedures for data recording and reporting as required by the regulatory authorities and the Sponsor;
- Permit monitoring, auditing, and inspection of study records as required by ICH GCP;
- Retain the essential clinical study documents as required by ICH GCP, local regulatory requirements, and the Sponsor.

Principal Investigator Signature:	
Principal Investigator Name:	
Date:	____/____/2023

2 INTRODUCTION AND RATIONALE

2.1 DISEASE BACKGROUND

The pathophysiological mechanism of hearing loss includes cellular mechanisms of hair cell loss, damage to stereocilia, and/or loss of synapses or cochlear neurons, and molecular mechanisms including calcineurin activation.[1, 2] Calcineurin, a calcium/calmodulin-dependent protein phosphatase, is activated after noise-induced trauma to the inner ear and can activate cell death pathways in outer hair cells within the cochlea.[3, 4] Calcineurin antagonists such as cyclosporin A and tacrolimus show activity in models of hearing loss, and tacrolimus was also shown to protect against cochlear injury.[4, 5] However, there are currently no medications approved by any regulatory agency to improve or treat hearing loss, and use of hearing aids and cochlear implant surgery are the main treatment options.

Cochlear implants started to be developed in the 1960s.[6-8] Since that time, rapid advances in digital technology have led to the development of highly sophisticated medical devices that can deliver patterned auditory information at rapid rates to surviving auditory neurons. Their basic principle is based on the transformation of sound waves into an electrical signal by a processor. Equipped with an electrode, the intact auditory nerve in the cochlea is directly stimulated.

Originally, cochlear implants were only indicated for total congenital bilateral deafness in new-borns and for profound acquired deafness in adults who could not achieve sufficient gain with conventional hearing aids. However, due to the improved performance and low complication rate of this technology, the indications for cochlear implants now extend to profound single ear hearing loss and severe high frequency hearing loss with residual hearing at low frequencies.

Cochlear implantation is now considered the "gold standard" treatment for neuro sensorial severe to profound hearing loss. However, one of the complications following the placement of a cochlear implant is the loss of residual hearing function. Apart from purely surgical technical considerations that can reduce this risk, there are non-surgical factors that can help to improve rates of hearing preservation after cochlear implant surgery.[9, 10]

These include the choice of electrode design (straight or perimodiolar and short or long), the use of corticosteroids such as dexamethasone for anti-inflammatory action, and more generally the use of other chemical entities with local protective effects against hearing damage induced by cochlear implant surgery, such as the peptide D-JNKI-1, which inhibits the apoptotic effects of the JNK mediated activation of c-Jun.[11-13]

Inner ear fluid (perilymph and endolymph) maintains homeostasis through a variety of regulatory mechanisms and includes a blood labyrinthine barrier, which is a major physical and biochemical barrier separating the inner ear from systemic circulation. Any drug with a potential protective profile administered systemically will need to reach the perilymph to act pharmacologically.[14]

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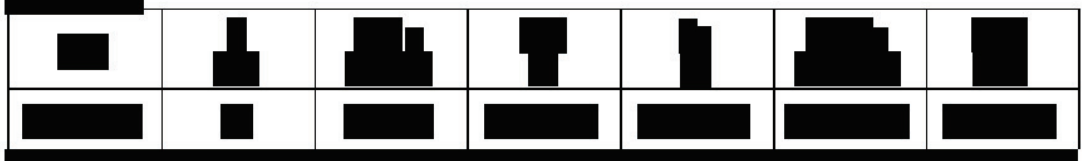

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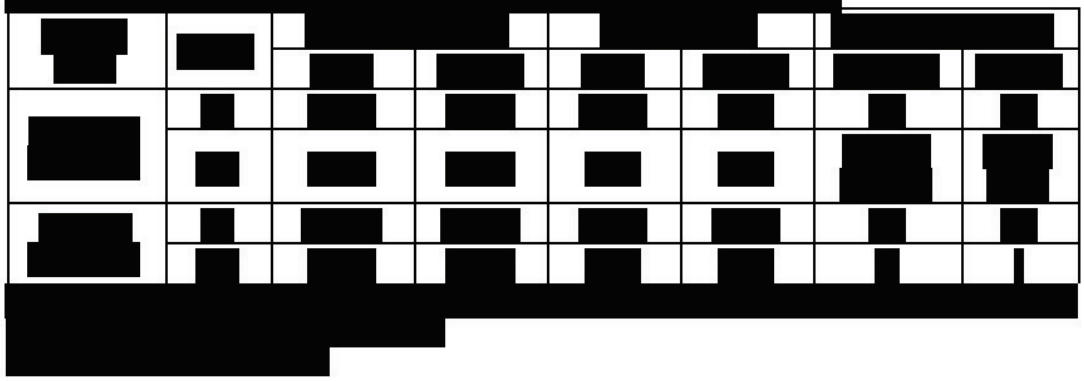

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3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
• To detect the presence of SENS-401 in the perilymph of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.	• Percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification on day of cochlear implant surgery after seven days of SENS-401.
Secondary:	
• To measure the SENS-401 concentrations in the perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401. • To compare the SENS-401 concentrations in perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.	• SENS-401 perilymph concentration on day of cochlear implant surgery after seven days of SENS-401. • SENS-401 plasma concentration on day of cochlear implant surgery after seven days of SENS-401
• To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery at the Day 49 visit and at EOS/ET.	• Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS/ET. • Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS/ET.
• To assess the safety and tolerability of SENS-401 given for the whole duration of the study.	• Incidence of treatment emergent AEs and SAEs in each participant until the end of their study participation.
Exploratory:	
• To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery; here performed on a subset of participants	In a subset of participants assessed by a neurophysiologist to have **no** electrophysiological evidence of basilar membrane fixation:

Objectives	Endpoints
with **no** electrophysiological evidence of basilar membrane fixation as described in Section 6.4.2.	• Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) • Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA).
• To explore the correlation between biomarkers already pre-identified (e.g., prestin) or that will be identified in the future with clinical features of interest.	• Serum/plasma concentrations of selected biomarkers at baseline (i.e., Day 1, and pre-dose for Arm A), at the Day 49 visit, and at EOS/ET.

4 INVESTIGATIONAL PLAN

4.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This is a Phase IIa, open-label, randomized and controlled study in adult participants with preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (i.e., ≤80 dB) at 500 Hz), who meet the locally approved indication for, and have already consented to receiving, cochlear implant Cochlear™ Nucleus® C1622. This model is medically indicated, is an appropriate choice for the type of participant to be enrolled in this study, and ensures a homogenous study population. Study assessments are indicated in the Schedule of Assessments (SOA) Table 1 (Section 1.3).

After a screening period of 1 to 42 days (including informed consent to this study prior to the first screening assessment), 27 eligible participants will be randomized on Day 1 to either Arm A (18 participants treated with oral 43.5 mg SENS-401 twice daily for 7 weeks [one to two weeks before cochlear implant surgery and 5 to 6 weeks after]) or Arm B (9 participants receiving no treatment with SENS-401).

For participants in Arm A, twice-daily oral dosing with 43.5 mg SENS-401 will commence on Day 1 with cochlear implant surgery performed between Day 8 and Day 14. If for any reason the surgery is delayed beyond Day 14 , the participant should cease taking SENS-401 and be withdrawn from the study (see Section 4.3.4). The participant may be screened again once a new date of surgery is identified (see Section 4.3.3).

Blood and perilymph will be sampled from Arm A participants for measurement of SENS-401 on the day of the cochlear implant surgery (blood sampling pre-morning dose of SENS-401 and perilymph sampling during surgery). Data from ECochG during cochlear implant surgery will be obtained for both Arm A and Arm B participants. During electrode insertion, the Investigator may use ECochG if desired and/or their usual practice. After electrode insertion, an ECochG electrode sweep will be performed for all participants to generate exploratory study data.

Arm A participants will continue to take SENS-401 twice daily including on day of surgery and until attending the Day 49 visit. Efficacy assessments including PTA and immittance audiometry, will be conducted with baseline assessments conducted during Screening and Day 1 pre-first dose.

Participants randomized to Arm B on Day 1 will not take SENS-401 at any time, but will similarly undergo their planned cochlear implant surgery between Day 8 to 14 and return for the Day 49 visit. Arm B participants will undertake the same audiometric tests as Arm A participants in order to evaluate trends of efficacy, but will not be required to provide blood or perilymph samples for PK analysis on the day of cochlear implant surgery If the cochlear implant surgery is delayed beyond Day 14, participants will be withdrawn from the study but may be re-screened once the revised date of surgery is confirmed (see Sections 4.3.3 & 4.3.4).

All participants will attend an EOS on Day 105 for final efficacy audiometric assessments. The Day 49 visit and EOS should ideally but not necessarily coincide with standard-of-care visits for switching on and programming of the cochlear implant respectively, for the convenience of the participant. Safety assessments according to the SOA will be performed at every site visit for all participants, and samples for exploratory biomarker analysis will be collected at baseline (Day 1), at the Day 49 visit, and at EOS .

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of assessment for the last participant in the study globally.

4.2 DISCUSSION OF STUDY DESIGN INCLUDING CHOICE OF CONTROL GROUPS

This study was designed to study mainly the trans-compartmental passage of SENS-401 into the cochlea indicated by detection of SENS-401 in the perilymph (primary objective). Eighteen participants will be treated with SENS-401 for at least 7 days preceding the collection of perilymph. This sample size is generally considered to be large enough to provide robust information on this PK objective. Moreover, this type of PK study does not generally require blinding or a placebo control group.

