Clinical study Protocol

NOTOXIS

Protocol Title:	A Phase IIa, Multicenter, Randomized, Controlled, Open label Study to Evaluate the Efficacy of SENS-401 to Prevent the Ototoxicity induced by Cisplatin in Adult Subjects with a Neoplastic Disease
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Study Product:	SENS-401
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– CONFIDENTIAL –

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

	20 SEPTEMBER 2023
[redacted] **Chief Medical Officer** [redacted]	**Date**

Protocol amendment summary of changes table

Version	Date	Main Reasons
1.0	22/10/2021	
2.0	17/01/2022	Response to French authorities' request
2.1	31/01/2022	Response to French authorities' request
2.2	28/02/2022	Response to the French Ethic Committee's request
3.0	19/08/2022	Change in the study design: - SENS-401 treatment duration - Primary endpoint and associated statistical analysis - Adaptive design for the determination of the final sample size
4.0	26/07/2023	Revisions to the inclusion and exclusion criteria aimed at reducing the screen failure rate and simplifying eligibility requirements. In addition, modifications to the study design to enhance its feasibility have been implemented.
4.1	20/09/2023	Correction of typos in the numbering of the inclusion criteria.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Efficacy of SENS-401 to Prevent the Ototoxicity induced by Cisplatin in Adult Subjects with a Neoplastic Disease.

Short Title: SENS-401 to Prevent the Ototoxicity induced by Cisplatin in Adult Subjects with a Neoplastic Disease.

Rationale: This study is intended to evaluate the efficacy of SENS-401 to prevent individuals from suffering cisplatin induced hearing loss. The pathophysiological mechanism of such hearing loss is not perfectly understood but it may include hair cell loss, damage to stereocilia, and/or loss of synapses or cochlear neurons. The dual effects of SENS-401 as a selective serotonin type 3 ($5HT_3$) antagonist and a calcineurin antagonist, as well as its ability to prevent damage to sensory hair cells, synaptic contacts, and potentially primary neuronal afferents in the inner ear, support its potential as an oral agent to prevent ototoxicity related to cisplatin.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
To evaluate the efficacy of SENS-401 given at the dose of 43.5 mg b.i.d. (*bis in die*) for up to 23 weeks to prevent the ototoxicity induced by cisplatin in subjects with a neoplastic disease, 4 weeks after the completion of the last cisplatin treatment.	Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 4 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject.
Secondary	
To further evaluate the efficacy of SENS-401 given at the dose of 43.5 mg b.i.d. for up to 23 weeks to prevent the ototoxicity induced by cisplatin in subjects with a neoplastic disease, 4 and 12 weeks after the completion of the last cisplatin treatment.	Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 12 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject. Change from baseline in the distribution of hearing loss severity at 4 and 12 weeks. The severity of the hearing loss being based on the CTCAE (version 5.0) classification and being evaluated as the shift of the average of the hearing threshold compared to the baseline of 2 or 3 contiguous frequencies in at least one ear evaluated with an audiogram from 1 to 8 kHz and as follows: Grade 1: threshold shift from baseline ≥15 dB averaged at 2 contiguous test frequencies Grade 2: threshold shift from baseline >25 dB averaged at 2 contiguous test frequencies. Grade 3: threshold shift from baseline >25 dB averaged at 3 contiguous test frequencies

Objectives	Endpoints
	Change from baseline in speech discrimination test score (assessed in noise and in quiet) 4 and 12 weeks after the completion of the cisplatin treatment. Change from baseline in Tinnitus Handicap Inventory (THI) Questionnaire score, 4 and 12 weeks after the completion of the cisplatin treatment.
Exploratory	
To explore the correlation between pre-identified biomarkers (e.g., prestin) or biomarkers that will be identified in the future, and clinical features of interest (like prediction of ototoxicity). To evaluate the performance of an application (headphone and tablet) to evaluate hearing level in a broad range of frequencies (500 Hz to 12.5 kHz).	Serum/plasma concentrations of selected biomarkers before each of the first three cisplatin treatments (just after rehydration), at the end of the day of the third cisplatin cycle and at visit 5. Sensitivity and specificity of hearing thresholds measured by auto-testing in each tested frequency compared to standard audiogram values performed in hospital sites.
Safety	
To confirm the good systemic safety profile of SENS-401 (43.5 mg given orally b.i.d. for 23 weeks).	Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs).

Overall Design:

Multicenter, randomized, controlled, two-arm, open-label efficacy and safety study in adults with neoplastic disease requiring treatment with cisplatin as part of the chemotherapy protocol plan. Cisplatin treatment per chemotherapy protocol must be given at a cumulative dose high enough to significantly increase the iatrogenic likelihood of ototoxicity (unit cisplatin dose of at least 70 mg/m^2 and cumulative cisplatin dose of at least 210 mg/m^2).

Subjects willing to participate in the study will sign an Informed Consent Form (ICF). They will be considered eligible based on the results of a Screening Visit performed within 28 days before the randomization.

Based on the statistical assumptions made on time-based hearing impairment due to cisplatin, it is expected that 25 subjects per study arm will be sufficient to evaluate the efficacy profile of SENS-401.

However, an intermediate blind analysis (i.e., parameters estimated on all patients, regardless of the treatment group) will be conducted once a sufficient number of subjects will allow for at least 16 ears per arm after three cycles of cisplatin, in order to determine the three most severely affected hearing frequencies (these frequencies will be used for quantitative analysis), estimate the standard deviation, assess the correlation between intra-subject and inter-ear hearing impairments, and re-evaluate the sample size if necessary.. No more than 29 subjects per arm will be randomized.

If all the eligibility criteria are met, subjects will be randomized to one of the two study arms as follows:

- **Study Arm A (control arm):** Subjects receiving cisplatin-based chemotherapy without receiving SENS-401. This control arm will provide the incidence of hearing impairment due to ototoxicity 4 and 12 weeks after the last cisplatin treatment.
- **Study Arm B:** Subjects receiving 43.5 mg of oral SENS-401 b.i.d. for up to 23 weeks: 1 week prior to the initiation of the cisplatin treatment, during the whole duration of the chemotherapy treatment

(estimated to last up to 18 weeks) and 4 weeks after stopping chemotherapy. This arm will provide data on the potential protective effect of SENS-401 on cisplatin induced ototoxicity.

All subjects will be followed up to 12 weeks after the completion of the cisplatin therapy.

The hearing function of all subjects will be evaluated at screening (baseline) and 4 and 12 weeks after the end of the last cisplatin cycle using:

- Otoscopy;
- Immittance audiometry;
- Pure-tone audiometry (PTA) spanning a band of frequencies from 500 Hz to 12.5 kHz;
- Speech-in-Noise Test;
- Speech-in-Quiet Test;
- Tinnitus Handicap Inventory (THI) questionnaire; and
- Auto-testing using a headphone and a tablet application (exploratory and optional).

All subjects, regardless of the study arm to which they have been allocated, will receive as established by the ear, nose and throat doctor (ENT), the current standard of care for the ototoxicity. Thus, cisplatin doses will be adapted to subject body surface and hyperhydration will be provided. The current practices include several recommendations as modifications to the medication, rescue therapy with intravenous corticosteroid and supporting hearing function with medical device.

Main Inclusion criteria

A subject is eligible to be included in the study only if all of the following criteria apply:

1. Age ≥ 18 years at the time of signing the ICF.
2. Capable of giving signed informed consent as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
3. A female subject is eligible to participate if she is not pregnant (see Appendix 6), not breastfeeding, and ≥ 1 of the following conditions apply:
    - Not a woman of childbearing potential (WOCBP) as defined in Appendix 6.
    - A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.
4. A male subject must agree to use contraception and refrain from donating sperm as detailed in Appendix 6 of this protocol for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.
5. Neoplastic subject that, regardless of participation in this study, is planned to be treated with a chemotherapy that includes a dose of cisplatin of at least 70 mg/m^2 per cycle and a cumulative dose of cisplatin of at least 210 mg/m^2.

6b. Subjects with a PTA threshold of ≤ 30 dB at 500 Hz AND ≤ 40 dB at 1-2 kHz AND ≤ 60 dB at 4-6 kHz AND ≤ 80 dB at 8 kHz, in either both ears or one ear for a maximum of 30% of the subjects in each study arm.

7. In the opinion of the Investigator, a life expectancy of ≥ 6 months.
8. Inclusion Criterion 8 about COVID-19 has been removed from study protocol v4.0.

