Docusign Envelope ID: D19CC9DA-F844-46E8-A298-733489158C52

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Statistical Analysis Plan	Version:	**2.0**
	Study Protocol:	20 SEP 2023 V4.1

Study Name	NOTOXIS
Study ID	SENS-401-202
EudraCT number	2021-002705-10

Customer	Sensorion
Study 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 Neoplastic Disease
Protocol Version	Version 4.1, 20 SEP 2023
CRF version	Version 7.0, 18 FEB 2025
Issue Date	29 SEP 2025

Change History

Version	Issue Date	Reason for change and changes to prior version
1.0	29 JUL 2024	Initial creation
2.0	29 SEP 2025	Updates following the Data Review meeting (see Section 7.2 Changes from the Analysis planned in the Protocol) Details on the calculation of the primary endpoint Adding analyses on the most affected ears at Visit 4 and Visit 5 Adding sensitivity analysis Adding subgroup analyses Adding an exploratory endpoint Removing MMRM for secondary endpoint analyses Adding supplementary analysis

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Signatures

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Contents

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1 ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
ASHA	American Speech-Language-Hearing Association
b.i.d.	Bis in die
BMI	Body Mass Index
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
eCRF	electronic Case Report Form
ENT	Ear, nose and throat doctor
FSR	Final Study Report
HIV	Human Immunodeficiency Virus
ICC	Intra Class Correlation
ICE	Intercurrent events
IMP	Investigational Medicine Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
NPV	Negative Predictive Values
PPV	Positive Predictive Values
PT	Preferred Term
PTA	Pure Tone Audiometry
R^2	Coefficient of determination
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SMD	Standardized Mean Difference
SOC	System Organ Class
THI	Tinnitus Handicap Inventory
TEAE	Treatment-emergent adverse event
VIF	Variance inflation factor

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2 INTRODUCTION

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.

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under SENSORION SENS-401-202 (NOTOXIS).

This SAP supersedes the statistical considerations identified in the protocol; If they are substantially different, they will be identified as such.

3 STUDY OBJECTIVES AND ESTIMANDS

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	• 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.

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Objectives	**Endpoints**
of the last cisplatin treatment.	• 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: o Grade 1: threshold shift from baseline ≥15 dB averaged at 2 contiguous test frequencies. o Grade 2: threshold shift from baseline >25 dB averaged at 2 contiguous test frequencies. o 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	• Serum/plasma concentrations of selected biomarkers before each of the first three cisplatin treatments (just after rehydration) at the end of

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Objectives	**Endpoints**
identified in the future, and clinical features of interest (like prediction of ototoxicity).	the day of the third cisplatin cycle and at visit 5.
• 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.
• To evaluate the rate of ototoxicity at V4 and V5	• Rate of ototoxicity defined according to American Speech-Language-Hearing Association (ASHA) criteria at Visits 4 and 5, according two ranges of frequencies: o 1 to 8 kHz o 8 to 12.5 kHz
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).

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4 STUDY DESIGN

4.1 Type of study

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.

4.2 Study plan

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 was 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 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 contiguous most severely affected hearing frequencies (these frequencies will be used for quantitative analysis), estimate the standard deviation, assess the intra-subject and inter-ear hearing impairments, and re-evaluate the sample size if necessary.

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.

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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
- 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 received, as established by the ear, nose and throat doctor (ENT), the current standard of care for ototoxicity. Thus, cisplatin doses will be adapted to subjects' body surface and hyperhydration will be provided. The current practice includes several recommendations such as modifications to the medication, rescue therapy with intravenous corticosteroid and supporting hearing function with hearing aids medical device.

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Table 1: 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	

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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
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)				
Randomization		x				

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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
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)

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Study Period	**Screening**	**Randomization**	**Evaluation**			
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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
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		

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Study Period	**Screening**	**Randomization**	**Evaluation**			
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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)				

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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
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	
Audio Tests						
Otoscopy	x			x	x	x
Immittance audiometry	x			x	x	x

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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
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 of the protocol.

[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.

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[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 (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.

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4.3 Duration of the study

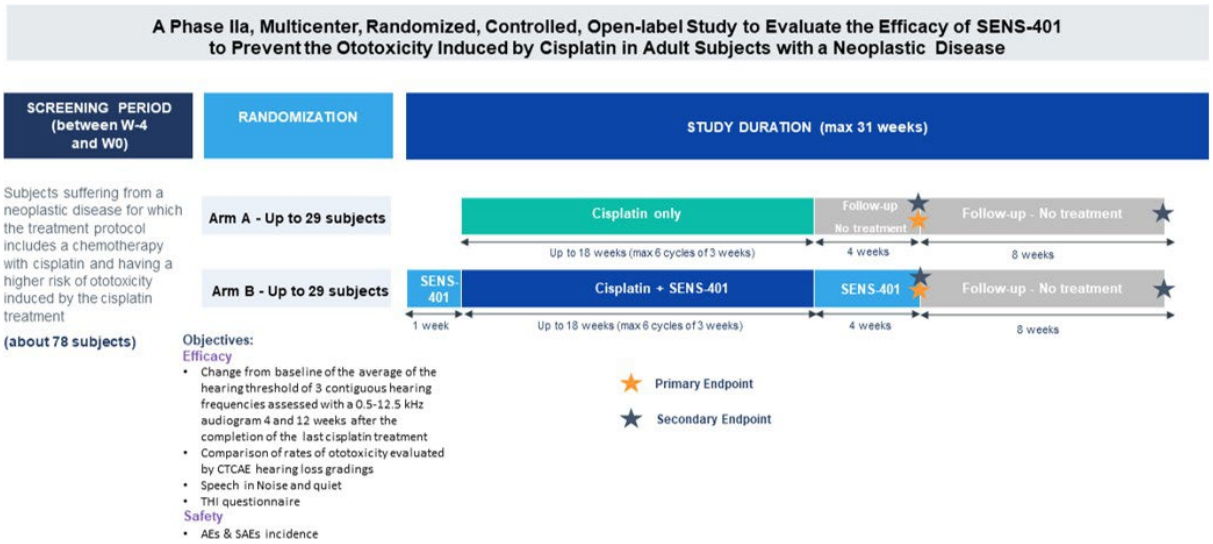

Figure 1: Study Scheme

The total study duration for each subject is variable as it depended 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 to exceed 35 weeks as detailed below:

- 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

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.

