[redacted]

STATISTICAL ANALYSIS PLAN

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

Protocol No.: SENS-401-203

Product Code: SENS-401

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AUTHOR: [redacted]

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the SENS-401-203 study:

Name	Title/ Company	Signature	Date
[redacted]			

SAP REVISION HISTORY

Version	Description/Updates	Date
1.0	The sponsor approved first version of SAP and mock shells.	02 May 2024
2.0	Efficacy analysis set was added and defined in the SAP. PK analysis set definition was revised for clarity. The CDISC section was removed as it was not required for this confirmed proof of concept study. The general analytical approach for continuous variables was updated to specify the presentation of decimal points in summary tables. Update to mock shells were made to reflect these changes.	03 July 2024

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1 INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the details of the planned statistical analyses of the data from the SENS-401-203 study.

The planned analyses identified in this SAP will be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post hoc exploratory analyses not identified in this SAP may be performed to further evaluate study data. Any post hoc analyses performed will be identified as such in the CSR.

2 PROJECT OVERVIEW

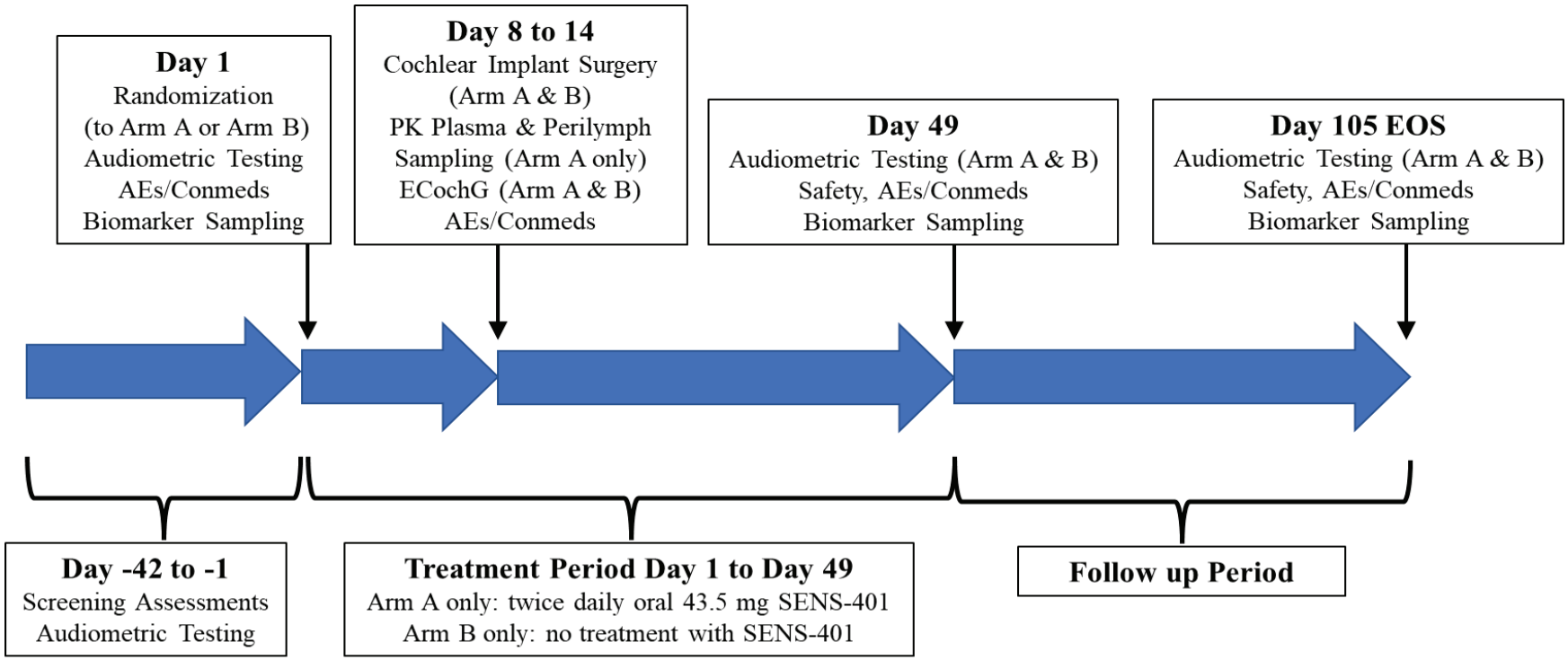
2.1 Study Design

This is a Phase IIa, open-label, randomized and controlled study investigating repeated twice-daily administration of oral SENS-401 in adult participants with preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (i.e., ≤80 dB) at 500 Hz), who meet the locally approved indication for, and have already consented to receiving, cochlear implant Cochlear™ Nucleus® C1622.