Exclusion Criteria

A subject is not eligible if any of the following criteria apply:

1. Any condition or past medical history that, in the opinion of the Investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study.
2. Subject is the Investigator or anyone from his/her team directly involved in the conduct of the protocol.
3. Mentally unable to understand the nature, objectives, and possible consequences of the study or refusing its constraints.
4. A congenital or hereditary disease known to decrease hearing function (e.g. Otoferlin [OTOF]-related deafness).
5. Any medical history affecting the middle ear function such as chronic otitis, cholesteatoma, or tympanic membrane perforation.
6. Any inner ear disease that is likely to decrease hearing function according to the Investigator's judgment (e.g. herpes zoster oticus; Meniere's disease; purulent labyrinthitis; vestibular schwannoma).
7. Having a history of sudden sensory neural hearing loss.
8. Having a fluctuating hearing loss (e.g. due to Meniere's disease, vestibular aqueduct syndrome, or autoimmune inner ear disease).
9. History of head trauma with hearing loss.
10. History of meningitis.
11. For a subject expected to receive radiotherapy during the course of the study, an anticipated risk of exposure of the auditory system (i.e. inner ear within the expected irradiation zone).
12. History of significant arrhythmia or conditions known to increase proarrhythmic risk (e.g. congestive heart failure, long QT syndrome, hypokalemia).
13. Significant clinically relevant electrocardiogram (ECG) abnormality that, in the opinion of the Investigator, precludes study eligibility.
14. Significant abnormal laboratory result, physical examination, vital signs, or ear-nose-throat (ENT) evaluation (otoscopy and immittance audiometry), in the opinion of the Investigator.
15. Neurological disorder including stroke, demyelinating disease, or brain stem or cerebellar dysfunction.
16. Moderate to severe renal impairment defined by a creatinine clearance ≤ 60 mL/min (calculated with the Cockcroft-Gault formula for subjects < 65 years old and with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or with the Modification of Diet in Renal Disease (MDRD) equation for subjects ≥ 65 years old; see Appendix 3).
17. Exclusion Criterion 17 about statins has been removed from study protocol v4.0.
18. Having received concomitant treatment known or suspected to induce an ototoxicity within 6 months prior to Screening (i.e. aminoglycosides, loop diuretics, quinine) and any other treatments listed in Appendix 5. Previous treatment with a platinum treatment should be considered as an exclusion criterion.
19. Treatment with any investigational agent within 4 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer).

20b. Known or suspected ongoing active infection of human immunodeficiency virus (HIV)

21. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction.
22. Known hypersensitivity, allergy or intolerance to cisplatin or any history of severe abnormal drug reaction.
23. Receiving phenytoin at screening (as it is contraindicated with cisplatin).
24. Myelosuppressed at screening (as it is contraindicated with cisplatin).
25. Any condition or health state at screening contraindicating the use of rehydration solution before each cisplatin cycle if requested (as dehydration state is contraindicated with cisplatin).

Number of Investigators and Study Centers:

Approximately 12 investigators and study centers are expected to participate in this study.

Number of Subjects:

A sufficient number of subjects will be screened in order to randomize the complete sample size of subjects. Based on the assumption of a screening failure of about 25%, it is estimated that no more than 78 subjects will be screened.

Treatment Groups and Duration:

The total study duration for each subject is variable as it will depend on the duration of the chemotherapy. It is assumed that the cisplatin treatment will not last more than 18 weeks, the maximum duration of the study per subject will not exceed 35 weeks:

- Screening period: up to 4 weeks.
- Evaluation period: up to 31 weeks
    - One week of treatment with SENS-401 prior to cisplatin initiation (for subjects in Arm B)
    - Up to 18 weeks of treatment with cisplatin ± SENS-401
    - Four weeks of treatment with SENS-401 after cisplatin treatment completion (for subjects in Arm B)
    - Follow-up period: 8 weeks

The investigational medicinal product (IMP) for this open-label study is SENS-401. SENS-401 will be administered orally at a dose of 43.5 mg b.i.d. for up to 23 weeks. Dose modifications are not permitted.

Statistical Analyses

Study Population:

The Full Analysis Set (FAS) is defined as the sample of eligible ears of all the randomized subjects.

Primary Efficacy Endpoint

Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 4 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject.

Statistical Inferential Model

The primary efficacy endpoint will be analyzed using a mixed linear model featuring an analysis of covariance (ANCOVA) with the treatment arm (SENS-401 *versus* no SENS-401) and eligible ear (right vs left) as fixed factors, cumulative cisplatin dose, age and baseline primary endpoint (3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram) values as fixed covariates, study center as random factor, and subject as random factor nested within each study center.

Sample size calculation

By assuming a medium efficacy defined as the standardized mean difference at less standardized mean difference (SMD) >0.5 (Cohen empirical rule), an assumed baseline-final correlation R=0.6, and a variance inflation determined by a Intra Class Correlation of 0.5, a significant difference tested as one-sided 0.05 confidence level will be detected with a power of ≥ 80% once the sample size per group exceeds n=50 ears/group.

However, an intermediate blind analysis (i.e., parameters estimated on all subjects, regardless of the treatment group) will be conducted once a sufficient number of subjects will allow for at least 16 ears per arm after three cycles of cisplatin, in order to determine the three most severely affected hearing frequencies (these frequencies will be used for quantitative analysis), estimate the standard deviation, assess the correlation between intra-subject and inter-ear hearing impairments, and re-evaluate the sample size if necessary. No more than 29 subjects per arm will be finally randomized.

Secondary Efficacy Endpoints

The studied drug efficacy according to the CTCAE (version 5.0) grades 1 to 4 (called the Grade Analysis) at 4 and 12 weeks after cisplatin completion will be assessed by a non-linear mixed model featuring a logistic ordinal regression according to the same adjustment variable as the primary analysis.

The mean change and grade analysis will be conducted at both 4 and 12 weeks on the population of ears (like the main analysis), and these four analyses will be also repeated on the population of subjects, in two ways: (a) for each subject included with both ears defined as eligible, the most affected ear will be analyzed, (b) the mean change measured on the two ears will be averaged.

Safety Analyses

Safety analyses will be performed on subjects who received any study treatment. Subjects will be analyzed according to the treatment they actually received. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of study treatment (SENS-401 or cisplatin-based chemotherapy) and prior to 30 days after the last administration of study treatment. AE summaries will be primarily based on TEAEs.

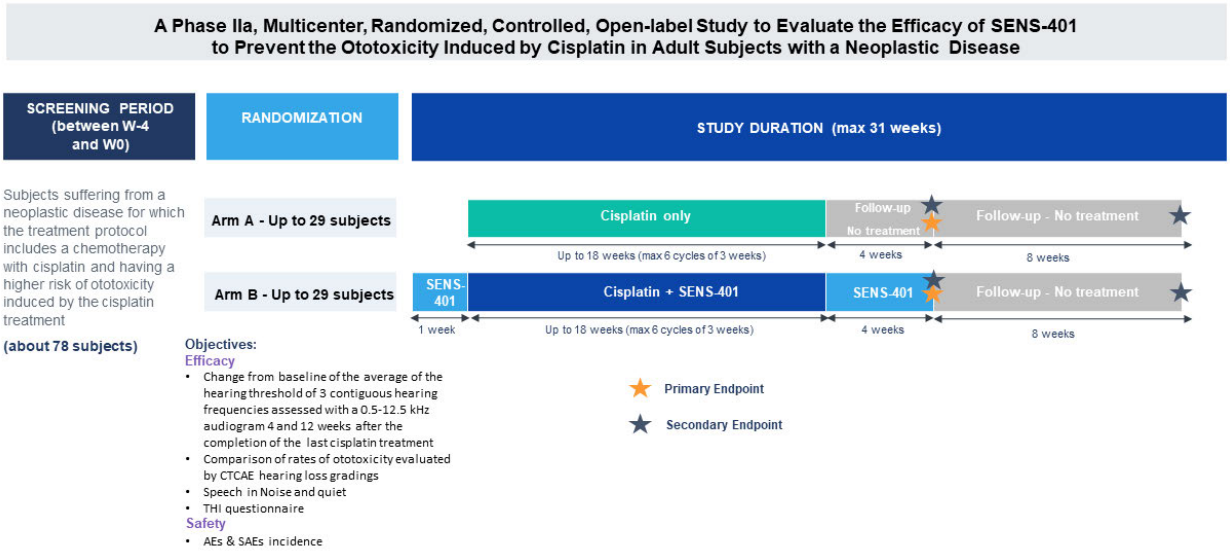
Other Analyses

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

Data Safety Monitoring Board: A data safety monitoring committee has been appointed to monitor the safety during the study.

1.2 Schema

Figure 1: Study Scheme



1.3 Schedule of Activities

Study Period	**Screening**	**Randomization**	**Evaluation**			
Visit Name	**V1** **Screening**	**V2** **Randomization** (Start of SENS-401 for subjects allocated to Arm B	**V3 1 to V3 6** Min number of cisplatin cycles: 3 Max number of cisplatin cycles: 6	**V4** **Time of primary efficacy analysis**	**V5** **Study End or Early Termination Visit**	**Unscheduled Visit**
Study Day (D) / Week (W)	W −4 to W0	W0		4W after the end of the last cisplatin treatment	12W after the end of the last cisplatin treatment	
Visit Window	N/A	N/A	N/A	(± 4 days)	(± 7 days)	N/A
Informed consent	x					
Demographic data (sex and age)	x					
Physical examination (including weight and height at Screening Visit only)	x	x (unless V2 and V1 are combined)	x	x	x	x
Vital signs ([body temperature, SBP, DBP and PR] obtained after ≥ 5 minutes of supine position and before any blood sampling)	x	x (unless V2 and V1 are combined)	x	x	x	x
12-lead ECG (obtained before any blood sampling)	x			x	x	
Blood sampling for local laboratory testing[a]	x		x (before the first cisplatin cycle if V1 lab tests performed more than 28 days before)	x	x	x
Pregnancy blood test (only for WOCBP)	x					
Inclusion and exclusion criteria	x	x (unless V2 and V1 are combined)				