4.4 Enrolment of sites and subjects

Inclusion criteria

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

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1. Age ≥ 18 years at the time of signing the ICF.
2. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.
3. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and ≥ 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP).
   - A WOCBP who agrees to follow the contraceptive guidance 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 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/m2 per cycle and a cumulative dose of cisplatin of at least 210 mg/m2.

6b. Subject with a PTA threshold ≤ 30 dB HL at 500 Hz AND ≤ 40 dB HL for 1-2-4 kHz, AND ≤ 60 HL dB for 8 kHz and above.

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 sensorineural hearing loss.

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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).
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 of the protocol. 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).

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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 DETERMINATION OF SAMPLE SIZE

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.
3. 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 $R^2 = 0.6$.
4. Dropout was not accounted for, as the Full Analysis Set (FAS) is the main selection.
5. 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 R2 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.

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

It is clinically admittable that a subject will 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)]n0 where n0 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 1 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 1 - 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

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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.

6 RANDOMIZATION

This is an open-label study; however, the subject was randomly assigned (1:1) to one of the two treatment groups (either cisplatin-based chemotherapy alone or with SENS-401) using an Interactive Voice/Web Response System (IVRS/IWRS).

The study center contacted the IVRS/IWRS prior to the start of IMP administration for each subject. The study center recorded the treatment assignment on the applicable electronic case report form (eCRF), if required. Potential bias was reduced by central randomization.

At the randomization visit, each subject will be indicated in the IVRS/IWRS as either having:

i) For subjects included under Protocol V3.0 or previous version:
Subject with a PTA threshold ≤ 30 dB HL at 500 Hz AND ≤ 40 dB HL for 1-2-4 kHz, AND ≤ 60 dB HL for 8 kHz and above;

ii) For subjects included from Protocol V4.0:
a PTA threshold of ≤ 30 dB HL at 500 Hz AND ≤ 40 dB HL for 1-2 kHz AND ≤ 60 dB HL for 4-6 kHz AND ≤ 80 dB HL for 8 kHz in one ear OR a PTA threshold of ≤ 30 dB HL at 500 Hz AND ≤ 40 dB HL for 1-2 kHz AND ≤ 60 dB HL for 4-6 kHz AND ≤ 80 dB HL 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.

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7 MODIFICATION FROM PROTOCOL

7.1 Changes in the Conduct of the Study

None.

7.2 Changes from the Analysis planned in the Protocol

- Updates of definitions of FAS and PP analysis populations (see Section 8 Analysis Populations). For each of these two populations, at least one exclusion criterion was added:
  - FAS: subjects who have not received at least one dose of trial medication (either cisplatin-based chemotherapy alone or in combination with SENS-401), failure to satisfy major entry criteria and without any data post randomisation will no longer be included in the FAS.
  - PP: subjects without complete follow-up through Visit 4 will no longer be included in the PP.
- Clarification on the determination of the three most impaired frequencies at Visit 4: these will be identified based on the control group to avoid potential influence of SENS-401 (Appendix C)
- Update of Section 9.4.5 Missing Data Assumptions: Multiple imputation will not be applied (see Section 9.2.1 for detailed justification),
- Adding sensitivity analysis excluding ears whose hearing improvement is strictly greater than 10 dB,
- Adding subgroup analyses (see Section 10 Subgroup analysis)
- Removing MMRM for secondary endpoint analyses,
- For supportive secondary analyses, the analyses will be performed on only one ear, based on the most affected eligible ear at the corresponding visit (V4 or V5, respectively) defined on the PTA (primary endpoint),
- For all analyses requiring analysis of the most affected ear, this is based on the previous definition (i.e., most affected eligible ear at V4 or at V5 – based on the PTA),
- Adding exploratory endpoint analyses using ASHA criteria (see Section 9.7 Exploratory analysis),
- Adding supplementary analysis using a different methodology to derive the primary endpoint (see Section 9.4.8 Supplementary analysis).

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8 ANALYSIS POPULATIONS

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.

Full Analysis Set (FAS)

Eligible ears of all subjects who have been randomized. Subjects could be excluded from the FAS in case of failure to satisfy major entry criteria (eligibility violations), failure to take at least one dose of trial medication (either cisplatin-based chemotherapy alone or in combination with SENS-401) and the lack of any data post randomization.

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 Set (PP)

Eligible ears of all subjects in FAS:

- with no major protocol deviation likely to affect the efficacy assessment,
- and with complete follow-up through Visit 4.

Major protocol deviations were reviewed and determined prior to database lock. Subjects to be excluded from the PP analysis set were 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.

Safety Set (SAF)

Randomized subjects who receive any 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.

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9 STATISTICAL METHODOLOGY

9.1 General Analysis Methods

9.1.1 Descriptive statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics and nomenclature: n = number of observations or ears or subjects, mean = arithmetic mean, SD = standard deviation, Q1 = first quartile value, Q3 = third quartile value, median = median value, min = minimum value and max = maximum value. Number of missing values will be specified.
Categorical data will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Percentages by categories will be based on the number of ears or subjects excluding those with missing values. Number of missing values will be specified as well.
For categorical data, the categories will be presented in the tables as they appear in the case report form (CRF).