Participants will be randomized unblinded to a treated group (Arm A) and untreated control group (Arm B) for the efficacy analysis as a secondary objective.

4.3 SELECTION OF STUDY POPULATION

4.3.1 Inclusion Criteria

Potential participants must fulfil all of the following inclusion criteria to be eligible for the study:

1. Adults aged from 18 years and older.
2. Meets the locally approved indication for cochlear implantation with the Cochlear™ Nucleus® C1622 and has preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (i.e., ≤80 dB) at 500 Hz. The individual must have freely consented to the cochlear implant surgery before being offered to participate in the SENS-401-203 study.
3. Signed and dated written informed consent.
4. Females who have or may have male sexual partners must meet one of the following criteria at Screening:
   - Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause), surgically sterile, or abstinent.

     or
   - A woman of childbearing potential (WOCBP) (any female who has experienced menarche and who is not permanently sterile or postmenopausal) practicing a method of highly effective birth control that is listed in Appendix 11.1 and is willing to continue to use highly effective contraception (as per Appendix 11.1) for the duration of study participation and for at least 30 days after the final dose of study drug.

   All WOCBP must have a negative serum pregnancy test at screening before the first dose of study drug is taken. Participants randomized to Arm B on Day 1 will not be required to further adhere to the contraception requirements of the study.

   Note: No contraception measures are needed for male participants, including those with pregnant or non-pregnant WOCBP partner.
5. Vaccinated against coronavirus disease 2019 (COVID-19) per local vaccination schema requirement or previously contracted the disease and recovered within the last six months.

4.3.2 Exclusion Criteria

Individuals will be excluded from the study if any of the following criteria apply:

1. Moderate to severe renal impairment defined by a creatinine clearance ≤ 60 ml/min (calculated with the Cockcroft-Gault formula for individuals <65 years old and with the the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or the Modification of Diet in Renal Disease Study (MDRD) equation for individuals ≥65 years old).
2. Any condition that, in the opinion of the Investigator, may compromise the safety or compliance of the participant or would preclude the participant from successful completion of the study.
3. Unable or unwilling to comply with the protocol requirements.
4. Any therapy known as ototoxic (e.g. aminoglycosides, cisplatin, quinine etc.) at the current time or in the past 6 months prior to study inclusion. Loop diuretics at normal therapeutic doses are permitted.
5. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction.
6. Pregnant or breast-feeding.
7. Treatment with any investigational agent within 4 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer).
8. Either a history of significant arrhythmia, or a history of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, long QT Syndrome, hypokalemia).
9. Radiological evidence of bony obliteration of the round window membrane on pre-operative high-resolution CT imaging of the temporal bone.
10. Loss of cochlear fluid signals on pre-operative MRI imaging, suggestive of fibrosis or ossification of the cochlea.
11. Any probihited concomitant therapy listed in the §5.8.1 Other prohibited concomitant therapies.

4.3.3 Screen Failures

Screen failures are participants who signed the PICF but are found to be ineligible for the study and are not randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. The minimum information for screen failures includes signed PICF, demographics, reason for screen failure, eligibility criteria, and any serious adverse events. Screen failure information will be monitored and entered into the eCRF.

Unscheduled visits may be planned to assess, confirm, and follow-up on out-of-range clinical laboratory test, vital sign, or ECG values that determine a volunteer's eligibility, with each assessment to be repeated once only. The result of any re-test must be considered for volunteer eligibility and must be available prior to randomization. Findings made during unscheduled visits will be reported in the source document.

Individuals who fail screening due to an underlying medical condition previously unknown to them (including COVID-19 but not including other acute self-limiting viral infections) will be provided with the appropriate referrals for guidance and counselling for their condition, if required.

Participants whose cochlear implant surgery is unavoidably delayed beyond Day 14 (including after commencing study drug for Arm A participants) may be re-screened for the study once a new surgery date is confirmed, if they agree. This will be decided on a case-by-case basis after discussion between the Investigator, Sponsor and Medical Monitor. The participant should first be fully withdrawn from their first enrolment in the study, including attending an ET. The participant will then sign a new informed consent, be assigned a new participant number, and undergo all screening procedures again within the required timeframe. They should be made aware that they may be randomized to a different arm than previously.

4.3.4 Withdrawal of Participants

Withdrawal of consent is when a participant wishes to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. Participants may withdraw from the study at any time upon request and irrespective of the reason. The Investigator will endeavour to obtain the reason for withdrawal, and if the participant gives a reason this will be recorded in the eCRF. The Investigator will ask the participant to attend an early termination visit (ET) where all procedures planned for EOS will be performed (see SOA Table 1). This includes audiometric testing and biomarker sampling if the participant agrees.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records.

The Investigator may also withdraw a participant from the study at any time for safety, behavioural, compliance or administrative reasons, including but not limited to:

- Pregnancy in an Arm A female participant (must be withdrawn). Arm B participants may continue to participate if willing, if the Investigator permits, and if cochlear implant surgery proceeds (or has proceeded) as scheduled;
- Significant non-compliance or major protocol deviation, including less than 70% compliance with study drug in the 3 days prior to cochlear implant surgery and less than 70% compliance in the entire dosing period prior to cochlear implant surgery;
- Cochlear implant surgery is delayed beyond Day 14 (the participant must be withdrawn and study drug ceased if applicable). See Section 4.3.3 for possible re-screening of these participants;
- Any clinical AE, laboratory abnormality or other medical condition or situation occurs that in the medical judgement of the Investigator would not be in the best interest of the person to continue to participate in the study. This includes serious and non-serious AEs regardless of relation to study drug (e.g., diagnosed with COVID-19);
- An exclusion criterion newly develops or was not previously recognized that precludes the person from continuing to participate in the study;
- Participating in any other investigational product study while enrolled in this study;
- Death;
- Other, such as termination of the study by the Sponsor.

If a participant stops taking study drug after the cochlear implant surgery and before the Day 49 visit, they may continue to participate in study assessments at the scheduled timepoints if willing to do so.

The Investigator will continue to provide medical care for any SAEs with the participant's permission, until symptoms resolve and/or the participant's condition becomes stable.

4.3.4.1 Replacement of Withdrawn/Discontinued Participants

Participants who have signed the PICF but have not been randomized to treatment may be replaced.

Participants who are randomized to treatment but withdraw or are withdrawn prior to cochlear implant surgery may be replaced on a case-by-case basis, in order to ensure 18 participants take SENS-401 according to pre-defined compliance limits (see Section 5.1.1) and undergo cochlear implant surgery. The Investigator must confirm with the Sponsor before proceeding with replacement.

Participants who are randomized to treatment and withdraw or are withdrawn from the study after cochlear implant surgery will not be replaced.

4.3.5 Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to attend scheduled visits and are unable to be contacted by the site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site must attempt to contact the participants and reschedule the missed visits as soon as possible and:
  - counsel the participant on the importance of maintaining the assigned visit schedule and returning dispensed study drug, and
  - acertain if the participant wishes to and/or should continue in the study. The reason will be reported to the Sponsor to identify a potential solution.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, three (3) telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).
- The study site must also contact the trusted person designated by the participant and the participant's attending physician (e.g., general practitioner or local equivalent).
- All attempts at contact must be documented in the participant's medical record.

If the participant continues to be unreachable, they will be considered to have withdrawn from the study.

4.3.6 Study Discontinuation

The Sponsor, Principal Investigator, approving EC/HREC, and regulatory authorities independently reserve the right to discontinue the trial at any time for safety or other reasons. Where practical, this will be done in consultation with the Sponsor and all parties notified in writing where applicable. The Sponsor and Principal Investigator will ensure that participants' interest and safety are protected, and the Principal Investigator must review all participants and complete all records as required.

4.3.7 Treatment Discontinuation – Safety Stopping Rules

At study entry and prior to first dose of study drug, a full eligibility check will be performed. Participants who do not meet the study protocol inclusion/exclusion criteria will not be randomized or dosed.

Treatment will be discontinued for a participant's safety if any of the following occur:

- SAE considered related to study drug;
- Adverse event of CTCAE Grade ≥3 considered related to study drug and discussed with Sponsor;
- Pregnancy in an Arm A participant.

Treatment may be discontinued for a participant's safety if any of the following occur:

- Clinically significant finding from 12-lead ECG (including but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF], as applicable) occurring after first dose: the Investigator will determine if the participant can continue in the study and if any change in participant management is required. This review of the ECG printed at the time of collection must be documented, and any new clinically relevant finding reported as an AE;
- If a participant tests positive for COVID-19 after commencing study drug, the Investigator will decide if study drug should be discontinued (study visits/contact must remain virtual until participant permitted to attend study site according to local and institutional regulations and requirements).

Temporary discontinuation of study drug (interruption) must be discussed on a case-by-case basis with the Sponsor and Medical Monitor. Rechallenge is not applicable for ECG abnormality but is applicable for renal/liver AEs if relevant laboratory results return to normal range (study drug may be restarted).

Treatment will be suspended for all participants if clinical development of the study drug is suspended by the Sponsor.

Treatment will only re-commence after timely appropriate safety review by the Sponsor Medical Director, Principal Investigator, and Study Medical Monitor, at a minimum. This process will be provided in advance in the Safety Plan. Extra internal or external experts may be consulted as necessary.