Study Period	**Screening**	**Randomization**	**Evaluation**			
Visit Name	**V1 Screening**	**V2 Randomization** (Start of SENS-401 for subjects allocated to Arm B	**V3 1 to V3 6** Min number of cisplatin cycles: 3 Max number of cisplatin cycles: 6	**V4 Time of primary efficacy analysis**	**V5 Study End or Early Termination Visit**	**Unscheduled Visit**
Study Day (D) / Week (W)	W −4 to W0	W0		4W after the end of the last cisplatin treatment	12W after the end of the last cisplatin treatment	
Visit Window	N/A	N/A	N/A	(± 4 days)	(± 7 days)	N/A
Randomization		x				
Blood collection for biomarkers biobank (just after rehydration)			x (only at V3_1 before the 1st cisplatin cycle, V3_2 before the 2nd cisplatin cycle, V3_3 before and after the first day of the 3rd cisplatin cycle)		x	
Cisplatin treatment per chemotherapy protocol and hydration status check and hydration solution if needed, before and after cisplatin treatment per chemotherapy protocol			x			x (if applicable)
THI subject questionnaire dispensation and completion by the subject		x	x	x	x	
Provide a subject diary card to record SENS-401 administration (in the same day as the IMP kit given to subject of Arm B)[c]		x	x (only at V3_3)			
IMP kit dispensation[b]		x	x (only at V3_3)			
IMP treatment[d]		x	x			
IMP return and treatment compliance[e] (only for Arm B)			x (only at V3_3)	x		

Study Period	**Screening**	**Randomization**	**Evaluation**			
Visit Name	**V1 Screening**	**V2 Randomization** (Start of SENS-401 for subjects allocated to Arm B	**V3 1 to V3 6** Min number of cisplatin cycles: 3 Max number of cisplatin cycles: 6	**V4 Time of primary efficacy analysis**	**V5 Study End or Early Termination Visit**	**Unscheduled Visit**
Study Day (D) / Week (W)	W −4 to W0	W0		4W after the end of the last cisplatin treatment	12W after the end of the last cisplatin treatment	
Visit Window	N/A	N/A	N/A	(± 4 days)	(± 7 days)	N/A
Return, checking and transcription of subject diary card[e]			x (only at V3_3)	x		
Return, checking and transcription of THI subject questionnaire		x	x	x	x	
Medical history	x					
Current medical conditions	x	x (if performed more than 24 hours ago)	x	x	x	x
Prior medications and vaccinations	x	x (if performed more than 24 hours ago)				
Concomitant medications	x	x (if performed more than 24 hours ago)	x	x	x	x
AEs/SAEs	x	x (if performed more than 24 hours ago)	x	x	x	x
Dispensation of headphones and tablets and training		x				
Return of headphones and tablets					x	

Study Period	**Screening**	**Randomization**	**Evaluation**			
Visit Name	**V1 Screening**	**V2 Randomization** (Start of SENS-401 for subjects allocated to Arm B	**V3 1 to V3 6** Min number of cisplatin cycles: 3 Max number of cisplatin cycles: 6	**V4 Time of primary efficacy analysis**	**V5 Study End or Early Termination Visit**	**Unscheduled Visit**
Study Day (D) / Week (W)	W −4 to W0	W0		4W after the end of the last cisplatin treatment	12W after the end of the last cisplatin treatment	
Visit Window	N/A	N/A	N/A	(± 4 days)	(± 7 days)	N/A
Audio Tests						
Otoscopy	x			x	x	x
Immittance audiometry	x			x	x	x
PTA (500 Hz to 12.5 kHz)	x			x	x	x
Speech-in-Noise Test	x			x	x	x
Speech-in-Quiet Test	x			x	x	x
Auto testing[f] (Exploratory and optional)			Weekly at home	Weekly at home	Weekly at home	

Abbreviations: AE: adverse event; DBP: diastolic blood pressure; ECG: electrocardiogram; IMP: investigational medicinal product; N/A: not applicable; PR: pulse rate; PTA: pure-tone audiometry; SAE: serious adverse event; SBP: systolic blood pressure; THI: Tinnitus Handicap Inventory; V: Visit; W: Week.

[a] Local laboratory testing: As described in Appendix 3.

[b] IMP kit dispensation: 2 IMP kits of 17 bottles will be allocated to the subjects of Arm B. IMP kit #1 will be dispensed to the subjects at V2 and IMP kit #2 at V3_3.

[c] Provide a subject diary card to record SENS-401 intakes (the same day as IMP kit is given to subject): Daily recording of IMP intake by the subject.

[d] IMP treatment: IMP treatment with **SENS-401** consists of a **maximum of 23 weeks after randomization** for all subjects of Arm B (**1 week before** and up to 22 weeks after the start of cisplatin Cycle 1). Three tablets to be taken daily in the morning and in the evening with a glass of water.

[e] IMP return and treatment compliance / Subject Diary return: IMP kit# 1 and Subject Diary# 1 will be returned by the subject at V3_3 (for a site intermediate checking of IMP compliance but subject should return home with IMP kit# 1 and Subject Diary# 1 to take unused tablets) and IMP kit#2 and Subject Diary# 2 at V4 or V5.

[f] Auto-test: To be conducted by the subject at home using the provided electronic tablet device and headphone. Weekly reminders for these tests will be provided via tablet notification.

Note: If a subject is not able to visit the study center (s he/she should contact the study center by telephone. AE and concomitant medication details may be collected during a telephone call. It may not be possible to collect all clinical laboratory samples or conduct clinical assessments during this time, but any details should be recorded in the electronic case report form (eCRF). If alternative arrangements can be agreed for the sample collection or clinical assessments, the details should be documented in the eCRF.

2.0 INTRODUCTION

SENS-401 is a novel selective serotonin type 3 (5-HT_3) antagonist that is being developed as a potential oral drug candidate to protect against or to reverse cochlear insults by virtue of its ability to prevent or reverse damage to sensory hair cells, synaptic contacts, or primary neuronal afferents in the inner ear.

2.1 Study Rationale

This study is intended to evaluate the ability of SENS-401 to prevent the ototoxicity induced by cisplatin in adult subjects with a neoplastic disease. The pathophysiological mechanism of such hearing loss is not perfectly understood but it may include hair cell loss, damage to stereocilia, and/or loss of synapses or cochlear neurons. The dual effects of SENS-401 as a selective 5-HT3 antagonist and a calcineurin antagonist is expected to prevent damage to sensory hair cells, synaptic contacts, and potentially primary neuronal afferents in the inner ear, thus supporting its potential as an oral agent to prevent ototoxicity related to cisplatin.

2.2 Background

2.2.1 Mechanisms of Cisplatin-induced Ototoxicity

Cisplatin is a platinum-containing pharmaceutical product marketed for several decades in many countries as anti-neoplastic treatment. In cancer cells, platinum agents target the deoxyribonucleic acid (DNA) of proliferating cells to exert tumoricidal effects. Inside the cell, after activation, platinum agents bind to DNA, forming intra- and inter-strand complexes that lead to the inhibition of DNA synthesis, the suppression of ribonucleic acid (RNA) transcription, cell cycle arrest, and apoptosis. The binding to DNA also activates the inflammatory cascade and generates oxidative stress in the cell.

Platinum agents induce dose-dependent death of cochlear hair cells, with outer hair cells more susceptible to cisplatin and inner hair cells more susceptible to carboplatin (G. Laurell et Bagger-Sjöbäck 1991; Hofstetter et al. 1997). Cochlear hair cell death starts at the cochlear base and progresses apically with continued exposure to the drug (Schaefer et al. 1985; G. Laurell et Bagger-Sjöbäck 1991).

Platinum agents are detected in cochlear tissues indicating that they cross the blood labyrinth barrier (BLB) (van Ruijven et al. 2005; Thomas et al. 2006; Neuwelt et al. 2008). They enter hair cells through several potential pathways including:

- A trans-strial trafficking route from strial capillaries to marginal cells, followed by clearance into endolymph.

- Traversing the BLB into perilymph and subsequently into endolymph via transcytosis across the epithelial perilymph/endolymph barrier. Once in endolymph, platinum agents enter hair cells across their apical membranes.
- Platinum agents in the scala tympani could also pass through the basilar membrane into extracellular fluids within the organ of Corti and enter hair cells across their basolateral membranes.

Cisplatin and other platinum agents penetrate into hair cells through passive diffusion or several different transporters, including copper transporter 1, organic cation transporter 2, possibly transient receptor potential vanilloid 1 (TRPV1), L-type and T-Type Ca channels and through inositol trisphosphate receptor and ryanodine receptor (Waissbluth et Daniel 2013; Harrach et Ciarimboli 2015).

In cochlear hair cells, cisplatin alkylation in mitochondria results in the release of pro-apoptotic factors leading to caspase activation (Matsui, Ogilvie, et Warchol 2002; Park, De Leon, et Devarajan 2002; Bragado et al. 2007; García-Berrocal et al. 2007). Cytosolic reactive oxygen species (ROS) has also been implicated as a major mediator of cisplatin-induced hair cell death. Increased pools of ROS damage proteins and lipids and deplete the intrinsic antioxidant molecules (glutathione peroxidase, superoxide dismutase, catalase and glutathione reductase) resulting in lipid, proteins and nucleic acids peroxidation with caspase system activation and apoptosis of auditory hair cells (L. P. Rybak et al. 1999; Alam et al. 2000; Dehne et al. 2001; Kalkanis, Whitworth, et Rybak 2004; Wang et al. 2004; Leonard P. Rybak et al. 2009; Karasawa et Steyger 2015).

Other mechanisms involve:

- The significant contribution of nicotinamide adenine dinucleotide phosphate oxidase 3 isoform to the generation of ROS within the cochlea (Ikeda, Sunose, et Takasaka 1993; L. P. Rybak et Ramkumar 2007).
- The activation of TRPV1 channel which increases calcium influx into the cell and NOX3 dependent generation of ROS to trigger signal transducer and activator of transcription 1 (STAT1) activation. The activation of STAT1 promotes intracellular inflammatory response and p53 activation resulting in cell death (Mukherjea et al. 2008; 2011; Karasawa et Steyger 2015).