Data will be presented using an appropriate number of decimal places (i.e., the number of decimal places used does not imply undue precision):

- Raw data: same number of decimals as collected,
- Derived data: The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers),
- Mean, median and standard deviation: reported to one decimal place greater than the raw/derived data that they summarize,
- Minimum and maximum: same precision as the raw data,
- Percentage: one decimal place,

9.1.2 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.

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9.2 Management of missing values

9.2.1 Missing data

Missing data will not be handled through multiple imputation, as the experimental conditions do not permit such an approach.

The initial strategy was intended to mitigate bias by aligning the imputation model with the presumed mechanism of missingness. During trial conduct, however, several findings challenged the feasibility and validity of this approach. Approximately 30% of primary endpoint data were missing at Visit 4, a proportion far higher than anticipated. A subject-level review confirmed that none of the early discontinuations were attributable to SENS-401. Instead, discontinuations were disproportionately concentrated in the control arm. While causality cannot be formally established, this imbalance strongly suggests that attrition reflected lack of motivation among untreated patients rather than safety or efficacy concerns.

In addition, the protocol had anticipated the collection of intermediate longitudinal assessments (audiometric measures before each cisplatin cycle) between baseline and Visit 4 to inform the imputation models. These data were not collected. As a result, only baseline and endpoint values are available, leaving the imputation model dependent solely on baseline covariates (age, sex, weight, baseline hearing threshold, cumulative cisplatin dose). These covariates have limited predictive value for the endpoint, and the absence of longitudinal trajectories means imputations would be poorly constrained and largely speculative.

Under these conditions, multiple imputation would fail to achieve its intended purpose. It would rely on weak predictors, inflate residual variance by introducing random noise rather than informative signal, and increase the risk of biased or misleading estimates, especially given that an MNAR mechanism cannot be excluded. In practice, the imputation would add uncertainty rather than reduce it.

For these reasons, multiple imputation is removed from the primary estimand analysis.

9.2.2 Missing or incomplete dates

For partial dates, if the day is missing, the convention is to use “15” (middle of the month). If the day and the month are missing and it’s a former date (for example

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date of birth), the convention is to use the value "1" for the day and "7" for the month (middle of the year). Missing day and/or month of adverse event start date will be replaced by the first date after the date of the last treatment application.

9.2.3 Outliers

Any outlier identified prior to database lock which is impossible/implausible will be excluded from the analysis. A search of outliers should be performed before the database lock and actions with the sponsor should be defined.

9.2.4 Management of Visit 4 completion

If only compliance data are collected at V4 for a subject (even if a visit date is entered), the V4 will be considered as not performed.

9.3 Baseline description

9.3.1 Disposition of subjects

A summary table will present the number of screened subjects/ears, randomized subjects/ears, and of each analysis set (i.e., FAS, PP, SAF) in each treatment group and at each assessment visit. The number of subjects with screening failure will be also presented by sites.

A statistic summary of the follow-up duration (in days – See Appendix A) will be presented overall and for each group.

The number and percentage of subjects/ears who withdrew from the study and the reasons for withdrawal will be presented by group/overall for each analysis set. Time between randomization and withdrawal (in days) will also be presented.

9.3.2 Protocol Deviations

All protocol deviations were identified and declared major or minor at a data review meeting that occured before the lock of the database of the study.

A list of all subjects to be excluded from PP due to one or more major protocol deviations affecting the analysis of the primary endpoint was finalized during the meeting.

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9.3.3 Baseline data

Summary statistics will be provided for baseline data by treatment group and overall on the FAS.

- Demographic characteristics at screening

Descriptive statistics for sex, age (in years, as collected in the eCRF), height (m), weight (kg) and BMI (kg/m^2) collected at screening will be provided.
The fertility and contraceptive status will also be summarized, including;

- childbearing potential, post-menopausal or surgically sterile for female subjects, and surgically sterile for male subjects;
- barrier methods, non-barrier methods for female subjects, or for female partner of male subjects.

- Medical history

- Diagnosis

The number and percentage of subjects according to the primary tumor location, as well as quantitative descriptive statistics on the time since the initial diagnosis (see Appendix A for details) will be presented.

- Medical history detail

Medical history will be coded using the latest MedDRA Dictionary Version.

A frequency table of the number and percentage of subjects will be provided for medical history by System Organ Class (SOC) and Preferred Term (PT) for each group/overall.

Medical occurrences that begin before visit 2 (randomization) will be considered as medical history.
Tables will be sorted by descending frequency of SOC and, within each SOC by descending frequency of PT in all subjects of the FAS.

- Prior and concomitant medications

Prior and concomitant medications will be coded using the latest WHO-Drug Dictionary version.

Medication ended before visit 2 (i.e., stop date of medication < date of randomization) will be considered as prior treatment. Ongoing medication or

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medication ended at or after visit 2 (i.e., stop date of medication ≥ date of randomization) will be considered as concomitant medication.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant medications – separately – by therapeutic class (ATC) and by WHO Drug Name for each treatment group/overall.

Tables will be sorted by descending frequency of ATC Chemical Subgroup and, within each ATC Chemical Subgroup by descending frequency of WHO Drug Name in all subjects of the FAS.

- Other baseline characteristics

Baseline findings for physical examination, vital signs and ECG as well as laboratory parameters are presented in Section 9.10 (Safety Analysis).