After written informed consent is obtained and screening procedures completed, 27 eligible participants will be randomized on Day 1 to either Arm A or Arm B in ratio 2:1 (18 participants in Arm A and 9 participants in Arm B). Arm A participants will commence dosing with twice-daily oral 43.5 mg SENS- 401 for 7 to 13 days prior to their cochlear implant surgery scheduled from Day 8 to Day 14. Dosing will continue on the day of surgery. Arm B participants will not receive any treatment other than their scheduled cochlear implant surgery. All participants will undergo audiometric testing at screening and Day 1 (baseline). From Day 1, Arm A participants will record each administration of SENS-401 into a study diary. Blood and perilymph samples for determining SENS-401 concentration will be collected from Arm A participants only on the day of cochlear implant surgery (blood sampling before the morning dose of SENS-401 and perilymph sampling during the surgery). Electrocochleography will be performed for all participants (Arm A and Arm B) during cochlear implant surgery. All participants (Arm A and Arm B) will attend the Day 49 visit, when efficacy and safety assessments will be performed. Arm A participants will continue to take SENS-401 until this visit. All participants (Arm A and Arm B) will then return to the study site for the EOS on Day 105 for final safety and efficacy assessments. Blood samples for exploratory biomarker research will also be collected from all participants (Arm A and Arm B) on Day 1, Day 49 visit, and EOS.

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

2.2 SCHEMA



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

2.3 SCHEDULE OF ASSESSMENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.4 Objectives

2.4.1 Primary objective

- To detect the presence of SENS-401 in the perilymph of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.

2.4.2 Secondary objective(s)

- To measure the SENS-401 concentrations in the perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.
- To compare the SENS-401 concentrations in perilymph and plasma of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.
- To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery at the Day 49 visit and at EOS.
- To assess the safety and tolerability of SENS-401 for the whole duration of the study.

2.4.3 Exploratory objective(s)

- To assess the efficacy of repeated oral administration with SENS-401 to protect against residual low frequency hearing loss in participants undergoing cochlear implant surgery and with no electrophysiological evidence of basilar membrane fixation.
- To collect and store a biobank of plasma and serum to be able if necessary and possible to explore the correlation between biomarkers already pre-identified (e.g., prestin) or that will be identified in the future with clinical features of interest.

2.5 Endpoints

2.5.1 Primary Endpoints

- Percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification on day of cochlear implant surgery after seven days of SENS-401.

2.5.2 Secondary Endpoints

2.5.2.1 Pharmacokinetic Endpoints

- SENS-401 perilymph concentration on day of cochlear implant surgery after seven days of SENS-401
- SENS-401 plasma concentration on day of cochlear implant surgery after seven days of SENS-401.

2.5.2.2 Efficacy Endpoints

- Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS.

- Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA) at the Day 49 visit and at EOS.

2.5.2.3 Safety Endpoints

Safety endpoints will include evaluation of the following:

- Incidence, severity and relationship of treatment emergent adverse events (AEs) and serious AEs.
- Change from baseline in vital signs.
- Change from baseline in 12-lead ECG parameters.
- Change from baseline in clinical laboratory parameters (serum chemistry, hematology, coagulation).

2.5.2.4 Exploratory Endpoints

➢ In a subset of participants assessed by a neurophysiologist to have no electrophysiological evidence of basilar membrane fixation:

- Change of hearing threshold from baseline in the implanted ear at 500 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA)
- Change of hearing threshold from baseline in the implanted ear at 250 Hz and 750 Hz after repeated administration of SENS-401, as assessed by pure tone audiometry (PTA).

➢ Serum/plasma concentrations of selected biomarkers at baseline (i.e., Day 1, and pre-dose for Arm A), at the Day 49 visit, and at EOS.

2.6 Sample Size

Overall, for this study, 27 participants will be enrolled and randomized to either Arm A or Arm B on Day 1 in ratio 2:1 (18 participants in Arm A and 9 participants in Arm B).