Cisplatin induces increased inducible nitric oxide synthase (iNOS) generating nitric oxide in stria vascularis and spiral ligament, which results in degeneration of the stria vascularis, decreasing the number of marginal and intermediate cells as well as spiral ganglion cells (Watanabe et al. 2002; Sergi et al. 2003; Göran Laurell et al. 2007). This degeneration of the stria, spiral ligament and supporting cells impacts the intricate endocochlear potassium recycling mechanisms (Hibino et Kurachi 2006) and compartmental separation between endo- and perilymph required to maintain the endolymphatic potential, thus rapidly reducing mechanotransduction and hearing sensitivity.

In spiral ganglia, an increase in high mobility group (HMG1) protein was observed following cisplatin treatment (Li, Liu, et Frenz 2006). An increased HMG1 expression sensitizes target cells to cisplatin cytotoxicity, leading to DNA damage-dependent apoptosis in these non-proliferating cells. Additional confirmation that cisplatin induces DNA damage-dependent apoptosis in spiral ganglion cells comes (Li, Liu, et Frenz 2006) from a study on nucleotide excision repair (NER) factors, in which cytoplasmic to nuclear translocation of NER proteins was detected in spiral ganglia from rats treated with cisplatin (Guthrie et al. 2008).

[redacted]

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[redacted]

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[redacted]

[redacted]

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of SENS-401 given at the dose of 43.5 mg b.i.d. (*bis in die*) for up to 23 weeks to prevent the ototoxicity induced by cisplatin in subjects with a neoplastic disease, 4 weeks after the completion of the last cisplatin treatment.	Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 4 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject.
Secondary	
To further evaluate the efficacy of SENS-401 given at the dose of 43.5 mg b.i.d. for up to 23 weeks to prevent the ototoxicity induced by cisplatin in subjects with a neoplastic disease, 4 and 12 weeks after the completion of the last cisplatin treatment.	Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 12 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject. Change from baseline in the distribution of hearing loss severity at 4 and 12 weeks. The severity of the hearing loss being based on the CTCAE (version 5.0) classification and being evaluated as the shift of the average of the hearing threshold compared to the baseline of 2 or 3 contiguous frequencies in at least one ear evaluated with an audiogram from 1 to 8 kHz and as follows: Grade 1: threshold shift from baseline ≥15 dB averaged at 2 contiguous test frequencies Grade 2: threshold shift from baseline >25 dB averaged at 2 contiguous test frequencies. Grade 3: threshold shift from baseline >25 dB averaged at 3 contiguous test frequencies Change from baseline in speech discrimination test score (assessed in noise and in quiet) 4 and 12 weeks after the completion of the cisplatin treatment. Change from baseline in Tinnitus Handicap Inventory (THI) Questionnaire score, 4 and 12 weeks after the completion of the cisplatin treatment.
Exploratory	
To explore the correlation between pre-identified biomarkers (e.g., prestin) or biomarkers that will be identified in the future, and clinical features of interest (like prediction of ototoxicity).	Serum/plasma concentrations of selected biomarkers before each of the first three cisplatin treatments (just after rehydration), at the end of the day of the third cisplatin cycle and at visit 5.

Objectives	Endpoints
To evaluate the performance of an application (headphone and tablet) to evaluate hearing level in a broad range of frequencies (500 Hz to 12.5 kHz).	Sensitivity and specificity of hearing thresholds measured by auto-testing in each tested frequency compared to standard audiogram values performed in hospital sites.
Safety	
To confirm the good systemic safety profile of SENS-401 (43.5 mg given orally b.i.d. for 23 weeks).	Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs).

4.0 STUDY DESIGN

4.1 Overall Design

Multicenter, randomized, controlled, two-arm, open-label efficacy and safety study in adults with neoplastic disease requiring treatment with cisplatin as part of the chemotherapy protocol plan. Cisplatin treatment per chemotherapy protocol must be given at a cumulative dose high enough to significantly increase the iatrogenic likelihood of ototoxicity (unit cisplatin dose of at least 70 mg/m^2 and cumulative cisplatin dose of at least 210 mg/m^2).

Subjects willing to participate in the study will sign an Informed Consent Form (ICF). They will be considered eligible based on the results of a Screening Visit performed within 28 days before the randomization.

Based on the statistical assumptions made on time-based hearing impairment due to cisplatin, it is expected that 25 subjects per study arm will be sufficient to evaluate the efficacy profile of SENS-401. However, an intermediate blind analysis (i.e., parameters estimated on all subjects, regardless of the treatment group) will be conducted once a sufficient number of subjects will allow for at least 16 ears per arm after three cycles of cisplatin, in order to determine the three most severely affected hearing frequencies (these frequencies will be used for quantitative analysis), estimate the standard deviation, assess the correlation between intra-subject and inter-ear hearing impairments, and re-evaluate the sample size if necessary No more than 29 subjects per arm will be finally randomized.

If all the eligibility criteria are met, subjects will be randomized to one of the two study arms as follows:

- Study Arm A (control arm): Subjects receiving cisplatin-based chemotherapy without receiving SENS-401. This control arm will provide the incidence of hearing impairment due to ototoxicity 4 and 12 weeks after the last cisplatin treatment.
- Study Arm B: Subjects receiving 43.5 mg of oral SENS-401 b.i.d. for up to 23 weeks: 1 week prior to the initiation of the cisplatin treatment, during the whole duration of the chemotherapy treatment (estimated to last up to 18 weeks) and 4 weeks after stopping chemotherapy. This arm will provide data on the potential protective effect of SENS-401 on cisplatin induced ototoxicity.

All subjects will be followed up to 12 weeks after the completion of the cisplatin therapy .

The hearing function of all subjects will be evaluated at screening (baseline) and 4 and 12 weeks after the end of the last cisplatin cycle using:

- Otoscopy;
- Immittance audiometry;
- Pure-tone audiometry (PTA) spanning a band of frequencies from 500 Hz to 12.5 kHz;
- Speech-in-Noise Test;
- Speech-in-Quiet Test;
- Tinnitus Handicap Inventory (THI) questionnaire; and
- Auto-testing using a headphone and a tablet application (exploratory and optional).

All subjects, regardless of the study arm to which they have been allocated, will receive as established by the ear, nose and throat doctor (ENT), the current standard of care for the ototoxicity. Thus, cisplatin doses will be adapted to subject body surface and hyperhydration will be provided. The current practices include several recommendations as modifications to the medication, rescue therapy with intravenous corticosteroid and supporting hearing function with medical device.

The total study duration for each subject is variable as it will depend on the duration of the chemotherapy. It is assumed that the duration of the cisplatin treatment will not last more than 18 weeks, the maximum duration of the study per subject will not exceed 35 weeks as follows:

- Screening period: up to 4 weeks.
- Evaluation period: up to 31 weeks
    - One week of treatment with SENS-401 prior to cisplatin initiation (for subjects in Arm B)
    - Up to 18 weeks of treatment with cisplatin ± SENS-401
    - Four weeks of treatment with SENS-401 after cisplatin treatment completion (for subjects in Arm B)
    - Follow-up period: 8 weeks

[redacted]

[redacted]

[redacted]

[redacted]

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed the evaluation phase of the study including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A subject is eligible to be included in the study only if all of the following criteria apply:

1. Age ≥ 18 years at the time of signing the ICF.
2. Capable of giving signed informed consent as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
3. A female subject is eligible to participate if she is not pregnant (see Appendix 6), not breastfeeding, and ≥ 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 6.
   - A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.
4. A male subject must agree to use contraception and refrain from donating sperm as detailed in Appendix 6 of this protocol for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.
5. Neoplastic subject that regardless of participation in this study is planned to be treated with a chemotherapy that includes a dose of cisplatin of at least 70 mg/m^2 per cycle and a cumulative dose of cisplatin of at least 210 mg/m^2.

6b. Subjects with a PTA threshold of ≤ 30 dB at 500 Hz AND ≤ 40 dB at 1-2 kHz AND ≤ 60 dB at 4-6 kHz AND ≤ 80 dB at 8 kHz, in either both ears or one ear for a maximum of 30% of the subjects in each study arm.

7. In the opinion of the Investigator, a life expectancy of ≥ 6 months.
8. Inclusion criterion 8 about COVID-19 has been removed from study protocol v4.0.

5.2 Exclusion Criteria

A subject is not eligible if any of the following criteria apply:

1. Any condition or past medical history that, in the opinion of the Investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study.

2. Subject is the Investigator or anyone from his/her team directly involved in the conduct of the protocol.
3. Mentally unable to understand the nature, objectives, and possible consequences of the study or refusing its constraints.
4. A congenital or hereditary disease known to decrease hearing function (e.g., Otoferlin [OTOF] related deafness).
5. Any medical history affecting the middle ear function such as chronic otitis, cholesteatoma, or tympanic membrane perforation.
6. Any inner ear disease that is likely to decrease hearing function according to the Investigator's judgment (e.g., herpes zoster oticus; Meniere's disease; purulent labyrinthitis; vestibular schwannoma).
7. Having history of sudden sensory neural hearing loss.
8. Having a fluctuating hearing loss (e.g., due to Meniere's disease, vestibular aqueduct syndrome, or autoimmune inner ear disease).
9. History of head trauma with hearing loss.
10. History of meningitis.
11. For a subject expected to receive radiotherapy during the course of the study, anticipated risk of exposure of the auditory system (i.e., inner ear within the expected irradiation zone).
12. History of significant arrhythmia or conditions known to increase proarrhythmic risk (e.g., congestive heart failure, long QT syndrome, hypokalemia).
13. Significant clinically relevant electrocardiogram (ECG) abnormality that, in the opinion of the Investigator, precludes study eligibility.
14. Significant abnormal laboratory result, physical examination, vital signs, or ear-nose-throat (ENT) evaluation (otoscopy and immittance audiometry), in the opinion of the Investigator.
15. Neurological disorder including stroke, demyelinating disease, or brain stem or cerebellar dysfunction.
16. Moderate to severe renal impairment defined by a creatinine clearance ≤ 60 mL/min (calculated with the Cockcroft-Gault formula for subjects < 65 years old and with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or with the Modification of Diet in Renal Disease (MDRD) equation for subjects ≥ 65 years old; see Appendix 3).
17. Exclusion criterion 17 about statins has been removed from study protocol v4.0.