9.4 Primary estimand analysis

9.4.1 Population

Adult subjects with neoplastic diseases defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval. The population will also be extended to the eligible ears of the subjects.

9.4.2 Endpoint

The primary endpoint (see Appendix B for derivation details) is defined as the change from baseline (See Appendix A) of the summary 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 (i.e., Visit 4) in each eligible ear of each subject.

Those values represent the minimum threshold that could be heard from the eligible ear for a particular frequency.

A positive absolute change from baseline result will signify a worsening in eligible ear perception capability.

The three contiguous most affected hearing frequencies will be identified from the control group (i.e., subjects receiving cisplatin-based chemotherapy without SENS-401). The same triplet will then be applied to both the control and the SENS-401

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groups, in order to assess the potential effect of SENS-401 on the most affected triplet under natural conditions.

9.4.3 Intercurrent events

Early termination of the study due to reasons related or not to the study treatments.

9.4.4 Population-level summary

Mean difference in primary endpoint between treatment arms (SENS-401 arm versus Control arm).

In alignment with the Addendum to ICH E9 [ICH, ICH E9 reference], the primary efficacy estimand is described by the following attributes:

Element	**Subject or outcome characteristic**
Target population	Adult subjects with neoplastic disease requiring treatment with cisplatin as part of the chemotherapy protocol plan and adhering to the inclusion/exclusion criteria
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 events (ICE)	• Early termination of the study due to reasons related to the study treatments (e.g., drug-related AE, perception of lack of efficacy). • Early termination of the study due to reasons unrelated to the study treatments.
Population level summary	Difference in primary endpoint means between SENS-401 arm and Control arm

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9.4.5 Missing Data Assumptions

Not applicable.

9.4.6 Statistical Analysis

Mixed Linear Model featuring analysis of covariance (ANCOVA) with the following characteristics will be performed to analyse the primary efficacy estimands:

- Dependent variable: primary efficacy endpoint
- Dichotomous factors: arm (SENS-401 vs no SENS-401, treatment categorical independent variable in ANCOVA), ear position (left vs right)
- Fixed covariates: cisplatin cumulative doses, age, exposure to cisplatin (duration), baseline average hearing threshold of the 3 contiguous hearing frequencies
- Random factors with hierarchical structure: study center (higher), subject (lower)

In case of a manifest departure on normality and variance homogeneity, a log-transformation and/or a residual variance variable depending on the treatment will be assessed.

The estimate of least square means (LS-means) difference between the two randomization arms will be provided. The 95% confidence interval (95%CI) of this LS-means difference will also be computed. P-value of the randomization arm effect will also be provided.

Outputs from SAS Mixed procedure will be presented in a summary table including LS-means of both arms and its associated 95%CI, adjusted means difference between randomization arm and its associated 95%CI and p-value.

In addition to the modelling, descriptive statistics of PTA and change from baseline will be presented at each visit by treatment group and overall. All thresholds by frequency, as well as the average of the hearing thresholds of 3 contiguous frequencies (dB HL) will be described.

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9.4.7 Sensitivity analysis

Same analysis as the one described above will be repeated on:

- the PP population
- the population of subjects instead of ears, in two ways:
  - The most affected ear at V4 for subjects included with both ears defined as eligible, and the eligible ear for patient with only one eligible ear,
  - The average of the two ears (i.e., the change from baseline) for subjects included with both ears defined as eligible, and the eligible ear for subjects with only one eligible ear,
- the population of ears whose hearing improvement between the screening and the Visit 4 is less or equal to 10 dB (i.e., change from baseline at V4 ≤ 10 dB). Ears with at least one improvement > 10 dB on at least one the range of frequencies 0.5-12.5 kHz will be excluded.

9.4.8 Supplementary analysis

A supplementary analysis will be performed using a different approach to define the endpoint.
The endpoint will be calculated for each ear individually as follows:

- For each hearing frequency (ranged from 0.5 to 12.5 kHz), the change from baseline at V4 will be calculated,
- The three contiguous most affected hearing frequencies will be selected,
- The mean of the values of the three frequencies selected will be calculated.

The calculated mean of the triplet will determine the value of the endpoint for each eligible ear.

The statistical analysis described in Section 9.4.6, as well as in Section 9.4.7, will be performed using this endpoint on the most affected ear.

9.5 Key secondary estimand analysis

9.5.1 Population

The FAS will be the population used for the key secondary estimand. The population will be also extended to all the eligible ears of the subjects.

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9.5.2 Endpoint

The key secondary endpoint is the 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 ear of each subject.

9.5.3 Intercurrent events

See section 9.4.3

9.5.4 Population-level summary

Mean difference in key secondary endpoint between treatment arms.

9.5.5 Statistical Analysis

Same analyses as the ones described in sections 9.4.6, 9.4.7 and 9.4.8 will be performed on the key secondary estimands (i.e., change from baseline to 12 weeks after the end of the last cisplatin treatment of the average of the hearing threshold of 3 contiguous hearing frequencies).

Regarding the analysis on the most affected ear, this will be based on Visit 5.

9.6 Supportive secondary analyses

The supportive secondary analyses will be based on the FAS. If the number of ears of subjects in PP is < 80% of the FAS, same analyses will be repeated on the PP.

Severity of the hearing loss

Severity of the hearing loss between baseline and 4 weeks (V4), as well as between baseline and 12 weeks (V5) after the completion of the last cisplatin treatment will be based on the CTCAE (version 5.0) classification.