The sample size is not calculated based on statistical significance on any clinical efficacy parameters but on empirical considerations for the pharmacokinetic evaluation. Eighteen subjects are generally considered sufficient to characterize the PK of a small molecule. The purpose of the PK sampling is to determine if SENS-401 can be detected in the perilymph and to compare the levels of SENS-401 in two different body compartments and the overall safety profile.

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

Enough participants will be screened to randomize 27 participants. The expected power and precision related to this sample size is further discussed for both the main endpoint and the secondary endpoint in sections 9 and 10.

2.7 Treatment Assignment and Randomization

All participants will be randomized as detailed in the randomization plan. Overall, for this study, 27 participants will be enrolled and randomized to either Arm A or Arm B on Day 1 in ratio 2:1:

- Arm A: treated with SENS-401. Eighteen (18) participants.
- Arm B: not treated with SENS-401. Nine (9) participants.

3 STATISTICAL CONSIDERATIONS

3.1 General Analytical Approach

Data analysis will be performed according to [redacted] Standard Operating Procedures (SOPs).

The general analytical approach for all endpoints will be descriptive in nature.

Unless otherwise stated, the following statistical approaches will be taken:

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

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

Imputation: No imputation will be performed for missing data.

Baseline: Baseline will be defined as the last available assessment prior randomization, excluding the audiogram values. For the audiogram values, the baseline will be determined based on the data collected on Day 1 after randomization of study participants.

Unscheduled visits: Unscheduled visits will be excluded from visit-based summary tables, but will be included in data listings.

Early termination visits: Early termination visits will be excluded from visit-based summary tables but will be included in data listings.

3.2 Data Capture

3.2.1 Database

The primary method of data collection is via the study database, developed within the third party validated, 21 CFR Part 11 compliant, technology solution [redacted]. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system. Site-collected data will be entered directlyfrom source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

Refer to the Data Management Plan for further details.

3.2.2 Third Party Data

3.2.2.1 Safety & PD Laboratory

Bioanalytical data will be received from [redacted] as specified in the Data Transfer Agreement (DTA). Data transfers will be reconciled against the CRF data.

The central reading of electrocochleography results will be sent back to the clinical site that will directly enter the data into the EDC system.

The final data transfer(s) will be incorporated into the End of Study analysis once the final transfer has been received, reconciled and all issues are considered resolved.

No unit conversion of laboratory data is planned.

3.3 Statistical Programming

3.3.1 Change from Baseline

Absolute Change from Baseline will be calculated as:

$$Change\ from\ baseline = postbaseline\ value - baseline\ value$$

3.3.2 Listings, Tables and Figures

Listings, tables and figures will be delivered as individual .RTF files in accordance with the mock listings, tables and figures.

Data listings will present all data, with participants grouped by the treatment arm. These are typically sorted by arm treatment, participant ID, and date/time of assessment.

Tabulations will summarize data by treatment arm, and total.

Tables are planned to be presented as:

Arm A (N=X)	Arm B (N=X)	Overall (N=X)

Where Arm A: treated with SENS-401; and Arm B: not treated with SENS-401

4 ANALYSIS SETS

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

Additional study populations or subgroups of interest may be required as part of post-hoc analyses. These will be detailed in the CSR.

The number and percentage of participants in each analysis set will be summarized.

4.1 Analysis Set Descriptions

4.1.1 PK Set

The PK set consists of study participant for whom perilymph and/or plasma was analysed.

4.1.2 FAS Set

The FAS will be comprised of all randomized participants. A randomized participant is defined as having a profile deemed suitable for participation in the study by the investigator, based on adherence to all eligibility criteria, which allowed the study participant to be randomly allocated to either Arm A or B. Participants will be analyzed according to the treatment received.

4.1.3 Efficacy Set

The efficacy set will consist of all FAS participants who have at least hearing threshold parameter data at Baseline and Day 49.

5 PROTOCOL DEVIATIONS

Analysis Set: FAS

5.1 Data Lists

All protocol deviations will be listed, grouped by the treatment arm.