18. Having received concomitant treatment known or suspected to induce an ototoxicity within 6 months prior to Screening (i.e., aminoglycosides, loop diuretics, quinine) and any other treatments listed in Appendix 5. Previous treatment with a platinum treatment should be considered as an exclusion criterion.

19. Treatment with any investigational agent within 4 weeks prior to screening or 5 half-lives of the investigational drug (whichever is longer).

20b. Known or suspected ongoing active infection of human immunodeficiency virus (HIV).

21. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction.

22. Known hypersensitivity, allergy or intolerance to cisplatin or any history of severe abnormal drug reaction.

23. Receiving phenytoin at screening (as it is contraindicated with cisplatin).

24. Myelosuppressed at screening (as it is contraindicated with cisplatin).

25. Any condition or health state at screening contraindicating the use of rehydration solution before each cisplatin cycle if requested (as dehydration state is contraindicated with cisplatin.)

5.3 Lifestyle Considerations

Subjects treated with SENS-401 should be advised to avoid skin exposure to strong sunlight and to wear sunglasses in bright sunlight for the duration of the study and for 1 week after the last dose of SENS-401.

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal

information includes informed consent, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the reason for failing to meet eligibility criteria is considered reversible in the short term (i.e. laboratory value out of range). Rescreened subjects should not be assigned the same subject number as for the initial screening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol. For the purposes of this protocol, study treatment is defined as SENS-401 OR cisplatin-based chemotherapy and IMP is defined as SENS-401.

6.1 Study Treatment(s) Administered

Table 2 Study Treatment Details

Study treatment name	SENS-401 (azasetron besylate)	Cisplatin
IMP and NIMP	IMP	NIMP
Dosage Formulation	SENS-401 is supplied for oral administration as white, oval, film-coated tablet debossed with "S401" on 1 side. The uncoated formulation consists of 14.5 mg of SENS-401 (10 mg as free base), methyl crystalline cellulose, starch, and magnesium stearate.	Cisplatin is presented as a concentrate solution for infusion
Unit Dose Strength(s)/Dosage Level(s)	43.5 mg (30 mg free base) of SENS-401 b.i.d.	According to subject's chemotherapy protocol plan
Route of Administration	Oral	Intravenous
Dosing Instructions	3 tablets of 14.5 mg SENS-401 to be taken by mouth with water b.i.d. (morning and evening) for 23 weeks	According to subject's chemotherapy protocol plan, cumulative cisplatin dose will be of at least 210 mg/m^2
Packaging and Labeling	SENS-401 film-coated tablets are packaged in high-density polyethylene (HDPE) bottles with child-resistant closure. SENS-401 is supplied in bottles of 30 tablets. Each bottle will be labeled as required per country requirements. IMP kit is composed by 17 bottles, and each subject will receive 2 IMP Kits.	Commercial packaging, cisplatin will be administered by the study site.
Sourcing	Provided centrally by the Sponsor.	Provided locally by the study site.

Abbreviations: b.i.d. = bis in die, IMP = investigational medicinal product, NIMP= non-investigational medicinal product, HDPE = high-density polyethylene.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

1. Only subjects enrolled in the study may receive IMP and only authorized study center staff may supply or administer IMP. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
2. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
3. Further guidance and information for the final disposition of unused IMP are provided in the pharmacy manual.

The Investigator, a member of the study staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

Based on available stability data, the SENS-401 10 mg as free base, film-coated tablets in high-density polyethylene (HDPE) bottles are stable for at least 48 months when stored at ≤ 30°C. Stability studies of SENS-401 10 mg as free base, film-coated tablets packaged in HDPE bottles are in progress to confirm that clinical supplies remain within the acceptance criteria defined in the specifications throughout the duration of the clinical studies.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each study center.

At the randomization visit, each subject will be indicated in the IVRS/IWRS as either having a PTA threshold of ≤ 30 dB at 500 Hz AND ≤ 40 dB for 1-2 kHz AND ≤ 60 dB for 4-6 kHz AND ≤ 80 dB for 8 kHz in one ear OR a PTA threshold of ≤ 30 dB at 500 Hz AND ≤ 40 dB for 1-2 kHz AND ≤ 60 dB for 4-6 kHz AND ≤ 80 dB for 8 kHz in both ears. The system will enforce a randomization limit of no more than 30% for subjects with the PTA threshold in only one ear for each study arm.

IMP will be dispensed at the study visits as summarized in the schedule of activities (SoA, see Section 1.3).

This is an open-label study; however, the specific treatment to be taken by a subject will be assigned using an IVRS/IWRS. The study center will contact the IVRS/IWRS prior to the start of IMP administration for each subject. The study center will record the treatment assignment on the applicable electronic case report form (eCRF), if required. Potential bias will be reduced by central randomization.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 6.6. Any departures from the intended regimen must be recorded in the eCRFs as must the date and time of the first administration of IMP.

At each visit (at V3_3 prior to dispensing IMP) previously dispensed IMP will be retrieved by the Investigator and compliance assessed via tablet count and review of subject diary for IMP accountability. Subjects exhibiting poor compliance, as assessed by tablet counts, should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of IMP during any evaluation period (visit to visit). See Section 8.4 for procedures regarding overdose.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded on the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.
- For vaccines (if applicable): include brand name and manufacturer (plus lot number if available).

Vaccination with live vaccines while on study is prohibited. Administration of inactivated vaccines is allowed (e.g., inactivated influenza vaccines or SARS-CoV-2 vaccines). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications/therapy is provided in Appendix 5. If a subject receives any excluded medication/therapy during the study, the Medical Monitor should be contacted, and the event discussed on a case-by-case basis.

6.5.1 Rescue Medicine

Although the use of rescue medications is allowed at any time during the study, the use of rescue medications should be delayed, if possible, following the administration of IMP. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose Modification

Dose modification for SENS-401 is prohibited in this study. In the event of a potential drug -related TEAE, IMP discontinuation is to be discussed with the Sponsor on a case-by-case basis. Additionally, the IMP should be discontinued in accordance to the criteria outlined in Section 7.0.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for neoplastic subjects with chemotherapy-induced ototoxicity.

7.0 DISCONTINUATION OF IMP AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of IMP

In rare instances, it may be necessary for a subject to permanently discontinue IMP. If study treatment is permanently discontinued, the Sponsor must be contacted, and the subject will discontinue the study. Subjects who discontinue IMP will not be replaced.

See the SoA for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

7.1.1 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from screening visit in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF], as applicable) after enrollment, the Investigator or qualified designee will determine if the subject can continue in the study and if any change in subject management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding will be reported as an AE.

7.1.2 Other Criteria

- Subjects who prematurely discontinue their cisplatin-based chemotherapy and have not received a cumulative dose of 210 mg/m² of cisplatin. Subjects who discontinue cisplatin will not be replaced.
- Pregnancy: Appendix 6 and Section 8.3.5.
- Disease-state criteria (e.g., progressive disease): Investigator's discretion
- Renal, liver and other impairments: See cisplatin summary of product characteristics (SmPC)
- Lost to follow-up: For subjects considered lost to follow-up, the eCRF must be filled in up to the last visit performed. The Investigator should make every effort to re-contact and to identify the reason why the subject failed to attend the visit and to determine his/her health status.

7.1.3 Coronavirus Disease 2019

If a subject tests positive for COVID-19 during the course of the study, the investigator will decide if he or she will discontinue IMP and will attend study visits virtually (i.e., by telephone) until a negative polymerase chain reaction (PCR) test is obtained.

7.1.4 Inadvertent Enrollment

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject must be discontinued from IMP and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study.

7.1.5 Temporary Discontinuation

Temporary discontinuation of IMP must be discussed on a case-by-case basis by the Investigator, per Sponsor's discretion.

7.1.6 Rechallenge

Not applicable for ECG abnormality but is applicable for renal/liver impairments. In case of renal /liver AEs, if the values come back to normal range, IMP could be restarted.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject will be considered to have completed the study when he or she completes the final assessment visit (Visit 5 at 12 weeks after the end of the last cisplatin treatment). A termination eCRF page should be completed for every subject who signed an informed consent, whether or not the subject completed the study.

If a subject is discontinued prematurely at any time after entering the study, the Investigator will make every effort to see the subject and complete an early termination visit.

The reason for any early discontinuation should be indicated on the termination page of the eCRF. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories of early termination:

- **Medical decision**: Clinical or laboratory events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious and nonserious AEs regardless of relation to study medication.
- **Death**: The subject died.
- **Pregnancy:** The subject became pregnant.
- **Withdrawal of consent:** The subject desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it should be recorded in the eCRF. If the subject 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 subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

- **Lost to follow-up**: The subject stopped coming for visits, and study personnel were unable to contact the subject.