4.3.8 Emergency Unblinding of Study Subjects

The study is open-label and as such emergency unblinding is not applicable.

5 TRIAL INTERVENTIONS/TREATMENTS

5.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1.1 SENS-401

SENS-401 (*(R)*-azasetron besylate) is the (R)-enantiomer of azesetron, a selective 5-HT_3 receptor antagonist. See Section 2.2 and the Investigator's Brochure for further information. Participants will be randomized to treatment as per Section 5.10.1.

Participants in Arm A only will take 43.5 mg SENS-401 (3 tablets) orally twice-daily (morning and evening) for a total of up to 56 days as follows:

- 7 to 13 days prior to the day of cochlear implant surgery commencing Day 1.
  - Participants must be at least 70% compliant for at least the 3 days prior to cochlear implant surgery and for the morning dose on the day of surgery (i.e. no more than 2 missing doses).
- On the day of cochlear implant surgery, with first dose given after the plasma collection for PK and second dose in evening as scheduled.
- For 42 to 56 days after day of cochlear implant surgery until attending the Day 49 visit.
  - If cochlear implant surgery was performed between Day 9 to Day 14 no additional tablets will be dispensed and all participants will complete dosing when attending the Day 49 visit.

Dosing Instructions:

- During the course of the study, participants should not take SENS-401 within 2 hours of any meal/food (before or after). This fasting restriction must be strictly followed for the 3 days prior to cochlear implant surgery and for the morning dose on the day of surgery.
- On Day 1, all participants should attend the study site in the morning ensuring that if randomized to Arm A they will adhere to the fasting restrictions outlined above. Once randomized, Arm A participants will take the first dose under supervision at the study site.
- For each dose, participants will swallow three (3) tablets with a glass of water.
- Tablets should be taken at approximately the same times (morning and evening) each day, with minimum of 8 hours and maximum of 16 hours between doses (i.e., approximately 12 hours between doses, e.g., 7AM and 7PM).
- A dose will be considered to be missed if more than 16 hours since the last dose. Missed doses should be skipped and must not be taken as a double dose at the next dosing time.
- If vomiting occurs, extra doses must not be taken. The participant should take the next dose as per the dosing schedule. In the event vomiting occurs within two hours post-drug intake in the three days before cochlear implant surgery, it is recommended that the participant contact the study site.

Other Requirements:

- Arm A participants must be advised to avoid skin exposure to strong sunlight and to wear sunglasses in bright sunlight for the duration of the study and for one (1) week after the last dose.

- Arm A participants will record each administration of IMP (date, time, number of tablets taken) and times of first and last meal per day in the study diary provided to them on Day 1, and will bring the completed diary and dispensed containers (even if empty) to each subsequent site visit for assessment of compliance. Study staff will transcribe drug administration details from the study diary into the eCRF.
- **Compliance**: Participants must be at least 70% compliant with dosing for at least the 3 days prior to cochlear implant surgery and for the morning dose on the day of surgery (i.e. no more than 2 missed doses), and no less than 70% compliant overall for the entire dosing period prior to cochlear implant surgery (i.e. no more than 4 missed doses if surgery occurred at Day 8, 5 if at Day 9 or 10, and 6 if at Day 11,..). If cochlear implant surgery is unavoidably rescheduled up to and including Day 14, participants will continue to take twice daily study drug without interruption as above until surgery.

Total maximum number of scheduled doses: 84 to 112 (252 to 336 tablets total)

5.2 SELECTION OF DOSE IN THE STUDY

See Section 2.3.2.

5.3 SELECTION AND TIMING OF DOSE FOR EACH PARTICIPANT

See Sections 5.1 and 5.10.1.

5.4 DOSE INTERRUPTIONS AND REDUCTIONS

No dose interruptions or reductions are permitted in the dosing period three days prior to cochlear implant surgery. Interruptions or reductions at other times pre-cochlear implant surgery will be evaluated as protocol deviations and discussed on a case-by-case basis.

Decisions regarding dose interruptions or modifications after cochlear implant surgery will be made by the Investigator after discussing with the Medical Monitor based on the clinical evaluation of the participant. See Section 7.5.6 for instructions in the event of overdose.

Treatment may be stopped by the Investigator and/or Sponsor if considered necessary for the safety of the participant(s) including as described in Section 4.3.7. If possible, the Investigator will discuss with the Medical Monitor before discontinuing treatment, and the Sponsor notified.

5.5 SUPPLY, PACKAGING AND LABELLING OF STUDY TREATMENTS

The IMP will be manufactured and packaged according to Good Manufacturing Practice (GMP) and all local regulations, and supplied to the study sites with an acknowledgement of receipt form. The IMP will be labelled for clinical trial use in compliance with local regulatory requirements including Annex 13 of GMP where applicable. The certificate of analysis will be provided.

SENS-401 is supplied for oral administration as 14.5 mg (10 mg free base) white, oval and film-coated tablets, debossed with ‘S401’ on one side. The tablets are packaged in high-density polyethylene (HDPE) bottles with intact induction seal and child-resistant closure (30 tablets per bottle). Formulation including excipients (methyl crystalline cellulose, starch, and magnesium stearate) is detailed in the Investigator’s Brochure.

On Day 1, Arm A participants will be dispensed one kit each containing 12 bottles (360 tablets in total) to ensure enough study drug for the entire dosing period. No additional

study drug will be dispensed in the event of permitted delay to the day of cochlear implant surgery.

Supplies of the IMP will be shipped to the study sites prior to study start.

5.6 STORAGE OF STUDY TREATMENTS

Refer to the Pharmacy Manual and Investigator's Brochure for required storage and handling of the IMP. Prior to dispensing, the IMP must be stored in a secure and locked storage area with limited access, and under monitored, temperature-controlled conditions as required.

Participants will be instructed to keep the IMP at room temperature (not exceeding 30ºC) out of reach of children.

The Principal Investigator or appropriate delegate (e.g., Study/Site Pharmacist) are responsible for the correct storage and handling of the IMP while it is at site. Deviations from the storage requirements, including corrective actions, must be documented.

5.7 ACCOUNTABILITY, RECONCILIATION AND RETURN OF THE STUDY TREATMENTS

The Investigator will ensure that:

- The IMP is dispensed only to eligible participants randomized to Arm A in this study, and
- Complete and current dispensing and inventory records are maintained.

The site's inventory/dispensing logs must record every episode of dispensing of IMP. The following information must be documented:

- Date of receipt.
- Number of tablets/containers received.
- Batch number(s).
- The identification of the participant to whom the tablets were dispensed.
- The date(s), time and quantity dispensed to the volunteer.
- The cumulative total of IMP at site.
- Tablets and containers damaged, destroyed, or returned.

The study monitor will perform drug accountability during routine, regular monitoring visits. Once the study has completed or been discontinued, final accountability and reconciliation will be performed. Any discrepancies will be investigated and the resolution documented.

Participants will bring all IMP containers (even if empty) including unused IMP to study visits. Study staff will perform drug reconciliation with reference to the participant study diary on Day 8 and at the Day 49 visit. Compliance should be as described in Section 5.1.1. Any discrepancies will be documented and reasons clarified with the participant. All IMP container(s) and unused IMP will be retained at site at the Day 49 visit for final monitoring. Study staff will also retain the participant diary at the Day 49 visit and file as source document.

All full, partially full, and empty containers of IMP must be returned to the Sponsor for destruction, after permission has been obtained from the Sponsor and final drug accountability has been performed by the study monitor.

5.8 PROHIBITED CONCOMITANT THERAPY

Any medication/therapy that is exclusionary for eligibility at Screening remains prohibited during the study (i.e., ototoxic therapies). Loop diuretics at normal therapeutic doses are permitted. Participants may be vaccinated during the study if necessary (e.g., COVID-19 vaccination or booster dose), but it is preferred if such vaccination(s) can be postponed until at least after the cochlear implant surgery.

Corticosteroid use: Investigators will consult the separate guidance manual for cochlear implant surgery prepared for this study for permitted use of corticosteroids associated with the cochlear implant.

Any use of concomitant medication (including vaccination) and/or treatment must be recorded by study staff in source document and the eCRF. Concomitant medication details should include at a minimum: name of medication, daily dosage, route of administration, duration of use (start/stop dates), and reason/indication for use. Concomitant medications for this study include all medications associated with the cochlear implant surgery (e.g., anaesthetic, pain relief). Concomitant treatment details should include at a minimum: treatment type, date, and reason/indication for use.