5.2 Analyses

The protocol deviation summary table will include:

- The total number of minor protocol deviations
- The total number of major protocol deviations
- The number of participants who reported at least one minor protocol deviation
- The number of participants who reported at least one major protocol deviation

6 PARTICIPANT DISPOSITION

Analysis Set: All participants

6.1 Data Lists

A listing of subject disposition will present:

- Date of informed consent
- Date of randomization
- Date of first treatment
- Date of last treatment
- Date of completion / early withdrawal
- Primary reason for early withdrawal

6.2 Analyses

The participant disposition summary table will include:

- Number of participants consented
- Number of participants screened
- Number of participants randomized
- Number of participants eligible for PK set
- Number of participants eligible for FAS set
- Number of participants eligible for Efficacy set
- Number of participants who received at least one dose of study drug (Arm A only)
- Number of participants who had the Cochlear Implant Surgery
- Number of participants withdrawn from the study early
- Reason for early study withdrawal
- Number of participants completing study

6.3 Death

Death-related details will be listed only if deaths occur.

7 DEMOGRAPHIC AND BASELINE INFORMATION

Analysis Set: FAS except for Eligibility where all subjects are included.

7.1 Demographics

7.1.1 Parameters

- Age (years)
- Sex
- Childbearing potential
- Menopause status
- Body Measurements
    - Height
    - Weight

7.1.2 Biostatistical methods

7.1.2.1 Data Lists

Demographic data will be listed for each participant.

7.1.2.2 Analyses

Demographic data will be summarized using descriptive statistics, tabulated by the treatment arm.

7.2 Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by system organ class (SOC) and preferred term (PT), by treatment arm and overall. Data on history will also be presented in listings.

7.3 Pregnancy Test

Pregnancy test data will be listed for all women of childbearing potential.

7.4 Eligibility

All eligibility data will be listed (include all participants).

7.5 Hearing Loss History

7.5.1 Data Lists

Hearing loss history will be listed for each participant by the treatment arm.

7.5.2 Analyses

Hearing loss history will be summarized using descriptive statistics, tabulated by the treatment arm.

7.6 SARS-CoV-2 Screening

Any SARS-CoV2 screening results will be listed.

8 TREATMENT EXPOSURE

Analysis Set: FAS

8.1 Study Drug Administration (Arm A only)

The diary data will be listed.

8.2 Study Drug Reconciliation (Arm A only)

8.2.1 Data Lists

Study drug reconciliation will be listed, including data on:

- Study drug dispensation date
- Number of tablets dispensed
- Study drug return date
- Number of tablets taken
- Number of tablets returned
- IMP compliance ≥ 70% in the 3 days prior to surgery
- IMP compliance ≥ 70% for dosing period prior to surgery
- IMP compliance ≥ 70% during the entire treatment period
- IMP compliance at 100% in the 3 days prior to surgery

8.2.2 Analyses

Treatment exposure will be summarized as:

- Total Number of tablets
- Number of participants with IMP compliance ≥ 70% in the 3 days prior to surgery
- Number of participants with IMP compliance ≥ 70% Dosing Period Prior to Surgery
- Number of participants with IMP compliance ≥ 70% during the entire treatment period
- Number of participants with IMP compliance at 100% in the 3 days prior to surgery
- Duration of exposure: Date of last dose - date of first dose + 1

9 PHARMACOKINETICS ENDPOINTS

Analysis Set: PK Set (Arm A only)

9.1 Primary endpoint

9.1.1 Data Lists

Data on sample collections before Cochlear implant surgery and on the surgery, will be listed, including:

- Date of perilymph sample collection
- Time of perilymph sample collection
- If surgery was complicated
- Date / Time of last drug intake before plasma sample collection
- Date / Time of plasma sample collection
- Time lapse between last drug intake and perilymph sample collection

9.1.2 Analyses

The number and percentage of participants from Arm A with levels of SENS-401 in the perilymph above the Limit of Quantification will be summarized.

9.2 Secondary endpoint

9.2.1 Data Lists

The evaluation of the secondary endpoints will be purely descriptive. It will involve listing the concentrations of SENS401 obtained in the plasma and in the perilymph for each participant in Arm A.

10 EFFICACY ENDPOINTS

Analysis Set: FAS Set

10.1 Hearing Threshold

10.1.1 Data Lists

Hearing threshold values for each patient, as assessed by bone and air conduction pure tone audiometry (PTA), will be listed at frequencies 125 to 4kHz (air) and 250 to 4kHz (bone), by treatment arm and timepoint.