  A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

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

  - The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. The reason should be reported to the Sponsor to identify a potential solution.
  - Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). The site must contact the trusted person designated by the subject as well as his or her attending physician. These contact attempts should be documented in the subject's medical record.
  - Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

- **Other:** The subject was terminated for a reason other than those listed above, such as termination of the study by the Sponsor.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue IMP.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL (in average 50 mL/per month). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Audiometric Tests

8.1.1.1 Otoscopy

Otoscopy is a clinical procedure used to examine structures of the ear, particularly the external auditory canal, tympanic membrane, and middle ear.

8.1.1.2 Immittance Audiometry

Immittance audiometry is an objective technique that evaluates middle ear function by 3 procedures: static immittance, tympanometry, and the measurement of acoustic reflex threshold sensitivity.

8.1.1.3 Pure-tone Audiometry (500 Hz to 12.5 kHz)

PTA is a behavioral subjective test used to identify hearing threshold levels. This test involves the peripheral and central auditory systems. Pure-tone thresholds indicate the softest sound audible to an individual ≥ 50% of the time. Hearing sensitivity is plotted on an audiogram displaying intensity as a function of frequency.

PTA is a gold standard test to assess whether hearing acuity is normal or impaired. Air conduction hearing thresholds are usually measured for tonal stimuli at the range of frequencies from 0.125 to

8 kHz with the use of headphones or insert earphones. 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.

8.1.1.4 Speech-in-Noise Test

Speech-in-noise tests are used regularly for diagnostic and functional testing, as well as for validation of hearing device benefit. These tests are useful for assessing "real-world" hearing ability to simulate how an individual might hear in a restaurant or noisy grocery store. This is typically a sentence test. The individual is asked to repeat as many of the words in the sentence they heard. They receive a point for each sentence they correctly repeat as well as for how many words in the sentence they correctly repeat.

The noise can become more complicated with how many people are speaking in the noise (e.g., the noise signal – also known as "multi-talker babble" - can be 4 people or as many as 20 people talking at once. A 4-talker babble is common and usually no more than 10-talker babble).

Noise tests will be "adaptive" (the noise level varies based on how the subject is performing so that the signal-to-noise ratio (SNR) of where they achieve 50% understanding is obtained). The number of sentences on a test will vary depending on how that specific test was validated.

8.1.1.5 Speech-in-Quiet Test

Speech in quiet is a monosyllabic word test with a consonant-nucleus-consonant structure. The subject is presented with a single word and asked to repeat what they heard. Each word typically has three phonemes/sounds within the word and the middle/nucleus is a vowel. Some tests only count if they get the full word correct (1 point/word). Other tests count a point for each word they correctly repeat as well as a point for each phoneme they correctly repeat (e.g., the word is "sun" but the subject said "some"; they will get 2 points – one for the /s/ and one for the /uh/ sound).

8.1.1.6 Tinnitus Handicap Inventory Subject Questionnaire

Tinnitus is a symptom with a labile character, often subjective. In most cases, it is difficult to objectify it. The subject's self-assessment using questionnaires and evaluation scales is the only way to measure the discomfort induced by the symptom. Among the most widely used tools is the Tinnitus Handicap Inventory (THI). The THI questionnaire allows the physician to evaluate the impact of tinnitus and thus to measure the psycho-affective and functional components of tinnitus-related disability.

The THI questionnaire was developed by Newman *et al.* (Newman, Jacobson, et Spitzer 1996) in 1996. It is a validated self-questionnaire which has the advantage of measuring the handicap linked to tinnitus in the daily life of a subject, and thus allows a physician to evaluate the impact of tinnitus on the social life of a subject.

It consists of 25 questions developed to explore three categories of disability: functional, emotional and catastrophic. Each question has 3 response options: “yes”, “no” or “sometimes” and a predefined score associated with each response option. A total score between 0 and 100 is obtained. The score distinguishes 5 degrees of disability, i.e. mild, moderate, medium, severe, and disabling.

It takes between 10 and 15 minutes to complete and calculate the score of a THI questionnaire.

8.1.1.7 Auto-testing

The experimental system used to evaluate the hearing function by auto-tests is based on hearing assessment application that was developed to perform PTA with a large band of frequencies (from 500 to 12500 Hz) tests at home. To do this, the subjects will use a cordless headphone connected to an electronic tablet device on which the hearing assessment application is installed. This test allows detection of hearing loss for each of the frequencies explored.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

- The physical examination will include height, weight, Body Mass Index and evaluation of main body systems/regions, including skin and mucous, eyes/nose/throat, pulmonary, cardiac, gastrointestinal and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Body temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse rate measurements will be assessed in supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate measurements should be preceded by ≥ 5 minutes of rest, in a supine position, for the subject in a quiet setting without distractions (e.g., television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Corrections of the QT interval will be calculated using Fridericia's and Bazett's formula. Refer to Section 7.1.1 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.4 Clinical Safety Laboratory Assessments

- The Investigator must review the routine laboratory analysis performed on site to monitor the oncology treatment, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 weeks after the last dose of IMP might be repeated per Investigator judgement until the values are no longer considered clinically significant by the Investigator or Medical Monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible, regardless of their relationship to IMP, for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the subject to discontinue IMP (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected and entered in the eCRF from the time a subject gives informed consent to the study completion.

Medical occurrences that begin before Visit 1 but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the Investigator's awareness of the event, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Any pregnancy that occurs during the study, with either the female subject or with the female partner of a male subject, must be recorded on a pregnancy notification form and reported to the Sponsor or designee within 24 hours of learning of the pregnancy (as described in Appendix 6). The pregnancy should be followed up to determine its outcome (i.e. healthy birth, spontaneous or voluntary abortion, presence or absence of any birth defects, congenital abnormality, or maternal and/or newborn complications). A pregnancy report should include the Investigator's assessment of any possible relationship between the outcome and the exposure to study products. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted

fetus, stillbirth, or neonatal death]), the Investigator should follow the procedures for reporting SAEs.

8.3.6 Adverse Events of Special Interest

Not applicable.

8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4 Treatment of Overdose

The maximum dose of SENS-401 administered to humans is 43.5 mg b.i.d.. For this study, any dose of SENS-401 greater than 43.5 mg b.i.d. within a 24-hour time period (± 6 hours) will be considered an overdose.

As there is no antidote for SENS-401, in case of overdose, intensive care admission should be considered according to clinical status, and treatment would be standard for nonspecific drug intoxication, including general support that may include immediate gastric lavage within the first hour after intake to diminish 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 should:

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

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject. 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 it may result in an AE. All AEs associated with an overdose or incorrect administration of a drug should be recorded on the AE CRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor or designee within no more than 24 hours after the Investigator's awareness of the event.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Efficacy parameters are considered as expressing part of the pharmacodynamic profile of SENS-401.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 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 subjects.
- Samples will be stored in a biobank. They might possibly be tested later to establish correlations between their levels and the incidence and time course of cisplatin induces hearing loss and the clinical responses observed.
- The accurate identification of biomarkers is not fully established yet. Some like 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 subject'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 the Sample Handling Manual.

8.9 Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Considerations

The population will be extended to the eligible ears of the subjects instead of the subjects themselves for the primary analysis, as well as all secondary analyses related to ears. This extension is rigorously acceptable conditionally to account for the expected correlation between both ears of a same subject with both eligible ears. The randomized subject's population will be used for the safety analysis. For purposes of analysis, the analysis sets in **Table 3** are defined.

Table 3 Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	Eligible ears of all subjects who have been randomized to a study treatment group (either cisplatin-based chemotherapy alone or with SENS-401). FAS will be the primary analysis set for all efficacy analyses, as well as baseline characteristics related to ears. Subject related data, e.g. disposition, demographics, will be analyzed for the subjects with ears in the FAS. Subjects and ears will be analyzed according to their randomized treatment.
Per Protocol (PP) Analysis Set	Eligible ears of all subjects in FAS with no major protocol deviation that would have an impact on the efficacy assessment. Major protocol deviations will be reviewed and determined prior to database lock. Subjects to be excluded from the PP analysis set will be determined based on a data review meeting prior to database lock. Subject related data will be analyzed for the subjects with ears in the PP. Subjects and ears will be analyzed according to their randomized treatment. Analyses based on PP analysis set will only be performed if the number of ears of subjects in PP is < 80% of those of the FAS.
Safety Analysis Set	Randomized subjects who receive any study treatment (either cisplatin-based chemotherapy alone or with SENS-401). This analysis set will be used for all safety analyses. Subjects will be analyzed according to the treatment they received.

9.2 Statistical Analyses

9.2.1 Subject Disposition and Demographics

Baseline characteristics and subject disposition events will be summarized by treatment groups.

9.2.2 Estimand of the Primary Efficacy Analyses

Population: adult subjects with neoplastic diseases defined by the inclusion/exclusion criteria. The population will be also extended to the eligible ears of the subjects.

Main endpoint: Change from baseline of the average of the hearing threshold of 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram 4 weeks after the completion of the last cisplatin treatment in each eligible ear of each subject.

Intercurrent event handling strategy: The allocation of treatment related/unrelated study discontinuation reasons will be attributed prior to database lock. Early termination of the study due to reasons related to the study treatments (e.g., drug-related AE, perception of lack of efficacy): final data will be imputed according to multiple imputation technique assuming a Non-Missing at Random missing data with a Jump to reference option, defined as after dropout, the participant's conditional outcomes are assumed to deteriorate to those of the reference group. For early termination of the study due to reasons unrelated to the study treatments, multiple imputation according Missing At Random assumption will be used.