5.8.1 Other prohibited concomitant therapies

- Initiation of antidepressant treatment containing serotoninergic agents within the previous 24 hours due to the risk of serotoninergic syndrome. The following is a non-exhaustive list of serotoninergic agents:
  - Selective serotonin reuptake inhibitors (SSRIs), antidepressants such as citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
  - Serotonin and norepinephrine reuptake inhibitors (SNRIs), antidepressants such as trazodone, duloxetine and venlafaxine
  - Bupropion, an antidepressant and tobacco-addiction medication
  - Tricyclic antidepressants, such as amitriptyline and nortriptyline
  - Monoamine oxidase inhibitors (MAOIs), antidepressants such as isocarboxazid and phenelzine
  - Anti-migraine medications such as triptans, carbamazepine and valproic acid
  - Pain medications such as opioid pain medications including codeine, fentanyl, hydrocodone meperidine, oxycodone and tramadol
  - Lithium, a mood stabilizer
  - Illicit drugs, including LSD, Ecstasy, cocaine and amphetamines
  - Herbal supplements, including St. John's wort, ginseng and nutmeg
  - Over-the-counter cough and cold medications containing dextromethorphan
  - Linezolid, an antibiotic
  - Ritonav, an anti-retroviral medication used to treat HIV/AIDS
- Substrates of BCRP (breast cancer resistance protein) and transporter (see non-exhaustive below)

Transporter	Gene	Inhibitor
P-gp	*ABCB1*	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	*ABCG2*	curcumin, cyclosporine A, eltrombopag
OATP1B1, OATP1B3	*SLCO1B1, SLCO1B3*	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	*SLC22A6, SLC22A8*	p-aminohippuric acid (PAH), probenecid, teriflunomide
MATE1, MATE2-K	*SLC47A1, SLC47A2*	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

- Calcineurin inhibitors (cyclosporine, and tacrolimus)

Participants should discuss use of any other new concomitant medication with the Investigator, where possible, particularly if they have concerns about ototoxicity.

5.9 TREATMENT COMPLIANCE

The first dose of study drug on Day 1 will be administered under supervision at the study site. Study staff will explain the required dosing regimen to the participant (see Section 5.1.1), and subsequent doses will be taken by the participant at home. In particular, study staff will emphasise treatment compliance for the period prior to and including the day of cochlear implant surgery as described in Section 5.1.1. Study staff will ask participants to retain all study drug bottles even if empty.

Part A participants will record administration details including date and time, number of study drug tablets taken, and times of first and last meal, in the study diary issued on Day 1. The participant will bring the study diary and all study drug bottles (including if empty) to each subsequent visit (day of cochlear implant surgery and the Day 49 visit) for IMP reconciliation and compliance check as described in Section 5.7.

5.10 MEASURES TO MINIMIZE BIAS

5.10.1 Randomization Procedures

Participants will be randomized to either Arm A or Arm B on Day 1:

- Arm A: treated with SENS-401 as described in Section 5.1.1. Eighteen (18) participants will be randomized to Arm A.
- Arm B: not treated with SENS-401 at any time. Nine (9) participants will be randomized to Arm B.

Randomization will be according to a randomization schedule and plan prepared prior to study start. A Randomization Procedure document will be provided to the site by the Sponsor or CRO.

5.10.2 Blinding

The study is open-label and randomized, with Arm A receiving treatment with IMP and Arm B receiving no IMP treatment. See Section 4.2.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 STUDY CONDUCT SCHEDULE

The schedules for all assessment and study activities are summarised in the Schedule of Assessments (SOA) provided in Table 1. Permitted visit windows are indicated in Section 6.1.8. All study assessments and procedures are as described in Sections 6.2 to 6.5 and in Section 7.

6.1.1 Screening Day -42 to Day -1

- Voluntary, written informed consent using EC/HREC-approved PICF is required prior to any screening or study procedure as per Section 9.1.2.
- Protocol waivers or exemptions are not permitted.
- See SOA Table 1 for required assessments.
- A thorough medical history, demographics, and prior and current medications/treamtents used within 3 months prior to screening will be recorded.
- A screening log will be used to record suitable details of all screened individuals and to confirm eligibility or record reasons for screen failure as applicable.
- All screening and eligibility evaluations (inclusion/exclusion criteria) must be completed and reviewed by the Investigator to confirm eligibility prior to randomization and first-dosing on Day 1. This must be clearly documented.
- Re-testing of any screening parameters can be conducted once only.
- Unscheduled visits and procedures for safety reasons are at the discretion of the Investigator and will be appropriately documented.

6.1.2 Day 1 Randomization and First dose

- See SOA Table 1 for required assessments.
- All participants will attend the study site on Day 1 ensuring that if randomized to Arm A, they will adhere to the fasting restrictions described in Section 5.1.1.
- Prior to randomization:
  - Testing for COVID-19
  - Check & record concomitant medications or treatments
  - Check & record AEs
  - Confirm eligibility
- Eligible participants will be randomized to either Arm A or Arm B as per Section 5.10.1.
- After randomization (and pre-firstdose for Arm A):
  - Hearing test PTA
  - Otoscopic examination
  - Immitance audiometry
  - Record AEs and concomitant medications/treatments at any time after randomization if required
- For participants in Arm A only:
  - The first dose of study drug will be taken under supervision at the study site (see Section 5.1.1).

- Study drug will be dispensed to cover the entire dosing period and study diary provided. Study staff will explain:
  - i) Dosing and storage instructions (see Section 5.1.1)
  - ii) How to document study drug administration details (date, time, number of tablets taken, daily first and last meal times) and in the study diary.
  - iii) Importance of treatment compliance, as described in Section 5.1.1.
  - iv) To return for scheduled cochlear implant surgery.
  - v) To bring the study diary and all study drug bottles (even if empty) to each study visit (including day of cochlear implant surgery) up to and including the Day 49 visit.
- The participant will also be given information on who to contact in case of queries or concerns about the study drug and/or study.

- For participants in Arm B:
  - No IMP will be dispensed
  - Study diary will not be provided.
  - The participant will also be given information on who to contact in case of queries or concerns about the study.

6.1.3 Pre-implant Outpatient Period

- Participants are not required to attend the study site between Day 1 and the day of cochlear implant surgery.
- Arm A participants should continue to take study drug twice daily as per Section 5.1.1 and document dosing information in the study diary.
- Participants may contact the study site in case of queries or concerns. Unscheduled visits to the study site for study-related safety are at the discretion of the Investigator. All unscheduled study-related visits, assessments and any AEs will be documented and results entered into the eCRF.

6.1.4 Day 8 to 14 Cochlear Implant Surgery

See SOA Table 1 for required assessments.

- Participants will attend the study site per Investigator decision (evening before or morning of surgery) for scheduled cochlear implant surgery as standard of care (see Section 6.5). Arm A participants will bring study drug containers and study diary for compliance check by study staff. Study staff will transcribe drug administration details from the study diary into the eCRF. Arm A participants: the morning dose of study drug will be taken as scheduled after the blood sample for PK is collected. The evening dose of SENS-401 should also be taken later as scheduled on the day of cochlear implant surgery.
- Study staff will review the study diary for treatment compliance (Arm A only) and perform drug reconciliation. Study drug administration details will be transcribed into the eCRF as applicable. Any discrepancies between the study diary and the returned study drug will be discussed with the participant and documented.
- Information on concomitant medication and AEs will be obtained from all participants and reported into the eCRF as required.
- All medications used for cochlear implant surgery will be documented and reported into the eCRF as concomitant medications.

- Blood and perilymph samples will be collected from Arm A participants only (see above and Section 6.2) and ECochG performed for all participants (see Section 6.4.2) during the cochlear implant surgery.
- Arm A participants will have their diaries and study drug returned to them to continue to record their study drug administration.
- AEs and concomitant medications/treatments will be reported for all participants as required.
- If unavoidable, cochlear implant surgery may be re-scheduled up to and including Day 14. Arm A participants should continue to take twice-daily study drug without interruption until surgery.

6.1.5 Post-implant Outpatient Period

- Participants are not required to attend the site for study-related reasons after cochlear implant surgery until the Day 49 visit.
- Arm A participants should continue to take study drug twice-daily as per Section 5.1.1 and document administration information in their study diary. See Section 5.1.1 in the event of delayed cochlear implant surgery up to and including Day 14.
- Participants may contact the study site in case of queries or concerns. Unscheduled visits to the study site for study-related safety are at the discretion of the Investigator. All unscheduled study-related visits, assessments and any AEs will be documented and results entered into the eCRF.

6.1.6 Day 49 Visit

All participants will attend the study site for a visit on Day 49. A visit window of ± 7 days is permitted. Arm A participants should continue to take study drug until attending the Day 49 visit. The visit should ideally but not necessarily coincide with a standard-of-care cochlear implant assessment visit.

- Assessments are as indicated in SOA Table 1.
- Arm A participants will return the following for final check of compliance and drug reconciliation:
  - Study diary (to be retained at site as source document).
  - All study drug containers (even if empty) and any unused study drug.
- Study staff will transcribe drug administration details from the study diary into the eCRF.

6.1.7 End of Study Visit (EOS)

All participants will attend the study site for the EOS on Day 105. A visit window of ± 21 days is permitted. The visit should ideally but not necessarily coincide with a standard-of-care cochlear implant assessment visit.

- EOS/ET assessments are as indicated in SOA Table 1.
- If required, ET assessments are as per EOS; At ET, audiometric testing and biomarker sampling should be performed if participant agrees.

All the subjects receiving SENS-401 will have before EOS at least 4 weeks of follow-up after their last dose of SENS-401.

6.1.8 Permitted Visit Windows

Table 4: Permitted Visit Windows

Visit	Permitted Window
Screening	Day -42 to Day -1
Day 8 to 14 days	Up to and including Day 14
Day 49*	± 7 days
EOS*	± 21 days

EOS = end of study visit
* Visit should ideally but not necessarily coincide with a standard-of-care cochlear implant assessment visit

6.2 PHARMACOKINETICS

6.2.1 Blood Sampling for SENS-401 Concentration

One blood sample of approximately 2.7 mL will be collected from Arm A participants only for PK analysis prior to the morning dose of SENS-401 on the day of the cochlear implant surgery (see Section 5.1.1). Details including handling and preparation of samples is described in the study Laboratory Manual. The concentration of SENS-401 in samples will be measured using a partially-validated method.