The evaluation of ototoxicity according to CTCAE classification is defined as the change from baseline, such that patient grading (not ears) by ventilation can only be performed in V4 and V5, and not at baseline. The change from baseline in

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average of the hearing threshold of 2 or 3 contiguous frequencies in at least one ear will be evaluated with an audiogram from 1 to 8 kHz and as follows:

- Severity of the hearing loss grade = 1, if change in threshold (i.e. difference between hearing thresholds between baseline and 4/12 weeks after the completion of the last cisplatin treatment) ≥ 15 dB averaged at 2 contiguous test frequencies
- Severity of the hearing loss grade = 2, if change in threshold (i.e. difference between hearing thresholds between baseline and 4/12 weeks after the completion of the last cisplatin treatment) > 25 dB averaged at 2 contiguous test frequencies
- Severity of the hearing loss grade = 3, if change in threshold (i.e. difference between hearing thresholds between baseline and 4/12 weeks after the completion of the last cisplatin treatment) > 25 dB averaged at 3 contiguous test frequencies

A Logistic Ordinal Regression will be performed on the severity of the hearing loss with the following model definition:

- Dependent variable: CTCAE version 5.0 (Grade 0 to 3 and above)
- Although it is usually carried out as censored model, we have the possibility of seeing how the Grades are calculated for the study, hence allowing us to make it uncensored.
- Dichotomous factors: arm (SENS-401 vs no SENS-401)
- Fixed covariates: cisplatin cumulative dose, exposure to cisplatin (duration), age, baseline average of the 2 or 3 contiguous audiogram frequencies
- Random covariates with hierarchical structure: study center (higher), subject (lower)

This type of model is usually applied when a censored dependent variable is substituted by an ordered categorical variable which presents an underlying measure of goodness (e.g. in our case Grade 3 is worse than Grade 2).
A dichotomous analysis will be generated for each grade i: each time the dependent variable will be of the type (0,1) where it is 1 if the variation is at least of grade i.

The multi-factorial model will be fitted using the maximum likelihood method. The Logit estimate of the Adjusted Odds-Ratio (AOR) and the associated Wald 95% CI

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will be calculated for each factor. For the computation of the AOR estimate of the group effect, the control group will be taken as the reference group.
Results from SAS Logistic procedure will be presented in a summary table including AOR and associated Wald 95% CI for each factor.

The analysis listed above will be conducted at week 4 (V4) and at week 12 (V5) after the completion of the last cisplatin treatment.

Longitudinal analysis of change in hearing score
Descriptive statistics will be performed on hearing and tinnitus tests/ questionnaires (i.e., speech-in-noise test, speech-in-quiet test and THI) in addition to the modelling of the supportive secondary endpoints described below.

All statistical analyses will be conducted at the subject level, defined by the most affected eligible ear at V4 and V5, respectively, according to the primary endpoint.

Speech-in-noise test
Descriptive statistics of the speech-in-noise test parameters and absolute change from baseline in parameters will be presented at each visit by treatment group and overall.

The parameters described will be the following: ear 50% threshold (dB), ear speech stimulation level (dB), ear noise stimulation level (dB), and ear signal/noise ratio (dB – see Appendix A for details).

The same analyses will be performed on the French subjects only.

Speech-in-quiet test
Descriptive statistics of the speech-in-quiet test parameters and absolute change from baseline in quantitative parameters will be presented at each visit by treatment group and overall, according to the intensity.

The parameters described will be the following: Number of presented words, Number of correct repeated word(s) and Percentage of correct response (%).

The same analyses will be performed on the French subjects only.

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THI

Descriptive statistics of the 25 items and the total score, as well as the absolute change from baseline in total score will be presented at each visit by treatment group and overall.

9.7 Exploratory analyses

For all the exploratory endpoints the analyses will be performed at subject level by selecting the most affected eligible ear at V4 and V5, according to the visit analyzed.

Biomarkers assessment

The biomarkers assessment analysis described below will not be performed at the time of the final analysis.

First exploratory objective is to assess the correlation between pre-identified biomarkers (e.g., prestin or other biomarkers of interest), and clinical features of interest (like prediction of ototoxicity).

In order to do so, plasma/serum biomarker samples will be extracted 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.

Values collected before any cisplatin treatment will be used as baseline, and changes from baseline will be calculated and described after each of the first 3 cisplatin treatments in visit 3 and in visit 5 (12 weeks after end of cisplatin treatment).

SON4SENS assessment

The second exploratory objective is to evaluate the performance of an application called SON4SENS and developed by [redacted] (headphone and tablet) to evaluate hearing level in a broad range of frequencies (500 Hz to 12.5 kHz).

i) The consistency between the two measurement tools (PTA and SON4SENS) will be assessed using the Intraclass Correlation Coefficient (ICC), based on mixed model, where the tools (PTA/ SON4SENS) were treated as fixed effects and the patients as random effects. This model estimates the reliability of the measurements obtained from the two instruments by quantifying the proportion

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of total variance attributable to differences between subjects, relative to the variance due to the measurement tools.

Measurements were analyzed for each patient at three timepoints (baseline, V4, V5), on both ears (left and right). The data were structured to incorporate repeated measures within subjects (visits and ears). The ICC will reflect how well the two tools agree across all time points:

- Recognizes that each subject has repeated measurements (over time and on both ears),
- Accounts for the fact that some patients may have naturally higher or lower values,
- Estimates how much of the absolute variation in measurements is due to differences between subjects vs. differences between tools.

ii) Sensitivity / specificity analysis: the PTA will be used as gold standard, and ototoxicity will be evaluated using ASHA criteria.