Statistical inferential Model: The primary efficacy endpoint will be analyzed using a mixed linear model featuring an analysis of covariance (ANCOVA) with the treatment arm (SENS-401 *versus*

no SENS-401) and ear left/right as a dichotomous factor, cisplatin cumulative dose, age and baseline values of the averaged of the 3 contiguous hearing frequencies assessed with a 0.5-12.5 kHz audiogram as fixed covariates, study center as random factor, and subject as random factor nested within each study center.

For sensitivity purposes, the same analysis will be repeated based on the population of subjects instead of ears, in two ways: (a) for each subject included with both ears defined as eligible, the most affected ear will be analyzed, (b) the mean change will be averaged on the two ears.

9.2.3 Sample Size Determination

The following parameters constituted the basis of the sample size calculation:

1. The hypothesized efficacy of the IMP was based on the empirical rule of Cohen [] hypothesizing that the standardized mean difference SMD is at least SMD ≥0.5.

2. The assessment was conducted at $p<0.05$ one-sided significance and a power of ≥ 80% was requested.

4. The correlation baseline-final resulting of the adjustment on age, baseline severity, and study center was assumed in the range $0.5 < R < 0.7$ with a fixed a priori value of $R^2 = 0.6$.

5. Dropout was not accounted for, as the Full Analysis Set (FAS) is the main selection.

6. The sponsor wishes to conduct the primary analysis on the ear population instead of the subject population, thus we must consider the correction of the variance inflation due to the between-ear correlation. In this case, VIF=1+(m-1) ICC = 1+ICC, where m=2 ears, ICC being the Intraclass coefficient of correlation (ICC) likely to vary within [0; 0.75], with ICC = 0.5 considered as the most likely value.

7. The sample size calculation was based on the power function of the analysis of Covariance (ANCOVA) (Frison et Pocock 1992) adapted for random and fixed factors.

As a result of these assumptions, by assuming a SMD of at least 0.5, an assumed determination coefficient of 0.6, a significant difference tested as one-sided 0.05 confidence level will be detected with a power of ≥ 80% once the sample size per group exceeds n=33 ears. Sensitivity analyses in iterating this calculation within the R^2 interval [0.5, 0.7] provided a relatively stable calculation within the interval n = [29, 38] per group. By considering the between-ear correlation within the same subject, depending on the ICC values of 0, 0.25, 0.5 and 0.75, the variance inflation factor (VIF) is 1, 1.25, 1.5 and 1.75, thus the corresponding needed sample size (ears) per group should be 33, 41, 50, and 58, respectively. By considering the ICC value = 0.5, we conclude into a sample size of ears per group.

Note: effect of selecting subjects with only one testable ear on the Statistical power

It is clinically admittable that a subjectwill be decreased. This effect will be the result of two different causes:

1-The sample size is reduced, and the expression based on the proportion k of subjects with only one eligible ear is easily derived from the expression $N= [2k+(1-k)]n_0$ where n_0 is the planned sample size of ears per group (n=50).

2- The sample size will be also influenced by a small change of the Variance Inflation Factor (VIF) caused by each pat of ears of the same subject, expected to slightly decrease when k increases, as for subjects with only one eligible ear, no such VIF exists.

Table 4 provides the power resulting from various values of the proportion K of subjects with only one eligible ear, with the sample size resulting. In the third column the minimum power is calculated as only based on the sample size reduction, and admitting a constant VIF, whereas in the fourth column the power is reported accounting for the decrease of the VIF when K increases:

Table 4 - Power resulting from various values of the proportion K of subjects with only one eligible ear

Coefficient K	Sample size	Power Minimum	Effective power
1	50	.800	.800
.9	48	.792	.794
.8	45	.772	.782
.7	43	***.751***	.771
.6	40	.729	.761
.5	38	.705	.751

Conclusions: The initially planned power of 80% is confirmed for K=1. The minimum power remains acceptable (loss of less than 5%) when the proportion K remains above 0.7, and the effective power remains acceptable even when the proportion of subject K is 50% of the whole sample. These results were confirmed by simulation on 3000 samples where it was found that the mean power was included between the theoretically estimate Minimum and effective power.

We conclude that a proportion of 30% of subjects with only one testable ear is acceptable with a loss of 5% power, and in case of extreme difficulties, this number can be reduced until K=50%, knowing that between 5% and 10% of the power will decrease.

We also recall that for sensitivity purposes, the same analysis will be repeated based on the population of subjects instead of ears, in two ways: (a) for each subject, the most affected ear will be analyzed, (b) the mean change will be averaged on the two ears. This analysis will also be slightly influenced according to the proportion coefficient K, as the standard deviation of the mean change averaged on the two ears will slightly increase.

9.2.4 Secondary Efficacy Analysis

1-Alternative calculations of the main endpoint

Although the main endpoint assesses the mean change of impairment over baseline, the drug efficacy according to the CTCAE (version 5.0) grades 1 to 4 (called the Grade analysis) at 4 weeks after cisplatin completion will be assessed by a non-linear mixed model featuring a logistic ordinal regression according to the same adjustment variable as the primary analysis. Separate analyses will be conducted separately for each grade.

Both the mean change and grade analysis will be conducted at both 4 and 12 weeks on the population of ears with the same design as the main analysis, and these four analyses will be repeated also on the population of subjects in two ways: (a) for each subject included with both ears defined as eligible, the most affected ear will be analyzed, (b) the mean change measured on the two ears will be averaged.

2- Longitudinal analysis of change

A mixed effects model approach (MMRM) will be used for assessing the change at 4 and 12 weeks in assuming a first level Autoregressive AR (1) correlation structure in time. In case of non-convergence of the model, other matrix structures will be tested. The choice of the matrix will be determined using Bayes' Information Criteria (BIC): the selected matrix chosen will be the one minimizing these criteria. The model will be defined with treatment arm (SENS-401 versus no SENS-401) as a dichotomous factor, age and baseline hearing threshold of the 3 most affected contiguous frequency values as fixed covariates, study center random factor, and subject random factor nested within each study center.

9.2.4.1 Multiplicity

The main endpoint will be conducted at the predetermined one-sided $\alpha = 0.05$. The analyses of the secondary efficacy, safety and exploratory endpoints will be considered as hypothesis generating and no adjustment for multiplicity will be applied.

9.2.5 Safety Analyses

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

Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of study treatment (SENS-401 or cisplatin-based chemotherapy) and prior to 30 days after the last administration of study treatment. The AE summaries will be primarily based on TEAEs. The number and percentage of subjects with TEAEs will be summarized by treatment arm, system organ class (SOC), and preferred term (PT) for all TEAEs, treatment-related TEAEs, serious

TEAEs, TEAEs leading to death, TEAEs leading to discontinuation of study treatment and commonly occurring TEAEs (defined as TEAEs occurring in more than 5% of the subjects in either study treatment arm). All TEAEs will be further summarized by maximum severity and causality.

All AEs will be presented in a by-subject listing. Serious AEs, TEAEs leading to death and TEAEs leading to discontinuation of study treatment will be presented in separate listings.

Clinical Laboratory Tests

Laboratory data will be summarized at screening by treatment arm. All screening laboratory data will be presented in the listings.

Physical examination and Vital Signs

Descriptive statistics will be used to summarize the observed and change from baseline values of the physical examination and vital signs parameters at each assessment time point by treatment arm. All physical examination and vital signs data will be presented in listings.

9.2.6 Other Analyses

Biomarker analysis might be performed to explore the correlation between pre-identified biomarkers (e.g., prestin) or biomarkers identified during the study period with clinical features of interest (like prediction of ototoxicity).

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

9.2.7 Intercurrent Events and Handling of Missing Data

Intercurrent events are defined in Section 9.2.2. Additional algorithms to handle missing data will be detailed in the SAP as appropriate.

9.2.8 Intermediate Blind analysis

The standard deviation, Coefficient of correlation R and Intra class correlation ICC have an important impact on the sample size and were approximated with pre-existing poorly accurate estimates. The optimization of the power requires an intermediate blind estimate of the three values once a sufficient number of subjects will allow for at least 16 ears per arm after three cycles of cisplatin, in order to determine the three most severely affected hearing frequencies . Based on these findings, a sample size re-calculation will allow a possible decrease or increase of sample size expected to control the pre-determined power of 80%. This intermediate measurement is not considered as an interim analysis, no intermediate comparison between the two arms will be performed, thus no further control of test multiplicity is needed.

9.2.9 Miscellaneous

The Statistical Analysis Plan (SAP) with detailed description of all statistical analyses will be developed and finalized before database lock. All statistical analyses, including summary tables and data listings will be performed using SAS® software (version 9.4 or higher). Continuous endpoints will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation, median, Q1, Q3, minimum, and maximum). Categorical endpoints will be summarized using frequency counts and percentages. All individual subject data will be present in listings.

9.3 Data Safety Monitoring Board

A data safety monitoring board has been appointed to monitor the safety during the study.