6.2.2 Perilymph Sampling for SENS-401 Measurement – Primary Endpoint

A sample that will allow storage of at least 1 µL of perilymph will be obtained from the round window during the cochlear implant surgery from Arm A participants only (Section 6.5). Obtaining the sample and subsequent handling of the sample is described in the separate guidance manual for cochlear implant surgery prepared for this study. The concentration of SENS-401 in perilymph will be measured using a partially-validated method.

As this is for the primary endpoint, the Investigator must take care to ensure perilymph sampling is performed and handled correctly according to the manual provided.

6.3 AUDIOMETRIC TESTING

6.3.1 Pure Tone Audiometry (PTA)

Pure tone audiometry (PTA) is a behavioural subjective test used to identify hearing threshold levels and will be performed according to standard AS ISO 8253-1:2010 Acoustics – Audiometric test methods – Part 1: Pure-tone air and bone conduction audiometry. This test involves the peripheral and central auditory systems. Pure-tone thresholds (PTTs) indicate the softest sound audible to an individual at least 50% of the time. Hearing sensitivity is plotted on an audiogram displaying intensity as a function of frequency.

Pure-tone audiometry is a “gold” standard test to assess whether hearing acuity is normal or impaired. Air conduction hearing thresholds are measured for tonal stimuli at the range of frequencies from 0.125 kHz to 8 kHz with the use of headphones. Then, bone conduction hearing thresholds are measured for tonal stimuli at the range of frequencies from 0.25 to 4 kHz, with the use of a headband with oscillator. Hearing thresholds are measured in dB HL units. In sensorineural hearing loss both air conduction and bone conduction curves worsen, and no air–bone gap is present. If a Type B tympanogram

indicating presence of fluid in the middle ear is obtained at the time of audiometric testing (see Section 6.3.2), hearing threshold shift should be measured using bone conduction thresholds rather than air conduction thresholds.

Frequencies specified for this study: 0.25, 0.5, 0.75, 1, 2, 3, and 4 kHz.

Participant PTA will be performed at Screening, on Day 1 after randomization (prior to first dose of study drug for Arm A), at the Day 49 visit, and at EOS/ET for all participants (Arm A and Arm B). The PTA results will be recorded by the audiologist/operator on a form provided by the Sponsor for each participant's assessment as described in the Investigator Manual.

6.3.2 Immitance Audiometry

Immitance audiometry evaluates middle ear function by three procedures: static immittance, tympanometry, and the measurement of acoustic reflex threshold sensitivity, and requires a small plastic probe to be placed in one or both ear canals for tympanometry.

Tympanometry tests the condition of the middle ear and mobility of the eardrum (tympanic membrane) and the conduction bones by creating variations of air pressure in the ear canal.

For this study, tympanometry will be performed at Screening, on Day 1 after randomization (prior to first dose of study drug for Arm A), at the Day 49 visit, and at EOS/ET for all participants (Arm A and Arm B).

If a Type B tympanogram indicating presence of fluid in the middle ear is obtained at the time of audiometric testing (PTA; see Section 6.3.1), hearing threshold shift should be measured using bone conduction thresholds rather than air conduction thresholds.

6.4 EAR EXAMINATION

6.4.1 Otoscopic Examination

Participants will undergo an otoscopic examination by the Investigator at Screening, Day 1 after randomization (prior to first dose of study drug for Arm A), at the Day 49 visit, and at EOS/ET, to examine the structure of the ear canal, tympanic membrane and the middle ear. Otoscopy is part of standard of care, to rule out possible outer-ear abnormality such as otitis media or tympanic perforation.

The Investigator will document abnormalities found and indicate their clinical significance, or indicate the examination as normal. Clinically signicant abnormalities will be described into the eCRF.

6.4.2 Electrocochleography

Electrocochleography (ECochG) records electrical potentials generated in the inner ear and auditory nerve in response to acoustic sound stimulation.[16] For this study's exploratory objective, sites will use the Cochlear™ Research Platform System (software and hardware) according to the Cochlear™ Research Platform User Guide (Version 1.2). Study sites that are not already fully trained to use this technology will be provided with the system and trained by the local Cochlear Ltd representative.

During cochlear implant surgery, surgeons will use the ECochG during electrode insertion according to their routine practice (if routinely used). For the study, the Investigator will record an electrode sweep in response to a 500 Hz acoustic stimulus presented at 108 dB HL at the end of each participant's surgery (Arm A and Arm B). The anonymised csv file generated will be exported to the co-ordinating Investigator for analysis by a

designated Central Reader. Each Investigator will ensure that the anonymised csv file exported is identified only by participant number, and not by any other participant-identifying details (e.g., names, initials). Refer to the Investigator Manual (or relevant guidance manual as provided).

Analysis by the Central Reader will report if there is evidence of basilar membrane fixation (yes/no), and if yes, on which electrode. Basilar membrane fixation (i.e., the electrode is touching the basilar membrane causing mechanical impairment) will be determined based on either (a) a latency shift of <0.05 msec from electrode 22 to 20 or (b) the maximum amplitude of the cochlear microphonic appearing on an electrode between 2 and 18.

6.5 COCHLEAR IMPLANT SURGERY

Cochlear implant is a technological tool developed more than 40 years ago. Different surgical approaches have been adopted with cortical mastoidectomy–posterior tympanotomy being the most commonly followed technique. The one used within the framework of this protocol is standardized and will be described in a guideline which will be communicated to all the sites participating in this study.

All participants were previously diagnosed to benefit from the Cochlear™ Nucleus® C1622 model. Cochlear implant surgery will be performed between Day 8 and Day 14.

Immediately prior to insertion of the cochlear implant, perilymph will be sampled from the round window as per Section 6.2.2. The cochlear implant electrode will be performed via the round window, unless surgical considerations that arise during surgery dictate implantation via a cochleostomy or extended round window approach. Investigators will refer to the separate guidance manual for cochlear implant surgery prepared for this study.

A blood sample for plasma PK analysis will also be collected on day of surgery as per Section 6.2.1.

Intraoperative monitoring (electrocochleography and/or impedances) will be undertaken during electrode insertion, according to the routine practice of the Investigator. An electrode sweep will be performed with electrocochleography after completion of the surgery as per Section 6.4.2, to inform the study outcomes.The following information will be collected:

- Electrode insertion depth (N electrodes outside cochlear)
- Was surgery complicated or uncomplicated?
  - Please explain

6.6 BIOMARKERS

Collection of samples for other biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all participants (Arm A and Arm B) in this study on Day 1 (pre-dose for Arm A), at the Day 49 visit, and at EOS/ET as specified in the SOA Table 1. For each of these visits, approximately 8 mL from each participant will be required.

Samples for biomarkers will be stored in a biobank. These may possibly be tested later to establish correlations between their levels and clinical features of interest .

The accurate identification of biomarkers is not fully established yet. Some (e.g. Prestin) are foreseen as biomarkers of potential interest. Samples may be stored for a maximum

of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to SENS-401.

Details regarding collection, storage, and handling of biomarker samples will be provided in an applicable laboratory or sample handling manual.

7 SAFETY ASSESSMENTS

- The schedules for all safety assessments/activities are provided in the SOAs Table 1.
- Protocol waivers or exemptions are not permitted.
- All safety assessments may be conducted at unscheduled visits or timepoints if required for the participant's safety at the discretion of the Investigator. Such visits and/or assessments will be documented and entered into the eCRF.
- Re-testing of any screening parameters can be conducted once only.

7.1 PHYSICAL EXAMINATION

A full physical examination will be performed by the Investigator at Screening, the Day 49 visit, and at EOS/ET.

Symptom-directed physical examination may be conducted during the study at the discretion of the Investigator if considered necessary for participant safety.

All physical examination findings (normal/abnormal) must be recorded in source document and clinical significance of any abnormality provided by the Investigator and entered into the eCRF.

See Section 6.4.1 for otoscopic examination.

7.2 VITAL SIGNS AND BODY MEASUREMENTS

7.2.1 Vital Signs

Vital signs will include systolic and diastolic blood pressure (BP; mmHg), heart rate (HR; beats per minute), respiratory rate (RR; breaths per minute) and body temperature (ºC). Body temperature method will be specified (e.g., tympanic, oral) and the same method should be used during the study.

Vital signs will be measured at Screening, the Day 49 visit, and EOS/ET after participant is supine for at least 5 minutes. Vital signs may be measured at other timepoints during the study at the discretion of the Investigator, if considered necessary for participant safety.

In source document, all measurements will be indicated as normal or abnormal, and the Investigator will indicate the clinical significance of abnormal results. All vitals signs values will be entered into the eCRF with clinical significance of abnormal results indicated.

7.2.2 Body Measurements

Height (cm) and weight (kg) will be measured at Screening only. It is not sufficient for the participant to provide this information without measurement.

7.3 12-LEAD ECGS

Standard 12-lead ECGs will be recorded at Screening, the Day 49 visit, and at EOS/ET using a validated ECG device after participant is in supine position for at least 10 minutes. An ECG may be conducted at other times during the study at the discretion of the Investigator if considered necessary for participant safety.

The ECG will include: date, time, participant number, signature of Investigator, and at least 3 complexes for each lead. The Investigator should document if normal, or indicate abnormalities and their clinical significance.

The Investigator's medical opinion on clinical significance and automatic values will be recorded in the eCRF.