		From PTA	
		Normal (Rate = 0)	Ototoxicity (Rate = 1)
From SON4SENS	Auto-evaluation normal (Rate = 0)	True positive (TP)	False positive (FP)
	Auto-evaluation ototoxic (Rate = 1)	False negative (FN)	True negative (TN)

For each frequency, at baseline, 4 weeks and 12 weeks, will be calculated:

- Specificity: TN/(TN+FP)
- Sensibility: TP/(TP+FN)

Since SON4SENS data were collected at different times compared to the PTA, time windows will be applied. For each timepoint assessed (i.e., V1, V4 and V5), the data used from SON4SENS will be the data collected closest to the PTA assessment date. If no SON4SENS data were collected in a time window ranged from [-7 ; 7] days around the PTA assessment date, then the SON4SENS data at the concerned timepoint will be missing.

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The comparison between the two measurement systems cannot be reliably performed for SON4SENS values equal to 80 dB, since the system is unable to capture hearing loss above this ceiling. In such cases, the corresponding PTA value will also be set to 80 dB.

- Change from baseline of the average of the hearing threshold assessed with an 8 kHz audiogram

  Same analysis as the one described in sections 9.4.6 will be performed at V4 and V5.

- Correlation between the THI total score and the hearing function

  The Pearson's correlation coefficient between the deterioration of the THI total score and the alteration of the hearing function (assessed by the primary endpoint, see Section 9.4.2 for details) will be determined using a linear regression. A graphical representation will be performed.

- Rate of ototoxicity using ASHA criteria

  ASHA defines an ototoxic change if one of the following criteria are met:
  (1) a ≥20-dB increase in audiometric threshold at any one test frequency,
  (2) a ≥10-dB increase in threshold at any two adjacent frequencies, or
  (3) loss of response at three consecutive frequencies where responses were previously obtained.

  ASHA criteria will be derived according to two ranges of frequencies to define ASHA:
  - from 1 kHz to 8 kHz,
  - from 8 to 12.5 kHz.

  For each of the two range of frequencies, descriptive statistics of the rate of ototoxicity will be presented at V4 and V5 by treatment group and overall.

  Same analysis as the one described in sections 9.4.6 will be performed at V4 and V5.

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These analyses will be performed on the FAS, on the PP, and at the subject level using the following two methods: most affected eligible ear at V4 and V5, respectively, as well as mean of both ears).

9.8 PK Analysis

PK parameters are not evaluated in this study.

9.9 PK/PD Analysis

PD parameters are not evaluated in this study.

9.10 Safety Analysis

All safety analyses will be performed on the Safety Analysis Set. Population is defined exclusively by subjects and not by ears.

- Exposure to Study Medication and Compliance

SENS – 401:
Quantitative statistics of duration of actual treatment in days, and the percentage of treatment compliance in terms of number of tablets taken by subject compared to the number of tablets the subject should have taken will be presented by summary statistics by visit and over the complete treatment time for subjects having received SENS-401. For subjects bringing back all their kits at V4, the compliance will only be assessed over the complete treatment time.

Cisplatin:
The number and percentage of subjects with an administration of cisplatin (Yes, , No) and the level of completion (see Appendix A for details) (Complete, Partial), as well as the action taken (Infusion put on hold, Drug permanently withdrawn) and the reason if the cisplatin was partially or not administered will be reported at each visit in a summary table by treatment group and overall.

In addition, for each administration of cisplatin, quantitative descriptive statistics will be provided for the duration of infusion (minutes – see Appendix A) and the actual dose/body surface area (in mg/m²),

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Over the complete cisplatin treatment time, the number of cycles and the number and percentages of subjects with all cisplatin complete cycles will be described. The number and percentages of subjects with at least 80% compliance will be also presented.

- Adverse Events

AEs will be coded with the latest MedDRA Dictionary version. All analyses presented below will be performed on treatment-emergent AE (TEAE).

TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of treatment (SENS-401 or cisplatin-based chemotherapy) and prior to 30 days after the last administration of treatment.

Summary of TEAEs and Serious TEAEs will be tabulated to provide an overview of TEAEs indicating the number of events along with the number and percentage of subjects with at least one:

- TEAE/Serious TEAE,
- TEAE/Serious TEAE linked to hearing or tinnitus,
- TEAE/Serious TEAE related to Cisplatin,
- TEAE/Serious TEAE related to study drug product (SENS401)
- TEAE/Serious TEAE leading to withdrawal.

Summary indicating the number of TEAEs along with the number and percentages of subjects with at least one TEAE according to the:

- seriousness (yes/no),
    - seriousness criteria (Death, Life-threatening, Hospitalization, Significant disability/incapacity, Congenital anomaly/birth defect, Important Medical Event)
- CTCAE grade (Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: Life-threatening, Grade 5: Fatal),
- action taken with SENS-401 (Dose not changed, Drug interrupted, Drug withdrawn, Unknown, Not applicable),
- action taken with cisplatin (Dose not changed, Drug interrupted, Drug withdrawn, Unknown, Not applicable),
- outcome (Not recovered/Not resolved, Recovering/Resolving, Recovered/Resolved, Recovered/Resolved with sequelae, Fatal, Unknown).

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The number of TEAEs along with the number and percentage of subjects with at least one TEAE will be presented by SOC and PT according to treatment group and overall.

The same tables by SOC and PT will be performed for:

- Non-serious TEAEs,
- Serious TEAEs,
- Serious TEAEs related to cisplatin,
- Serious TEAEs related to SENS-401,
- Serious TEAEs leading to death

In addition, all the analyses by SOC and PT listed above will be duplicated for TEAEs linked to hearing.

Listings of TEAEs

TEAEs will be listed for all subjects. This listing will present a complete description of all adverse events including SOC, PT and investigator description, start date, end date (or ongoing status), duration (days), linked to hearing, seriousness, CTCAE grade, action taken (SENS-401/cisplatin), outcome, relationship to SENS-401/cisplatin.