For each participant, a 3-frequency average of the hearing threshold values (250-500-750 Hz) will be calculated and listed by treatment arm and timepoint. For each timepoint, if there is a missing hearing threshold value at any of these 3 frequencies, the average will not be calculated.

10.1.2 Analyses

Analyses will be conducted on air conduction hearing threshold results only and not on bone conduction hearing threshold results.

10.1.2.1 Hearing Threshold by Air Conduction PTA – Covariance Analysis

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

Change from baseline of the average hearing threshold values for frequencies 250-500-750 Hz will be summarized as continuous variables by visit and treatment arm using simple descriptive statistics.

Some threshold results are recorded as “No response” or “Vibrotactile only”. A “No response” and “Vibrotactile only” result is never to be considered a threshold. Therefore 5 dB will be added to each threshold value associated to a “No response” or “Vibrotactile only” result (Sijgers et al., 2023).

Analysis of covariance model (ANCOVA) will be used to assess changes in the values from baseline at the Day 49 visit and at EOS, comparing between treatment groups. The treatment group will be used as a fixed factor and the baseline as a covariate. If baseline is not available at a frequency, the post-baseline value will be excluded from the descriptive table and the ANCOVA for that frequency. For the average of the 3 frequencies, if there is a missing value at one of the 3 frequencies, the participant will be excluded from the descriptive table and the ANCOVA.

10.2 Immittance Audiometry

Immittance audiometry assessment data will be listed for each participant by treatment arm and timepoint.

10.3 Exploratory

10.3.1 Hearing Preservation

Hearing preservation will be calculated for each participant by treatment arm at baseline, Day 49, and Day 105. This will be done at measured frequencies 125, 250, 500 and 750 Hz, as well as using the average of 125 to 750 Hz and 250 to 750 Hz.

The degree of hearing preservation will be quantified using the Hearing Preservation Classification System technique (Skarzynski et al).

The Hearing Preservation Classification System defines four categories of hearing preservation (HP)%:

- Category HP1 is complete or near complete preservation. with a HP of more than 75%.
- Category HP2 is partial preservation with a HP of 25 to 75%.
- Category HP3 is minimal HP with a HP 0 to 25%.
- Category HP4 is loss of hearing/no hearing when no measurable hearing is preserved.

Hearing Preservation (HP)% = 1 - (PTA postoperative - PTA baseline) / (PTA max - PTA baseline) * 100

Where:

- PTA baseline is pure tone average measured preoperatively.
- PTA postoperative is pure tone average measured postoperatively.
- PTA max is the maximal sound intensity at the frequency.

For frequency 125 Hz, PTA max = 90 dB HL → PTA postoperative upper limit = 90 dB HL
For frequency 250 Hz, PTA max = 105 dB HL → PTA postoperative upper limit = 105 dB HL
For frequency 500 Hz, PTA max = 110 dB HL → PTA postoperative upper limit = 110 dB HL
For frequency 750 Hz, PTA max = 120 dB HL → PTA postoperative upper limit = 120 dB HL

For the average frequencies from 125-750 Hz:

- PTA baseline is the average dB HL across the 4 frequencies.
- PTA postoperative is the average dB HL across the 4 frequencies.
- PTA max is the average of the 4 maximums: (90+105+110+120/4)

For the average 250 – 750 Hz:

- PTA baseline is the average dB HL across the 3 frequencies.
- PTA postoperative is the average dB HL across the 3 frequencies.
- PTA max is the average of the 3 maximums: (105+110+120/3)

The HP outcomes will be listed for each participant by treatment arm, by individual frequency (125 – 750 Hz), by 4-frequency average (125-750 Hz), by 3-frequency average (250 – 750 Hz) and by timepoint.

The HP outcomes will be summarized by visit and by percentage of participants per treatment arm for each category of hearing preservation. There will be a summary table per individual

frequency (125 – 750 Hz), a second per 4-frequency average (125-750 Hz), and a third per 3-frequency average (250 – 750 Hz).

If the PTA baseline is not available at one of the 3 (250-750 Hz) or 4 (125-750 Hz) frequencies, the participant will be excluded from the summarized tables of the 3 or 4-frequency average.