7.4 CLINICAL LABORATORY TESTS

7.4.1 Safety Blood Tests – Chemistry and Haematology

- Blood will be collected from all participants (Arm A and Arm B) at Screening, at the Day 49 visit, and EOS/ET for standard clinical laboratory safety tests conducted at the site's local/preferred laboratory.
- Participants are required to fast for at least 8 hours prior to collection of samples.
- Clinical laboratory tests may be conducted at other times during the study at the discretion of the Investigator if considered necessary for participant safety.
- Screening results must be available and reviewed to confirm eligibility prior to randomization on Day 1.
- The Investigator will indicate the clinical significance of abnormal results.

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	<u>RBC Indices</u>: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)	<u>White Blood Cell Count with Differential</u>: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red Blood Cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine and creatinine clearance GFR (calculated with the Cockcroft-Gault formula for subjects < 65 years old and CKD-EPI creatinine equation or with MDRD equation for subjects ≥ 65 years old;	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) International normalized ratio (INR)	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	

NOTES:
Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration, GFR = glomerular filtration rate,MDRD = modification of diet in renal disease.

7.4.2 Pregnancy Testing

A blood sample will be collected from all WOCBP at Screening for serum hCG pregnancy testing. Individuals will not be permitted to continue with the study if testing positive (screen failure).

A urine sample will be collected from Arm A WOCBP at the Day 49 visit and at EOS/ET for hCG pregnancy testing.

7.4.3 Testing for SARS-CoV-2 (COVID-19)

For this study, participants will be tested via rapid antigen test for SARS-CoV-2 on Day 1 prior to randomization. A positive result will constitute a screen failure, and the participant must not be randomized and must follow local regulatory requirements for receiving a positive rapid antigen test result for SARS-CoV-2.

At all other times, study sites will follow their institutional and local regulatory requirements for screening/testing for COVID-19, and for handling of participants with signs and symptoms of COVID-19. Participants should not attend the study site if results of a COVID-19 test are still pending. Appropriate measures and procedures will be in place to ensure the safety of participants and study staff. The site visits scheduled for this study are the minimum required and cannot be conducted remotely.

If a participant taking study drug tests positive for COVID-19 during the study (by polymerase chain reaction [PCR] test or rapid antigen testing), the Investigator will decide if the participant should discontinue study drug and how the follow-up visit and assessments can be performed. The participant must abide by local regulations and restrictions.

7.5 ADVERSE EVENTS (AES)

The Principal Investigator or delegate and study site staff are responsible for detecting, recording and reporting events that meet the criteria and definition of adverse events as described below. Adverse events may be reported by the participant or observed by the Principal Investigator, delegate or other clinical site staff. When enquiring about AEs, the Investigator and study staff will take care to not introduce bias and will use open-ended and non-leading verbal questions.

All AEs will be proactively followed at each subsequent visit or contact as medically indicated until the event has resolved, no further medically relevant information from the event can be expected and it is acceptable to discontinue follow-up of the event in the assessment of the Principal Investigator. The Principal Investigator should continue to follow up SAEs that were unresolved at the participant's EOS/ET as long as medically required (resolution or stabilization), the event is otherwise explained, the participant is lost to follow-up or satisfactorily referred to a general practitioner or medical specialist as appropriate. The Sponsor or designee may request further measurements and/or evaluations (e.g., laboratory tests or investigations, histopatholigical examinations, or consultations with other health care professionals) to elucidate the nature of the AE or SAE as fully as possible.

Adverse events will be recorded from the time of informed consent to study completion and entered into the eCRF.

Investigators are not obligated to seek AE or SAE information after the conclusion of study participation, however if the Investigator learns of any SAE (including death) at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the IMP or study participation, the Investigator must promptly notify the Sponsor or designee.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.

7.5.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant administered a medicinal product, and that does not necessarily have a causal relationship with this treatment.

Adverse events include, but are not limited to:

- A new symptom, sign or medical condition
- A disease or medical condition detected or diagnosed during the study even though it may have been present prior to the start of the study
- An exacerbation of a pre-existing medical condition/disease
- An increase in frequency or intensity of a pre-existing episodic disease or medical condition
- Continuous persistent disease or symptoms present at the start of the study that worsen during the study
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- 'Lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE or SAE as such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if fulfilling the definition of AE/SAE (except for 'loss of residual hearing' as below).
- A clinically significant abnormal assessment (e.g., change on physical examination, ECG finding) that was not present at the start of the study or worsened during the study
- A clinically significant abnormal laboratory test result (e.g., CTCAE grade 2 or above), symptomatic or not, which:
  - Was not present at the start of the study, and/or
  - worsened during the study, and/or
  - led to the study drug dose being reduced, or
  - led to the study drug treatment being interrupted, or
  - led to the study drug treatment being permanently discontinued.

Abnormal laboratory findings and other objective assessments should NOT be routinely captured and reported as AEs unless the following criteria are met:

- considered by the Investigator or Sponsor to be clinically significant or represent a clinically significance change from baseline, and/or
- meets the criteria of serious for reporting as an SAE, and/or
- associated with accompanying symptoms, and/or
- requires additional diagnostic testing or medical/surgical interventions, and/or
- leads to change in study drug dosing, or discontinuation from the study, significant additional concomitant medication or other therapy.

The abnormal result/finding should then be documented and reported in the AE Section of the eCRF (see Section 7.5.4).

Adverse events will not include:

- A medical or surgical procedure such as surgery (including the scheduled cochlear implant surgery), endoscopy, tooth extraction or transfusion (although the condition that led to the procedure may be an AE);
- A pre-existing disease or medical condition present at the start of the study that does not worsen (in intensity and/or frequency) during the study, except for loss of residual hearing (see below). This includes day-to-day fluctuations that do not worsen.
- Any situation where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery or social admissions).
- Any clinically significant abnormal laboratory findings or other safety assessment findings which are associated with the underlying disease/condition, unless judged by the Investigator to be more severe than expected for the participants condition.

Untoward medical occurrences during or after the cochlear implant surgery (including if expected or known side-effects of the cochlear implant and/or surgery) will be reported as AEs. Any such AEs considered related to the cochlear implant or the surgery by the Investigator are defined as adverse device effects (ADEs). However, loss of residual hearing will not be recorded as an AE or ADE as it is part of the efficacy endpoint, unless it is considered to be an AE/ADE by the Investigator.

7.5.2 Causal Relationship to Investigational Medicinal Product and Other Study Treatments/Procedures

The Investigator is required to assess the causality for all AEs, and must indicate this in source document and eCRF. An adverse event with reasonable causal relationship to the IMP, cochlear implant (medical device), study sample collection procedure, or cochlear implant surgery means there is evidence or argument to suggest a causal relationship. The Investigator should also take into account any relevant information provided in documents including but not limited to the Investigator's Brochure (for IMP), device instructions for use (cochlear implant), and/or study Laboratory Manual (study sample collection procedure).

If considered related:

- The temporal relationship between the event and the administration of the IMP (or cochlear implant, study sample collection, or cochlear implant surgery) is compelling and/or follows a known or suspected response pattern to that product/procedure, and the event cannot be explained by the participant's medical condition, other therapies or accident.

If considered not related:

- The event can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy or accident and no plausible temporal or biologic relationship exists between the IMP (or cochlear implant, study sample collection, or cochlear implant surgery) and the event.

7.5.3 Severity Grading of Adverse Events

The severity of AEs will be recorded by the Investigator in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 November 2017. This guidance provides a common language to describe levels of severity, to analyse and interpret data, to scale the aggregate AE score, and to articulate the clinical significance of all AEs.

If there is not CTCAE grading available for a specific AE, the severity of AEs will be graded as follows:

- Grade 1: Mild; asymptomatic or mild symptoms, easily tolerated; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated (e.g., short course of antibiotics); discomfort enough for limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling/incapacitation; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences/risk of death; urgent intervention indicated.
- Grade 5: Death related to AE/fatal outcome.

An AE that is assessed as severe is not the same as a serious AE. Severity is a category utilized for rating the intensity of an event and both AEs and SAEs can be assessed as severe. An AE is defined as 'serious' when it meets one of the pre-defined serious outcomes as described in Section 7.6.1.

7.5.4 Documentation of Adverse Events

The Principal Investigator or delegate is responsible for reviewing all documentation related to each AE, and for recording all relevant AE/SAE information in source document and in the CRF. The Principal Investigator or delegate will attempt to establish a diagnosis of the AE based on signs, symptoms and/or other clinical information, and where possible the diagnosis will be documented as the AE/SAE (and not individual signs or symptoms).

The following information should be recorded for all AEs:

- Description
- Dates and times of onset and resolution
- Seriousness
- Severity
  - In the source data, the description of the AE will report the various severities observed over time. If the severity of an AE increases, separate AEs per severity grading will be recorded into the eCRF.
  - If the AE resolves and then reoccurs, then two AEs will be reported.
- Action taken in response to the AE regarding IMP:
  - Interrupted, or

- Permanently discontinued, or
- No action taken, or
- Unknown/not applicable.

- Outcome of AE:
  - Recovered/resolved, or
  - Recovering/resolving, or
  - Not recovered/not resolved, or
  - Recovered with sequelae/resolved with sequelae
  - Fatal
  - Unknown
- Relationship to the:
  - IMP,
  - cochlear implant = medical device,
  - study sample collection procedure, and/or
  - cochlear implant surgery.