In addition, deaths, if any, Serious TEAEs, as well as TEAEs leading to SENS-401 withdrawal will be listed.

- Laboratory Safety Parameter

The following analyses of laboratory parameters (See Appendix A for the list and units of laboratory parameters) will be performed:

- Quantitative descriptive statistics of Clinical Chemistry and Haematology will be computed by treatment group/overall and assessment time:
  - Only at screening for haematology parameters
  - At screening and before the first cisplatin cycle, V4 and V5 for clinical chemistry parameters.

  Number and percentage of subjects above, below or within normal ranges in use in each laboratory involved will also be computed for each parameter (if applicable).

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- Change in clinical chemistry parameters from baseline will be computed and described by treatment group at each assessment time before each cisplatin cycle.

- Qualitative descriptive statistics according to clinical assessment (normal, abnormal not clinically significant, abnormal clinically significant) will be presented by parameter and assessment time for clinical chemistry parameters.

- Vital Signs

Body temperature (°C), systolic (SBP) and diastolic (DBP) blood pressure (mmHg) and heart rate (beats/min - bpm) will be presented as descriptive statistics at each assessment time by treatment group and overall.

Vital sign measurements were performed at V1 (screening), V2 (randomization), V3 (before each cisplatin cycle), V4 (W23) and V5 (W35).

Descriptive statistics of absolute change from baseline (i.e., Visit 2–- randomization) of body temperature, heart rate, SBP and DPB will be presented by parameter and visit.

- Physical Examination

Physical examination (normal, abnormal, not done) was collected according to the pre-defined body systems: general appearance; dermatological; lymphatic; HEENT; chest/lungs; cardiovascular; abdomen; genitourinary/reproductive; musculoskeletal/extremities; neurologic/psychiatric; other.

The number and percentage of subjects with abnormal physical examination results will be presented globally and per each body system by treatment group and overall, at each visit. Within each visit, the table will be sorted by descending frequency of body system.

Physical examination was performed at V1 (screening), V2 (randomization), V3 (before each cisplatin cycle), V4 (W23) and V5 (W35).

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- ECGs

The number and percentage of subjects with normal or abnormal result will be presented at each visit by treatment group and overall, as well as the clinical significance (Not clinically significant / Clinically significant) for abnormal results.

12-lead ECG was performed at V1 (screening), V4 (4 weeks after the last cisplatin cycle) and V5 (12 weeks after the last cisplatin cycle).

In addition, a listing will be performed to present all the parameters for abnormal values (i.e., Heart rate (beats/min), PR (sec), QRS (msec), QT (msec), QTcB (msec) and QTcF (msec)).

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9.11 Other Analysis

Otoscopy

The number and percentage of subjects with a result of the otoscopic examination allows the performance of an audiometric examination will be presented at each visit by treatment group and overall.

The results of the audiometric examination will be described at each visit by treatment group and overall, according to the ear. Clinical significance (Normal, Abnormal NCS, or Abnormal CS) of the middle ear, tympanic membrane and ear canal were collected at V1 (screening), V4 (W23) and V5 (W35).

Shift table presenting clinical significance at V4 and V5 versus clinical significance at baseline (i.e., V1 – screening) will be displayed by parameter (i.e., middle ear, tympanic membrane, and ear canal) according to the eligible ear (left and/or right).

Immittance audiometry

The number and percentage of subjects with an immittance audiometry test performed, as well as the number of ears concerned by the test (only one, both) will be summarized at each visit by treatment group and overall.

Quantitative descriptive statistics of the volume (mL), pressure (Decapascal) and compliance (mL), as well as the number and percentage of the type (As, Ad, A, B or C) and the clinical significance (Normal, Abnormal NCS, or Abnormal CS) will be summarized at each visit by treatment group and overall, according to the eligible ear (left and/or right).

The absolute changes in quantitative parameters from baseline (i.e., V1 – screening) will also be performed.

Shift table presenting clinical significance at V4 and V5 versus clinical significance at baseline (i.e., V1 – screening) will be displayed according to the eligible ear (left and/or right).

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10 SUBGROUP ANALYSIS

Rationale and Strategy for Subgroup Analyses

There are clinical and medical reasons to consider that the response to SENS-401 may be influenced by (i) the cumulative dose of cisplatin received and (ii) the baseline hearing level prior to exposure to cisplatin. These two parameters define relevant subgroups for which specific statistical analyses will be conducted as follows:

1. Subgroups based on cumulative cisplatin dose
   Three potential thresholds will be used to define these subgroups:
   - 250 mg/m²
   - 300 mg/m²
   - 350 mg/m²

   These three thresholds will be used simultaneously in a descriptive analysis to assess whether any apparent treatment effect varies according to cisplatin global exposure. If the median value is very close (within 10 mg/m²) to either of the fixed thresholds (250 or 300 mg/m²), it will not be analyzed separately.

   Subgroups will be defined as follows for each threshold:
   - < selected threshold
   - ≥ selected threshold

2. Subgroups based on baseline hearing level
   Two subgroups will be defined based on the median of the average hearing threshold across frequencies from 1 kHz to 8 kHz, calculated per ear:
   - average threshold < median
   - average threshold ≥ median

   Analyses to be conducted within subgroups
   Analyses will be performed both at the ear level (for each eligible ear) and at the study participant level, using:
   - The most affected eligible ear at V4 and V5
   - The average of both ears at V4 and V5

The following analyses will be reproduced in each subgroup:

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- Primary estimand analysis at Visits 4 (see Sections 9.4.6, 9.4.7 and 9.4.8),
- Key secondary estimand analysis at Visit 5 (see Section 9.5.5),
- Exploratory analysis of ototoxicity rates according to ASHA criteria (see Section 9.7).