10.3.2 Assessment of Basilar Membrane Fixation

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

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

10.3.3 Hearing Threshold assessment excluding participants with IBM

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

10.3.4 A Biomarker Analysis

Biomarker exploratory analyses will not be performed presently and serum/plasma samples will be stored for biobank. If performed, analysis plan will be documented separately from this SAP.

11 SAFETY

Analysis Set: FAS Set

11.1 Adverse Events

11.1.1 Definition of Variables

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

- A serious adverse event (SAE) is any AE that results in death, or is life-threatening, and/or requires inpatient hospitalization or prolongs existing hospitalization, and/or results in persistent or significant disability or incapacity, and/or is a congenital anomaly or birth defect. Important medical events that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other mentioned outcomes should also be considered as SAEs.

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

11.1.2 Biostatistical methods

AEs will be coded using MedDRA. The MedDRA version used will be displayed in the output footer.

11.1.3 Data Lists

All AEs recorded during the study will be listed, grouped by participant and treatment arm.

11.1.4 Analyses

An overview summary table of AEs will be provided by treatment arm including:
Number of participants reporting at least one of the following:

- AE
- Grade 3+ AE
- Related AE (to study drug treatment, sample collection procedure, Cochlear implant surgery and implant)
- Serious AE
- Serious and study drug-related AE
- Serious and sample collection procedure related AE
- Serious and Cochlear implant surgery related AE
- Serious and Cochlear implant related AE

Number of participants discontinued from study drug treatment due to an AE

Number of participants interrupted from study drug treatment due to an AE

Number of participants withdrawn from the study due to an AE
Number of deaths

A similar overview summary table will be provided for the TEAE for arm A participants only.

The following summary tables will be provided for TEAEs for participants in arm A.

- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Grade 3 or greater TEAEs by SOC and PT
- Study drug related TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum severity
- TEAEs related to the study sample collection procedure by SOC and PT
- TEAEs related to Cochlear implant surgery by SOC and PT
- TEAEs related to Cochlear implant by SOC and PT

For the TEAE summaries, participants who experience the same TEAE more than once, the participant will be counted only once for that event within each category (PT, SOC or overall).

If a participant experiences multiple occurrences of the same TEAE with different relationship categories, the participant will be counted once as a relationship category of Related.

If a participant experiences multiple occurrences of the same TEAE with different intensity toxicity grades, the participant will be counted once for the maximum (most severe) toxicity grade. TEAEs with a missing intensity will be presented in the summary table with a toxicity grade of Missing. Grade 3 or greater is defined as Grade 3, Grade 4, Grade 5, or Missing.

11.2 Prior and Concomitant Medications

11.2.1 Definition of Variables

- Prior medications will be identified as medications commenced prior to randomization, regardless of when it ended.
- Concomitant medications will be defined as any medication that is taken at or after randomization, regardless of when it started. All medications used for cochlear implant surgery will be documented and reported into the eCRF as concomitant medications. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial treatment or concomitantly, it will be considered as both prior and concomitant.

11.2.2 Biostatistical methods

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug). The WHODrug version used will be displayed in the output footer. Prior and concomitant medications will be presented in separate listings and tables.

All prior and concomitant medications will be listed separately.

Prior and concomitant medication summaries will be presented in separate tabulations by treatment arm, with data summarized by ATC Level 3 and Preferred Name.

11.3 Otoscopic Examination

Otoscopic assessment data will be listed for each participant by treatment arm and timepoint.

11.4 Electrocochleography (ECochG)

11.4.1 Data Lists

ECochG assessment data will be listed for each participant by treatment arm and timepoint.

11.4.2 Analyses

The number of participants with Impairment of the Basilar Membrane (IBM) will be summarized by the treatment arm.

11.5 Cochlear Implant Surgery

Cochlear implant surgery data will be listed for each participant by the treatment arm.