7.5.5 Adverse Events of Special Interest

Not applicable for this study.

7.5.6 Treatment of Overdose

Symptomatic overdose of IMP is an event suspected by the Principal Investigator or delegate, or notified by the participant. Overdose is defined as any dose greater than 43.5 mg twice daily within a 24 hour period (±6 hours). Such an event should be reported promptly to the Sponsor as an SAE. Asymptomatic overdose will be reported as a standard AE.

As there is no antidote for SENS-401, in cases of overdose intensive care admission should be considered according to clinical status, and treatment will be as standard for nonspecific drug intoxication. General support may include immediate gastric lavage within the first hour after intake to reduce the amount absorbed, continuous monitoring of vital signs, supportive care for cardiovascular function, respiratory aid in case of compromise, hydroelectrolyte balance, and other measures as clinically indicated.

In the event of an overdose, the Investigator will:

- Contact the Medical Monitor as soon as possible according to the level of medical emergency
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until SENS-401 can no longer be detected (at least 7 days)
- Obtain a plasma sample for PK analysis within 7 days from the last dose of IMP if requested by the Medical Monitor.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions of modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant. The Sponsor must be immediately notified of any instances of overdose and the protocol deviation must be thoroughly documented and reported per local regulations. An overdose or incorrect administration of a drug is not itself an AE, but may result in an AE(s). All AEs associated with an overdose or incorrect administration of a drug should

be recorded in the AE CRF. If the associated AE fulfills the serious criteria, the event should be reported as an SAE (see Section 7.6.3).

7.6 SERIOUS ADVERSE EVENTS (SAEs)

7.6.1 Definitions of Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that:

1. Results in death, or
2. Is life-threatening, and/or
3. Requires inpatient hospitalisation or prolongs existing hospitalisation, and/or
4. Results in persistent or significant disability or incapacity, and/or
5. Is a congenital anomaly or birth defect, and/or
6. Are important medical events that are not immediately life-threatening or do not result in death or hospitalization but may jeopardise the participant or may require intervention to prevent one of the other outcomes above should also be considered serious. Medical and scientific judgement should be exercised in deciding whether an AE should be classified as serious in these situations. Examples include: invasive or malignant cancers, intensive treatment in emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note:

- Life-threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at a hospital or emergency ward for observation and/or treatment that would have not been appropriate in the setting of a physician's office or as an outpatient. Complications occurring during hospitalization are AEs and if meeting definition of serious (e.g., prolongs hospitalization) then the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Planned procedures (including cochlear implant surgery) that require admission to hospital or medical facility for this study, or any planned elective procedure that requires hospitalization, are not considered SAEs unless the underlying condition has worsened since the start of the study and/or the participant's condition worsens after the procedure, resulting in extension of hospitalization or re-hospitalization, and/or other serious criteria are met.
- The term disability means substantial disruption to a person's ability to conduct normal life functions. It is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, or accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life function but do not constitute a substantial disruption.
- If an event is not defined as an AE (see Section 7.5.1), it cannot be an SAE even if serious conditions are met.

7.6.2 Pregnancy

Pregnancy in a study participant or participant's partner is not in itself defined as an AE/SAE. Any complication or termination of pregnancy for medical reasons are to be reported as an AE/SAE. Spontaneous abortion, still birth or congenital anomaly must be reported as an SAE.

Where possible, the Investigator will attempt to collect and report information regarding pregnancy outcomes of participants or female partners of any male participants who were administered IMP in this study and the following 60 days after the last dosing. Appropriate signed informed consent will be required directly from pregnant female partners to obtain and report this information. The Investigator will report as for an SAE. Any participant or participant's female partner who becomes pregnant during the study should be followed through delivery or termination of the pregnancy.

Follow-up will generally not be required for longer than 12 months beyond the delivery date.

7.6.3 Reporting for Serious Adverse Events (24 hours)

If any SAE occurs, the Investigator will take immediate appropriate action and aim to identify the causes of the event/s.

The Investigator must notify the SAE(s) to [redacted] within 24 hours of becoming aware of the event by emailing the designated paper SAE report form to [redacted] In cases where the email system is unavailable, site staff will send the SAE by fax to [redacted]

The Investigator must always provide an assessment of causality at the time of the initial report and is responsible for reviewing all documentation related to the event.

Any copies of participant's medical records provided for SAE reporting must have all participant identifiers (such as name, address etc.) other than study participant number redacted before submission.

The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the Investigator. If the Investigator does not have all information regarding an SAE, they must not wait to receive additional information before reporting the event. A follow-up SAE report should be completed within 14 days, or if there is no new information, the SAE report form should be updated when additional information is received. The Investigator will submit any updated SAE data within 24 hours of receipt of the information.

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory and EC/HREC requirements related to the reporting of SAEs (including suspected unexpected serious adverse reactions [SUSARs]) to the EC/HREC. The Sponsor retains responsibility for appropriate reporting of SUSARs to regulatory authorities, including Sponsor assessment of causality if required.

7.7 SAFETY REVIEW COMMITTEE OR DSMB

No SRC or DSMB will be used in this study.

8 STATISTICAL ANALYSES

8.1 SAMPLE SIZE

Overall, for this study, 27 participants will be enrolled and randomized to either Arm A or Arm B on Day 1 in ratio 2:1 (18 participants in Arm A and 9 participants in Arm B). The sample size is not calculated based on statistical significance on any clinical efficacy parameters but on empirical considerations for the pharmacokinetic evaluation. Eighteen subjects are generally considered sufficient to characterise the PK of a small molecule. The purpose of the PK sampling is to determine if SENS-401 can be detected in the perilymph and to compare the levels of SENS-401 in two different body compartments and the overall safety profile.

For efficacy, 27 participants are empirically expected to provide enough data to evaluate a trend of efficacy.

Enough participants will be screened to randomize 27 participants.

8.2 GENERAL STATISTICAL APPROACH

The following is an outline of the statistical methodology that will be used to report and analyse this study. A more detailed description will be provided in a separate Statistical Analysis Plan (SAP) that may include additional exploratory analysis not explicitly mentioned in the following sections. The SAP will be finalised prior to final database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the clinical study report (CSR).

The general analytical approach for all endpoints will be descriptive in nature. Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables: Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the eCRF; mean, median and SD will be presented to one more decimal place than the raw data.

Categorical variables: Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of participants in the relevant population with non-missing data.

Imputation: No missing data will be imputed.

Baseline: The baseline will be defined as the last available assessment prior to study drug administration.

Confidence intervals (CIs): If required, CIs will be two sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.

Unscheduled assessments: Unscheduled visits will be excluded from visit-based summary tables.

Early termination visits: Assessments conducted at Early Termination will be excluded from visit-based summary tables.

8.3 ANALYSIS SETS

Two analysis datasets will be used for study analyses: Pharmacokinetics (PK) Set and Full Analysis Set (FAS).

Additional study populations or subgroups may be detailed in the SAP.

8.3.1 PK Set

The PK Set will be comprised of all randomized participants who were at least 70% compliant with SENS-401 in the three (3) days prior to cochlear implant surgery and for the morning dose on the day of surgery and at least 70% compliant overall for the dosing period prior to surgery.

8.3.2 Full Analysis Set (FAS)

The FAS will be comprised of all randomised participants. Participants will be analysed according to the treatment received.

8.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristic data will be summarised using the FAS.

8.4.1 Demographics

Demographic data will be listed for each participant and summarised descriptively by treatment group and overall.

8.4.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by system organ class (SOC) and preferred term (PT), per treatment group and overall.

8.4.3 Prior Medications

Prior medications will be coded using WHODRUG and will be summarised by Anatomical Therapeutic Class (ATC) code and preferred name (PN), per treatment group and overall.

Prior medications will be identified as medications commenced prior to the time of first study drug administration, regardless of whether the medication was continued after study drug administration.

8.5 PROTOCOL DEVIATIONS

All protocol deviations will be listed using the FAS.

Protocol deviations will be summarised by deviation type, per treatment group and overall.

8.6 PARTICIPANT DISPOSITION

A listing of participant disposition, using the FAS, will present dates of informed consent, randomisation, treatment commencement, treatment completion, as well as reasons for treatment and study discontinuation.

Participant disposition variables will be summarised per treatment group and overall.

Early treatment and study discontinuation will also be detailed in a separate listing.

8.7 TREATMENT COMPLIANCE

All study drug administration data will be listed, using the PK Set.

8.8 PHARMACOKINETIC ENDPOINTS

The PK analyses will be performed using the PK Set.

8.8.1 Primary Endpoint

The number and percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification on surgery day (visit 3) will be summarised.

8.8.2 Secondary Endpoint

SENS-401 concentration data will be listed for each participant from Arm A and summarised descriptively for plasma and perilymph. A paired t-test will be used to compare the SENS-401 concentrations in the perilymph and plasma if the data is normally distributed. If the data is not normally distributed, we will calculate medians (with their interquartile range [IQR]) and use the Wilcoxon signed ranks test.

8.9 EFFICACY ENDPOINTS

8.9.1 Hearing threshold

Change of hearing threshold from baseline in the implanted ear at 500 Hz, 250 Hz and 750 Hz will be summarized as continuous variables by visit and treatment using simple descriptive statistics.

Analysis of covariance model (ANCOVA) will be used to assess changes in the values from baseline at the Day 49 visit and at EOS/ET, comparing between treatment groups. The treatment group will be used as a fixed factor and the baseline as a covariate.