Depending on the distribution of participants across subgroups, the statistical methodology described in Sections 9.4.6, 9.4.7, 9.4.8, 9.5.5, and 9.7 — particularly the statistical models — could be adapted for subgroup analyses.

11 INTERIM 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 at V4, 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.

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12 SOFTWARE/SYSTEM DOCUMENTATION AND TESTING/VALIDATION

12.1 Software

All tables, listings and figures will be produced, and statistical analysis performed using SAS® Viya, version 9.4 or higher. All outputs will be edited in Microsoft Word Format and PDF.

12.2 CDISC

Not applicable.

12.3 Validation of programs

Validations will be done according to the procedure of the CRO [redacted] The program reviewer is responsible for reviewing each project program and output provided to the sponsor. Program logs are reviewed for logical, syntax and fatal errors.

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13 REFERENCES

Not applicable.

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14 APPENDICES

Appendix A: DERIVED DATA

- **Study duration**

Study duration in months will be calculated as: (LPLV – FPFV + 1)/30.4375

- **Follow-up duration**

Follow-up duration in months will be calculated as: (Date of last follow-up visit – Date of screening visit + 1)/30.4375.

- **Absolute change from baseline**

Absolute change from baseline will be calculated as: (Value at Visit X – Baseline (V1 or V2 according to the criteria assessed).

- **Time since the initial diagnosis**

The time since the initial diagnosis in years will be calculated as: (Date of screening visit – Date of initial diagnosis + 1)/365.25.

- **Level of cisplatin completion**
  - Complete if "planned dose" = "actual dose administered". The dose administered could be higher than the planned dose of 5%.
  - Partial if "planned dose" is not equal to "actual dose administered".

- **Duration of cisplatin infusion**

Case 1 - No infusion interruption: The duration of infusion in minutes will be calculated as: (Infusion end time – Infusion start time + 1).
Case 2 - Infusion interruption: The duration of infusion in minutes will be calculated as: ((Infusion end time – Infusion Restart Time) + (Infusion Stop Time – Infusion start time)+ 1).

- **Ear signal/noise ratio (dB)**

The ear signal/noise ratio will be calculated from speech-in-noise test as: Ear speech stimulation level - ear noise stimulation level.

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- **Laboratory data: unit used**

For laboratory data having more than one unit possibly recorded in the eCRF, the units used will be the followings:

Parameter	Final Unit
Clinical Chemistry	
Potassium	mmol/L
Aspartate Aminotransferase	IU/L
Total Bilirubin	μ mol/L
Direct Bilirubin	μ mol/L
Creatinine	μ mol/L
Sodium	mmol/L
Alanine Aminotransferase	IU/L
Total Protein	g/L
Calcium	mmol/L
Alkaline Phosphatase	IU/L
International normalized ratio	%
Blood Urea Nitrogen	mmol/L
Fasting Glucose	mmol/L
Blood Hematology	
Platelet count	10^9/L
MCV	fL
Reticulocytes	G/L
White Blood Cell (WBC) count	10^9/L
Neutrophils	10^9/L
Lymphocytes	10^9/L
Monocytes	10^9/L
Eosinophils	10^9/L
Basophils	10^9/L
Red Blood Cell (RBC) count	10^{12}/L
Hemoglobin	g/L
Hematocrit	%
Mean Corpuscular Hemoglobin	pg

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Appendix B: DERIVATIONS RELATED TO PRIMARY/SECONDARY END-POINTS

- **Three contiguous most affected hearing frequencies**

The endpoint will be calculated as follows (statistical unit = eligible ear):

- For each hearing frequency (ranged from 0.5 to 12.5 kHz), the change from baseline at V4 will be calculated,
- The mean of the change from baseline at V4 will be calculated according to the frequencies,
- The three frequencies with the highest value (in change from baseline) will be considered as the three contiguous most affected hearing frequencies and will be selected solely based on the results obtained in the control group,
- The mean of the values of the three frequencies selected will be calculated. If a threshold value is missing for at least one of the three selected frequencies, then the calculated mean will also be missing.

The calculated mean will determine the value of the endpoint for each eligible ear.

- **Severity of the hearing loss grade**

The endpoint will be calculated as follows (statistical unit = eligible ear):

- Select the frequencies ranged from 1 to 8 kHz,
- For each hearing frequency, the change from baseline at V4/V5 will be calculated,
- Calculate the mean of the 3 contiguous frequencies with the highest value (in change from baseline),
- If the mean of the 3 contiguous frequencies > 25 dB then "Grade = 3"
- If not, then calculate the mean of the 2 contiguous frequencies with the highest value (in change from baseline),
- From the mean of the 2 contiguous frequencies:
  - If the mean > 25 dB then "Grade = 2",
    If not, then:
  - if the mean ≥ 15 dB then "Grade = 1".

- **ICE derivations**
  - If the subject does not complete the study according to the protocol, then:
    - If the subject reports at least one AE related to SENS-401 study treatment and the corresponding action taken is "Drug

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withdrawn" then ICE = "Early termination of the study due to reasons related to the study treatment SENS-401"
(i.e., if (Relationship to study drug product (SENS401) = "Related" and Action taken with SENS-401 = "Drug withdrawn") then ICE = "Early termination of the study due to reasons related to the study treatments")

- Else, ICE = "Early termination of the study due to reasons unrelated to the study treatment SENS-401".

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Statistical Analysis Plan	Version:	**2.0**
	Study Protocol:	20 SEP 2023 V4.1
Study Name	NOTOXIS	
Study ID	SENS-401-202	
EudraCT number	2021-002705-10	

[redacted]