11.6 Laboratory Assessments

Data for each of the assessments below will be presented in listings:

11.6.1 Parameters

HAEMATOLOGY	CHEMISTRY
Hemoglobin	Sodium
Hematocrit	Potassium
Red Blood Cell (RBC) Count	Calcium
Mean corpuscular volume (MCV)	Creatinine
Mean corpuscular hemoglobin (MCH)	Creatinine clearance GFR (calculated with the Cockcroft-Gault formula
White Cell Count	Urea
Neutrophils	Total Protein
Lymphocytes	Alkaline Phosphatase (ALP)
Monocytes	Alanine-aminotransferase (ALT) / ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)
Eosinophils	Aspartate-aminotransferase (AST) / Serum Glutamic-Oxaloacetic Transaminase (SGOT)
Basophils	Total Bilirubin
Platelet Count	Direct Bilirubin
	Glucose Fasting
	International normalized ratio (INR)

CKD-EPI = chronic kidney disease epidemiology collaboration, GFR = glomerular filtration rate,
MDRD = modification of diet in renal disease.
Creatine Clearance conversion: ml/min = (ml/min/1.73m^2 value * BSA) / 1.73 m^2
with BSA = 0.007184 * Height (cm) $^{0.725}$ * Weight (kg) $^{0.425}$.

11.6.2 Biostatistical methods

11.6.3 Data Lists

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

11.6.4 Analyses

Observed values (including change from baseline) will be summarized descriptively for hematology and chemistry parameters at baseline and each post-baseline scheduled visit. Both parameters will be presented categorically (Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS)) at baseline and each post-baseline scheduled visit. Tables will be presented by the treatment arm.

11.7 Vital Signs

11.7.1 Parameters

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats per minute)
- Respiration rate (breaths per minute)
- Temperature (°C)

11.7.2 Biostatistical methods

Vital sign parameters will be listed for each participant by treatment arm and timepoint, and assessment date/time, with abnormal values flagged.

11.8 Physical Examination

11.8.1 Parameters

- General appearance
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Blood and Lymphatic
- Respiratory System
- Neck (including Thyroid)
- Renal System
- Gastrointestinal System
- Neurological System
- Skin
- Cardiovascular System
- Musculoskeletal System

11.8.2 Biostatistical methods

Physical examination data will be listed for all abnormal clinical assessments.

11.9 12-lead ECG

11.9.1 Parameters

- PR interval (msec)
- QT interval (msec)
- QRS duration (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Ventricular rate (bpm)
- Overall ECG assessment:
    - ECG status (Normal, Abnormal), including specified abnormality.
    - Clinical significance

11.9.2 Biostatistical methods

11.9.3 Data Lists

ECG data will be listed for all participants and time points per treatment arm.

11.9.4 Analyses

Parameters will be presented categorically (Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS)) at baseline and each post-baseline scheduled visit. Tables will be presented by the treatment group. An additional table will present the frequencies of participants who fulfill the following prolongation (change from baseline) criteria, considering all scheduled and non-scheduled visit data:

- QTcB prolongation >30
- QTcF prolongation >30
- QTcB prolongation >60
- QTcF prolongation >60
- QTcB>450 msec for males
- QTcF >450 msec for males
- QTcB >470 msec for females
- QTcF >470 msec for females

12 CHANGES TO THE PLANNED ANALYSIS

Baseline definition will be the last available assessment prior to randomization, not prior to study drug administration as defined in the protocol.
Descriptive statistics will be rounded to one decimal place, except for SD which will be reported to two decimal places. This differs to reporting the minimum and maximum values to the same number of decimal places as recorded in the eCRF; mean, median and SD to one more decimal place than the raw data, as reported in the protocol.

Prior medications will be identified as medications commenced prior to randomization, regardless of when it ended, not prior to first administration of study drug as stated in protocol. Concomitant medications will be defined as any medication that is taken at or after randomization, regardless of when it started. Not clearly stated in protocol.

Evaluation of the SENS-401 concentration data will be done descriptively and not by applying a paired t-test as mentioned in the protocol.

Any changes in the analyses from the SAP will be described fully in the CSR.

13 INTERIM AND FINAL ANALYSIS

There will be no Interim analysis. A data review will be conducted.

14 SOFTWARE

SAS® Version 9.4 will be used to perform the statistical analyses. Any other software used to analyze data (including PK) will be noted in the CSR.

15 REFERENCES

1) SENS-401-203_Protocol_Clean_V3.0_08 February 2023_Signed.pdf
2) Sensorion, SENS-401-203_3.1_Annotated.pdf
3) S. Bourn et al. Hearing Preservation in Elderly Cochlear Implant Recipients. 2020
4) H. Skarzynski et al. Towards a Consensus on a Hearing Preservation Classification System. 2013
5) Sijgers et al. Classification of Acoustic Hearing Preservation After Cochlear Implantation Using Electrocochleography. 2023