8.9.2 Exploratory Endpoints

8.9.2.1 Assessment of Basilar Membrane Fixation

Participants who have impairment of the basilar membrane (IBM) as detected by the ECochG latency shift and/or mid peak amplitude will be listed, grouped by arm.

The number and percentage of participants with IBM will be summarised by arm.

8.9.2.2 Hearing threshold assessment excluding participants with IBM

Supplementary analyses will be conducted, whereby the ANCOVA analysis and descriptive statistics to assess changes in hearing threshold from baseline, will be repeated excluding participants with IBM.

8.9.2.3 Biomarker Analysis

Biomarker exploratory analyses (if performed) will be described in the statistical analysis plan (SAP) finalized before database lock.

8.10 SAFETY ENDPOINTS

8.10.1 Adverse Events

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term, classified from verbatim terms.

All AEs recorded during the study will be listed, grouped by participant and treatment group. The duration of AEs will be determined and included in the listings.

A Treatment Emergent Adverse Event (TEAE) is defined as any untoward medical occurrence reported or observed after treatment administration. Conditions present before the first dose of study drug that increase in severity after the first study drug administration will also be considered TEAEs. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE started after treatment administration, it will be assumed to be a TEAE.

AEs will be summarized by the number of AEs and number and percentage of participants experiencing:

- any AEs,
- any severe and potentially life-threatening AEs,
- any drug-related AEs,
- any SAEs,
- any drug-related SAEs, and
- any AEs leading to study drug interruption.

Adverse events will also be summarized by:

1) system organ class and preferred term;

2) system organ class, preferred term, and severity; and

3) system organ class, preferred term, and relationship to study drug.

If a participant experienced more than 2 AEs for a given preferred term, severity is defined by the most severe event and relationship to study drug is defined by the most related event.

8.10.2 Vital Signs

All vital sign data will be listed for all participants. For each parameter, observed values will be summarised descriptively per treatment group and overall.

The incidence rates of clinically significant vital sign abnormalities will be summarized.

8.10.3 Body Measurements

Height (cm) and weight (kg) data will be listed for all participants. For each parameter, observed values will be summarised per treatment group and overall.

8.10.4 Physical Examination

Physical examination findings will be listed only.

8.10.5 12-Lead ECG

ECG data will be listed, with abnormal values and clinical significance flagged. All ECG variables will be summarised per treatment group and overall.

8.10.6 Clinical Laboratory Tests

All laboratory parameters will be listed with flags for values outside the reference ranges and values considered to be clinically significant.

Each parameter will be summarised descriptively.

The number and percentage of participants with clinically meaningful laboratory test findings will also be summarized by treatment group.

8.10.7 Pregnancy

Pregnancy data will be listed only.

8.10.8 Testing for SARS-CoV-2 (COVID-19)

COVID-19 data will be listed only.

9 STUDY ADMINISTRATION

9.1 ETHICAL CONSIDERATIONS

9.1.1 Ethical Principles

This clinical study was designed and shall be implemented and reported in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable ICH GCP Guidelines including the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) dated 09 November 2016, (for Australian sites) the National Statement on Ethical Conduct in Human Research, (2007 – updated 2018), and all applicable laws and regulations.

9.1.2 Informed Consent

Eligible participants may only be included in the study after providing voluntary, written (witnessed, where required by law or regulation), IRB/IEC/HREC-approved informed consent. Informed consent to participate in the study must be obtained according to GCP and local regulatory requirements before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant source documents, including stating that written informed consent was obtained before the participant was entered into the study and the date obtained, and a copy of the signed participant information and consent form (PICF) provided to the participant.

If new information becomes available that may be relevant to the participant's willingness to continue to participate in the study, a new PICF will be prepared and approved by the IEC/HREC. The study participants will be informed about the new information and re-consent obtained. Participants who are re-screened must sign a new PICF.

9.1.3 Ethics Committee/Human Research Ethics Committee (HREC) Approval

Before initiating a trial, the Investigator/institution will obtain written approval/favorable opinion from the EC/HREC for the trial protocol, written PICFs, PICF updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants.

The Investigator is responsible for ensuring that any necessary extensions or renewals of EC/HREC approval are obtained, and that EC/HREC approval of changes to the study such as protocol amendments, updated PICFs or other study documents is obtained prior to implementing the changes. The Investigator will also report promptly to the EC/HREC any new information that may adversely affect participant safety or study conduct, provide EC/HREC-requested reports or summaries, and notify the EC/HREC when the study has ended.

9.2 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. In this instance, the Sponsor medical monitor must be advised before or as soon as possible after such assessments are conducted.

Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational

drugs. Investigators will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment and cannot be implemented unless such an amendment is agreed upon by the Sponsor and approved by the HREC.

All protocol deviations will be recorded during the study, and listed in the clinical study report (CSR), including but not limited to the following deviation categories:

- Informed consent
- Eligibility
- Visit not done
- Visit performed out of window
- Study procedure not done
- Study procedure done out of window
- Safety reporting
- Investigational Product
- Privacy and Data Protection
- Concomitant Medication
- Other (including disruptions to the trial due to COVID-19 that are not per protocol)

Major protocol deviations may significantly impact the completeness, accuracy, and/or reliability of the study data or may significantly affect a participant's rights, safety, or well-being. These include:

- Participant entered the study even though they didn't satisfy entry criteria;
- Participant developed withdrawal criteria during the study but was not withdrawn;
- Participant received the wrong treatment or incorrect dose;
- Participant received an excluded concomitant medication.

9.3 PROTOCOL AMENDMENTS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor and the HREC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the Sponsor's medical monitor is notified as soon as possible after the event and the reviewing HREC is subsequently notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the Medical Monitor and Sponsor must be notified immediately.

9.4 DATA HANDLING AND RECORD KEEPING

Participants will be assigned a unique identifier when participating in the study, and any participant datasets or records that are transferred to the Sponsor or CRO will be associated only with this identifier. Any other identifiable information about the participant, such as names, will not be transferred. The Principal Investigator will ensure procedures are in place to appropriately protect the confidentiality of the participant records and data, including adequate safeguards for digital/computer access by authorized personnel only. Participants will be informed that their personal study-related data will be

used by the Sponsor in accordance with local data protection law and that their medical records may be examined by auditors and regulatory agencies.

Study-related participant data will be entered into electronic case report forms (eCRFs) by authorized study personnel, except for data that may be transmitted to the Sponsor or CRO electronically (such as laboratory data). Guidelines for completion of the eCRF including correction of entries and responding to data queries will be provided by the Sponsor or CRO. Data will be entered into the eCRF by authorized study personnel in a timely fashion and as requested by the study monitor. The Principal Investigator is responsible for i) ensuring that accurate source documents for all data entered into the eCRF are maintained at the study site, and ii) for verifying CRF data entries are accurate and correct by signing (electronically or physically) the eCRF after all queries have been resolved. Corrections to source document (whether paper or electronic) must have an audit trail (i.e., must not obscure or delete the original entry, and the date/time of correction and identity of the person making the correction must be clearly indicated). Participant study diaries are considered source document, and should be collected from the participant at EOS/ET for filing.

All study documents including source documents and signed PICFs must be retained by the Principal Investigator for at least 15 years and according to local regulatory requirements. No study documents may be destroyed or transferred during the retention period without the Sponsor being directly notified in writing.

9.5 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor assumes accountability for actions delegated to other parties (including to the CRO). A risk-based approach to quality management will be applied to all stages of protocol development and study conduct to ensure protection of participants and reliability of trial results. The Sponsor or CRO maintains responsibility for quality assurance and for data management, with quality control applied to each stage of data handling to ensure reliability and correct processing.

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor-appointed monitors, auditors, Quality Assurance representatives, EC/HREC representatives, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

Study monitors appointed by the Sponsor or CRO will conduct ongoing, regular visits to the study sites to verify the eCRF data is accurate and complete according to source documents, the safety and rights of participants are being protected, and that the study is being appropriately conducted according to the protocol, other study agreements, ICH GCP and local regulatory requirements. Monitoring visits may be conducted remotely if required due to the ongoing COVID-19 pandemic. Details will be provided in a Monitoring Plan. See also Section 9.4.

After monitoring, the eCRF data will be validated by Sponsor-designated data management using a series of programmed checks and listing reviews according to relevant internal standard operating procedures (SOPs). Queries will be either automatically or manually generated and added to the eCRF to be resolved promptly by authorized site personnel. After all data discrepancies are resolved, medical coding

completed, serious adverse events (if any) reconciled with the CRF, and external data integrated, the database will be locked and provided to the Statistician for analysis.

Data will be retained as required by ICH GCP and local regulatory requirements.

9.6 PUBLICATION POLICY

Neither the complete nor partial results of the study achieved under this protocol, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published, presented at scientific meetings, or otherwise passed on to any third party without the consent of the study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete study results and all data derived from the study.

Results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

9.7 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor sufficient, accurate financial information as requested and according to local regulations, with information on financial interests to be provided during the study and for one (1) year after completion. This is to permit the Sponsor to submit complete and accurate financial certification or disclosure statements to regulatory authorities, where required.

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11 APPENDICES

11.1 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Female Participants (WOCBP only):

The following methods of contraception can achive a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal / contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Same-sex partner may also be considered an effective method of birth control for this study.

Male Participants:

No contraception measures are needed for male participants, including those with pregnant or non-pregnant WOCBP partner.