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11.0 APPENDICES

Appendix 1. Abbreviations

Abbreviation	Definition
5-HT_3	Serotonin type 3
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	bis in die
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ENT	Ear, Nose and Throat doctor
FAS	Full Analysis Set
HDPE	High-Density Polyethylene
HIV	Human immunodeficiency virus
HMG1	High mobility group
ICC	Intra-class correlation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
NER	Nucleotide excision repair
NIMP	Non- Investigational medicinal product
PK	Pharmacokinetic
PP	Per-protocol
PTA	Pure-tone audiometry
OTP	Ototoxicity proportion

Abbreviation	Definition
RNA	Ribonucleic Acid
ROS	Reactive oxygen species
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SoA	Schedule of activities
SSNHL	Sudden sensorineural hearing loss
STAT1	Signal transducer and activator of transcription 1
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
THI	Tinnitus Handicap Inventory
WOCBP	Woman of childbearing potential

Appendix 2. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/independent ethics committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the study center and adherence to requirements of title 21 of the Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 10). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

The Sponsor certifies that it has taken out a liability insurance policy which covers the liability of the Investigator and his/her coworkers and which is in accordance with local law and/or national regulations and/or ICH guidelines, whichever is applicable. An insurance certificate will be provided to the Investigator in countries requiring this document and the terms of the insurance will be kept in the study files.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of samples collected for biobank (Biomarkers) for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature for consenting subject's clinical data use by [redacted] to develop their technology.

Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

Table 5 Study Administrative Structure

Function	Responsible Organization
Study Operations Management Medical Monitoring	CRO
Study Master File	CRO
Randomization Code	CRO
Data Management	CRO
Clinical Supply Management	Third party
Quality Assurance Auditing	CRO
Biostatistics Medical Writing	CRO
Hearing auto-test	Third party
Laboratory Assessments	Clinical sites (local laboratory)
Biobank for biomarkers	Third party
Electrocardiogram Collection, Review, and Analysis	Clinical sites
Pharmacokinetic Sample Testing	Not applicable
Safety Monitoring Committee (see Section 9.3)	Not applicable

Abbreviation: CRO = Clinical research organization.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the EU database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic Case Report Forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Clinical Monitoring Plan.

No data will be recorded directly on the eCRF without a prior written or electronic record of the data.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study

completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further IMP development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

Appendix 3. Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory and the visits are described in the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Clinical chemistry will be performed at visits 1; 3_1; 4; 5 and at any unscheduled visit to monitor renal and liver functions, as part of the current practices.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 6 Protocol-required Local Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (visits 1; 3_1 [before the first cisplatin cycle if V1 lab tests performed more than 28 days before]; 4; 5 & uns.)	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	<u>RBC Indices</u>: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) G/L Reticulocytes	<u>White Blood Cell Count with Differential</u>: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry (visits 1; 3_1 [before the first cisplatin cycle if V1 lab tests performed more than 28 days before]; 4; 5 & uns.)	Blood Urea Nitrogen	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; (Livio, Biollaz, et Burnier 2008))	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) International normalized ratio (INR)	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	
Other Tests (visit 1)	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Serology: human immunodeficiency virus (HIV) antibody The results of each test must be entered into the eCRF.			
NOTES: Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration, GFR = glomerular filtration rate, MDRD = modification of diet in renal disease, uns. = unscheduled.				

Appendix 4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject administered with a medicinal product and which does not necessarily have a causal relationship with the product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of 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 treatment 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. 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 they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an 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.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately. • It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the Safety Event Report Form.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor or Designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5.0[1]. For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines:

- Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed
- Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)
- Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity
- Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent intervention indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.
- Grade 5: Fatal outcome.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe, or according to NCI CTCAE); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

[1] Please refer to the CTCAE v5 published on November 2017 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Assessment of Causality

An assessment of causality for study treatment must be provided by the Investigator. Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) pre-existing condition, concomitant medication, relevant history, pattern of the AE and temporal relationship to the study treatment.

- **Yes**: there is a reasonable possibility that the study treatment caused the event; one or more of the following criteria apply:
  - The event follows a reasonable temporal sequence from administration of the study treatment.
  - The event could not be reasonably attributed to the known characteristics of the Subject's general health and past medical history, environmental or toxic factors or other modes of therapy administered to the subject.
  - The event follows a known pattern of response to other "XXX" drugs.
  - The event disappears or decreases on clearance of the study treatment from the subject's circulation. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon study treatment clearance despite other clear indications of relatedness).

- If a relationship to an AE is not clearly unrelated or related to another cause, then it should be considered causally related to the study treatment.

- **No**: there is no reasonable possibility that the study treatment caused the event; one or more of the following criteria apply:
  - The event does not follow a reasonable temporal sequence from administration of the study treatment.
  - The event could be reasonably attributed to the known characteristics of the subject's general health, a concurrent illness, environment or toxic factors or other modes of therapy administered to the subject.
  - The event does not follow a known pattern of response to other "XXX" drugs.
  - The event does not disappear on clearance of the study treatment from the subject's circulation.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject 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.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

Safety Event Reporting to [redacted] via Paper CRF
• 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. • Subject identifiers (such as name, address etc.) other than study subject number will be 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.

Appendix 5. Excluded Medications/Therapy

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF. Any excluded medications used by a subject during the study are to be discussed on a case-by-case basis with the Sponsor's medical representatives.

- Corticosteroids by intratympanic route (including but not limited to prednisone, methyl prednisolone, dexamethasone) is not permitted unless used as rescue medication (see Section 6.5.1).
- Other intratympanic treatments
- Hyperbaric oxygen
- Antivirals, vasodilators, vasoactive substances, or antioxidants. In case of chronic treatment for reasons other than inner ear diseases, these agents can be continued but the dose regimen must not be modified until the end of the treatment period
- Any investigational drug
- Any ototoxic treatment (eg, aminoglycosides, loop diuretics, quinine etc., except cisplatin)
- 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 venlafaxin
    - 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 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)

Permitted concomitant medication for this study will be per the standard of care, and in particular, the investigator will be free to prescribe the antiemetic treatment of his choice.

Appendix 6. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1]:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of cisplatin.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Implantable intrauterine devices
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for the duration of the study and for at least 30 days after the last dose of SENS-401 if cisplatin is not received or 6 months after the last dose of Cisplatin.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing is not required during the treatment period.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive SENS-401.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate

classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Appendix 4.

- Any post-study pregnancy related SAE considered reasonably related to SENS-401 by the Investigator will be reported to the Sponsor or designee as described in Appendix 4. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

Reporting Pregnancy Information

Email transmission of the paper Pregnancy Report Form is the preferred method to transmit safety event information to [redacted] with facsimile as a back-up method.
Safety events should be reported to [redacted] at:
Email: [redacted]
Fax: [redacted]

Appendix 7. Tinnitus Handicap Inventory

TINNITUS HANDICAP INVENTORY

Patient Name: _____ Date: _____

INSTRUCTIONS: The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.

1. Because of your tinnitus, is it difficult for you to concentrate?	Yes	Sometimes	No
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3. Does your tinnitus make you angry?	Yes	Sometimes	No
4. Does your tinnitus make you feel confused?	Yes	Sometimes	No
5. Because of your tinnitus, do you feel desperate?	Yes	Sometimes	No
6. Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7. Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	Sometimes	No
8. Do you feel as though you cannot escape your tinnitus?	Yes	Sometimes	No
9. Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
11. Because of your tinnitus, do you feel that you have a terrible disease?	Yes	Sometimes	No
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14. Because of your tinnitus, do you find that you are often irritable?	Yes	Sometimes	No
15. Because of your tinnitus, is it difficult for you to read?	Yes	Sometimes	No
16. Does your tinnitus make you upset?	Yes	Sometimes	No
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	Sometimes	No
18. Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	Sometimes	No
19. Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20. Because of your tinnitus, do you often feel tired?	Yes	Sometimes	No
21. Because of your tinnitus, do you feel depressed?	Yes	Sometimes	No
22. Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23. Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24. Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25. Does your tinnitus make you feel insecure?	Yes	Sometimes	No

FOR CLINICIAN USE ONLY

Total Per Column							
	x4		x2		x0		
Total Score		+		+		=	

Newman, C.W., Jacobson, G.P., Spitzer, J.B. (1996). Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg, 122, 143-8.

To interpret the score please refer to the Tinnitus Handicap Severity Scale shown on the reverse side.

TINNITUS HANDICAP INVENTORY SEVERITY SCALE

GRADE	SCORE	DESCRIPTION
1	0-16	Slight: Only heard in quiet environment, very easily masked. No interference with sleep or daily activities.
2	18-36	Mild: Easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities.
3	38-56	Moderate: May be noticed, even in the presence of background or environmental noise, although daily activities may still be performed.
4	58-76	Severe: Almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities affected adversely.
5	78-100	Catastrophic: Always heard, disturbed sleep patterns, difficulty with any activity.

Appendix 8. Common Terminology Criteria for Adverse Events (CTCAE) – Version 5.0, published November 27, 2017

Only "Ear and labyrinth disorders" category is presented in this appendix. Please refer to the complete version if necessary.

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear. **Navigational Note:** -					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region. **Navigational Note:** -					
Hearing impaired	**Adults** enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB hearing loss (HL) (i.e., 25 dB HL or greater); sensorineural hearing loss (SNHL) above 4 kHz (i.e., 6 or 8 kHz) in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention not indicated; limiting instrumental ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention indicated; limiting self care ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 2 to < 4 kHz in at least one ear	**Adults:** Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing **Pediatric:** Audiologic indication for cochlear implant; > 40 dB HL (i.e., 45 dB HL or more); SNHL at 2 kHz and above	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. **Navigational Note:** -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear. **Navigational Note:** -					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking. **Navigational Note:** -					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). **Navigational Note:** -					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems. **Navigational Note:** -					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Appendix 9. Country-specific Requirements

Not applicable.

Appendix 10. Signature of Investigator

PROTOCOL TITLE: A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Efficacy of SENS-401 to Prevent the Ototoxicity induced by Cisplatin in Adult Subjects with a Neoplastic Disease

PROTOCOL NO: SENS-401-202 (NOTOXIS)

VERSION: 4.1

This protocol is a confidential communication of Sensorion. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____